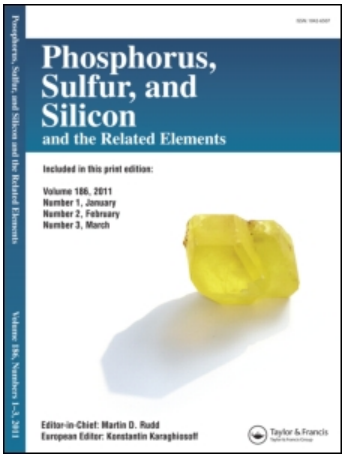


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

HETEROCYCLIC SYNTHESIS WITH ISOTHIOCYANATE AND SULFUR: A NOVEL ROUTE FOR THE SYNTHESIS OF PYRIDINO[2,3-*d*]THIAZOLE, THIAZOLO[4',5':2,3] PYRIDINO[4,3-*d*]PYRIDAZINE AND THIAZOLO[4,5-*b*]ISOQUINOLINE DERIVATIVES

Hussein F. Zohdi[a]; Rafat M. Mohareb[a]; Wagnat W. Wardakhan[a]
[a] Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

To cite this Article Zohdi, Hussein F. , Mohareb, Rafat M. and Wardakhan, Wagnat W.(1995) 'HETEROCYCLIC SYNTHESIS WITH ISOTHIOCYANATE AND SULFUR: A NOVEL ROUTE FOR THE SYNTHESIS OF PYRIDINO[2,3-*d*]THIAZOLE, THIAZOLO[4',5':2,3] PYRIDINO[4,3-*d*]PYRIDAZINE AND THIAZOLO[4,5-*b*]ISOQUINOLINE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 101: 1, 179 — 187
To link to this Article: DOI: 10.1080/10426509508042515
URL: http://dx.doi.org/10.1080/10426509508042515

Phosphorus, Sulfur, and Silicon, 1995, Vol. 101, pp. 179–187
Reprints available directly from the publisher
Photocopying permitted by license only

HETEROCYCLIC SYNTHESIS WITH ISOTHIOCYANATE AND SULFUR: A NOVEL ROUTE FOR THE SYNTHESIS OF PYRIDINO[2,3-*d*]THIAZOLE, THIAZOLO[4′,5′:2,3] PYRIDINO[4,3-*d*]PYRIDAZINE AND THIAZOLO[4,5-*b*]ISOQUINOLINE DERIVATIVES

HUSSEIN F. ZOHDI, RAFAT M. MOHAREB* and
WAGNAT W. WARDAKHAN

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

(Received September 22, 1994; in final form November 7, 1994)

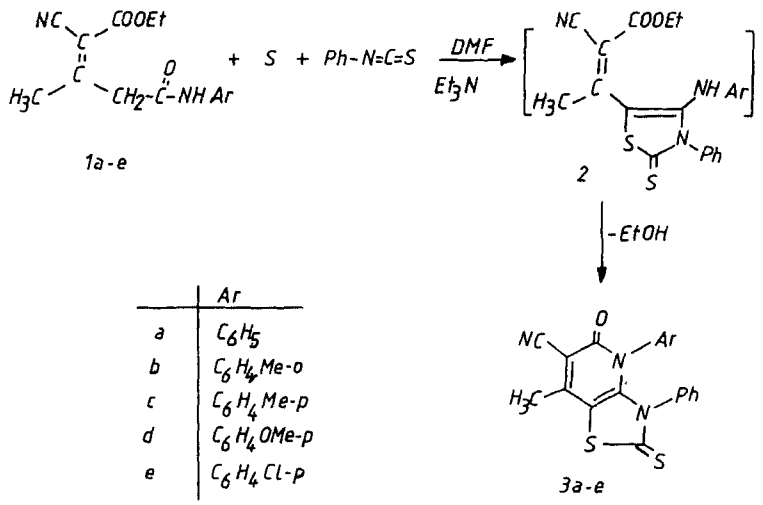
The reaction of phenyl isothiocyanate and sulfur with the Knovenagel condensated adducts **1a–e** afforded the pyridino[2,3-*d*]thiazole derivatives **3a–e**. The latter compounds proved to be versatile starting materials for the synthesis of polyfunctionally substituted thiazolo[4′,5′:2,3]pyridino[4,3-*d*]pyridazine and thiazolo[4,5-*b*]isoquinoline derivatives. Chemical and spectroscopic evidence for the structures of the new compounds, along with a sequence leading to their formation is described.

Key words: Pyridino[2,3-*d*]thiazoles, thiazolo[4′,5′:2,3]pyridino[4,3-*d*]pyridazines, thiazolo[4,5-*b*]isoquinolines.

INTRODUCTION

Thiazoles and their fused derivatives are very versatile reagents that have been utilized for the synthesis of various heterocyclic compounds.[1–5] Moreover, they possess interesting and diverse pharmacological potential.[6–8] Recently we investigated the reaction of phenyl isothiocyanate with Knovenagel condensated adducts **1a–c,e** followed by heterocyclization of the resulted adducts with α-halogenated ketones.[9] There has been an interest in utilizing the reaction of phenyl isothiocyanate and sulfur with simple active methylene reagents to develop an easy and efficient route for the synthesis of polyfunctionally substituted fused thiazole derivatives.[10–12] We now report an extension of such a synthetic route utilizing the Knovenagel condensed adduct **1a–e**. This resulted in the synthesis of pyridino[2,3-*d*]thiazole derivatives, which have latent functional substituents that can be utilized for further chemical transformations.

Thus, the reaction of the Knovenagel condensed adducts **1a–e**, obtained via the simple condensation of acetoacetanilide derivatives and ethyl cyanoacetate,[13,14] with phenyl isothiocyanate and elemental sulfur in refluxing dimethylformamide containing a catalytic amount of triethylamine afforded the pyridino[2,3-*d*]thiazole derivatives **3a–e** (Scheme I). Evidence for the assigned structure **3** was provided by elemental analysis and spectral data. The ^{1}H nmr spectrum of **3a**, for example, revealed the presence of a singlet at δ 2.21 ppm due to the methyl protons and a multiplet at δ 7.23–7.49 ppm corresponding to the two phenyl protons. Moreover,



SCHEME I

TABLE I

Physical and analytical data of the newly synthesized compounds

Compd (Color)	Solvent	m.p. (°C)	Yield[††] (%)	Mol. Formula (M.Wt.)	Analysis Calcd. / Found (%) C	H	N	S
3a[‡]	Dioxane	148	71	$C_{20}H_{13}N_3OS_2$	63.9	3.5	11.2	17.1
(Orange)				(375.47)	63.8	3.2	11.0	16.8
3b	Dioxane	210-13	79	$C_{21}H_{15}N_3OS_2$	64.7	3.9	10.8	16.5
(Orange)				(389.49)	64.5	4.2	10.9	16.1
3c[‡]	DMF	245-8	79	$C_{21}H_{15}N_3OS_2$	64.7	3.9	10.8	16.5
(Yellow)				(389.49)	64.4	4.2	10.6	16.6
3d[‡]	DMF	178	66	$C_{21}H_{15}N_3O_2S_2$	62.2	3.7	10.4	15.8
(Yellow)				(405.49)	62.0	3.9	10.8	15.4
3e	Dioxane	210-12	67	$C_{21}H_{12}ClN_3OS_2$	58.6	2.9	10.2	15.6
(Orange)				(409.96)	58.9	3.3	10.0	15.3
4a	Dioxane	162	72	$C_{20}H_{15}N_5OS$	64.3	4.0	18.7	8.6
(White)				(373.43)	64.0	3.6	18.5	8.6
4b	Dioxane	140	78	$C_{21}H_{17}N_5OS$	65.1	4.4	18.1	8.2
(Yellow)				(387.46)	65.0	4.7	18.3	8.3
4c	DMF	199	73	$C_{21}H_{17}N_5OS$	65.1	4.4	18.1	8.2
(Yellow)				(387.46)	65.0	4.1	18.3	7.9
4d	Dioxane	206	66	$C_{21}H_{17}N_5O_2S$	62.5	4.2	17.3	7.9
(Yellow)				(403.46)	62.2	4.0	17.2	7.8
4e	Dioxane	133	63	$C_{20}H_{14}ClN_5OS$	58.9	3.5	17.2	7.8
(Yellow)				(407.93)	58.6	3.5	17.1	8.2

TABLE I (*Continued*)

Compd (Color)	Solvent	m.p. (°C)	Yield (%)	Mol. Formula (M.Wt.)	Analysis Calcd. / Found (%) C	H	N	S
4f	EtOH/DMF	135	55	$C_{26}H_{19}N_5OS$	69.5	4.3	15.6	7.1
(Orange)				(449.53)	69.3	4.0	15.7	7.0
4g	EtOH	188-90	65	$C_{27}H_{21}N_5OS$	69.9	4.6	15.1	6.9
(Orange)				(463.56)	69.6	4.4	15.3	6.8
4h	MeOH	245-7	80	$C_{27}H_{21}N_5OS$	69.9	4.6	15.1	6.9
(Brown)				(463.56)	70.2	4.8	15.0	7.4
4i	EtOH	166-9	52	$C_{27}H_{21}N_5O_2S$	67.6	4.4	14.6	6.7
(Buff)				(479.59)	67.5	4.0	14.4	6.6
4j	Dioxane	161	68	$C_{26}H_{18}ClN_5OS$	64.5	3.7	14.4	6.6
(Brown)				(484.02)	64.2	4.1	14.3	6.9
5a	EtOH	133	63	$C_{26}H_{17}N_5OS_2$	65.1	3.6	14.6	13.4
(yellow)				(479.58)	64.8	3.4	14.9	13.2
5b	Dioxane	145	69	$C_{27}H_{19}N_5OS_2$	65.1	3.8	14.6	13.0
(Orange)				(493.61)	64.7	4.2	14.5	13.2
5c	EtOH	201-4	63	$C_{27}H_{19}N_5OS_2$	65.1	3.8	14.6	13.0
(Yellow)				(493.61)	65.4	4.2	14.2	13.1
5d	EtOH	169	74	$C_{27}H_{19}N_5O_2S_2$	63.6	3.7	13.7	12.6
(Yellow)				(509.60)	63.4	4.0	13.5	12.4
5e	EtOH	222	58	$C_{26}H_{16}ClN_5OS_2$	60.7	3.1	13.6	12.5
(Yellow)				(514.07)	60.6	3.2	13.2	12.1
6a	DMF	>300	73	$C_{25}H_{16}N_4O_2S_2$	65.0	3.3	11.6	13.3
(Orange)				(480.56)	64.7	3.0	11.4	13.0
6b	DMF	224-7	80	$C_{27}H_{18}N_4O_2S_2$	65.6	3.7	11.3	13.0
(Brown)				(494.59)	65.4	3.8	11.1	12.6
6c	Dioxane	>300	62	$C_{27}H_{18}N_4O_2S_2$	65.6	3.7	11.3	13.0
(Yellow)				(494.59)	65.4	4.0	11.6	12.9
6d	Dioxane	231-4	74	$C_{27}H_{18}N_4O_3S_2$	63.5	3.5	10.9	12.5
(Yellow)				(510.58)	63.3	3.8	11.2	12.9
6e	DMF	190	69	$C_{26}H_{15}ClN_4O_2S_2$	60.6	2.9	10.9	12.4
(Yellow)				(515.05)	60.5	3.1	10.6	12.0
8	Dioxane	>300	79	$C_{23}H_{15}N_4OS_2$	62.6	3.3	15.8	14.5
(Orange)				(441.52)	63.1	2.8	16.2	14.8
9	Dioxane	189	64	$C_{20}H_{13}N_3OS_3$	58.9	3.2	10.3	23.6
(Buff)				(407.53)	59.4	3.0	10.5	23.4
11	DMF	141	76	$C_{23}H_{14}N_4OS_2$	64.5	3.3	13.1	15.0
(Orange)				(426.52)	64.1	3.6	13.3	14.7
12	DMF	231-4	72	$C_{24}H_{13}N_4O_4S_2$	61.1	2.7	8.9	13.6
(Yellow)				(471.49)	61.0	3.0	9.4	13.2

‡ Mass spectra showed the correct molecular ion.

‡‡ *Calculated before crystalization.*

TABLE II

Spectroscopic data for the compounds listed in Table I

Compd.	Ir (cm^{-1}) (Selected bands)	^1H nmr (δ ppm)
3a	2220 (CN); 1690 (CO).	2.21(s, 3H, CH_3); 7.32-7.49(m, 10H, aromatic protons).
3b	2220 (CN); 1690 (CO); 1200 (C=S).	2.23, 2.79(2s, 6H, $2CH_3$); 7.30-7.52(m, 9H, aromatic protons).
3c	2225 (CN); 1695 (CO); 1190 (C=S).	2.26, 2.81(2s, 6H, $2CH_3$); 7.32-7.45(m, 9H, aromatic protons).
3d	2220 (CN); 1690 (CO); 1190 (C=S).	2.25, 3.87(2s, 6H, CH_3, OCH_3); 7.29-7.45(m, 9H, aromatic protons).
3e	2225 (CN); 1685 (CO); 1200 (C=S).	2.24 (s, 3H, CH_3); 7.32-7.52(m, 9H, aromatic protons).
4a	3450, 3420 (NH_2); 2225 (CN); 1695 (CO).	2.22(s, 3H, CH_3); 3.82(s, 2H, NH_2); 7.32-7.50(m, 10H, aromatic protons).
4b	3455, 3420 (NH_2); 2225 (CN); 1685 (CO).	2.22, 2.79(2s, 6H, $2CH_3$); 3.79(s, 2H, NH_2); 7.33-7.48(m, 9H, aromatic protons).
4c	3460, 3410 (NH_2); 2220 (CN); 1680 (CO).	2.21, 2.80(2s, 6H, $2CH_3$); 3.98(s, 2H, NH_2); 7.33-7.48(m, 9H, aromatic protons).
4d	3460, 3425 (NH_2); 2225 (CN); 1690 (CO).	2.24, 3.83(2s, 6H, CH_3, OCH_3); 3.79(s, 2H, NH_2); 7.33-7.47(m, 9H, aromatic protons).
4e	3465, 3440 (NH_2); 2225 (CN); 1690 (CO).	2.22(s, 3H, CH_3); 3.72(s, 2H, NH_2); 7.33-7.45(m, 9H, aromatic protons).
4f	3430 (NH); 2220 (CN); 1685 (CO).	2.25(s, 3H, CH_3); 7.33-7.58(m, 15H, aromatic protons); 8.27(s, 1H, NH).
4g	3440 (NH); 2225 (CN); 1690 (CO).	2.24, 2.77(2s, 6H, $2CH_3$); 7.34-7.52(m, 14H, aromatic protons); 8.44(s, 1H, NH).
4h	3435 (NH); 2220 (CN); 1695 (CO).	2.25, 2.79(2s, 6H, $2CH_3$); 7.32-7.53(m, 14H, aromatic protons); 8.72(s, 1H, NH).
4i	3420 (NH); 2220 (CN); 1695 (CO).	2.23, 3.83(2s, 6H, CH_3, OCH_3); 7.35-7.57(m, 14H, aromatic protons); 8.79(s, 1H, NH).
4j	3445 (NH); 2225 (CN); 1695 (CO).	2.24(s, 3H, CH_3); 7.32-7.48(m, 14H, aromatic protons); 8.43(s, 1H, NH);
5a	3425 (NH); 2225 (CN); 1695 (CO); 1195 (C=S).	5.98(s, 1H, CH=N); 7.32-7.59(m, 15H, aromatic protons) 8.32(s, 1H, NH).
5b	3430 (NH); 2225 (CN); 1695 (CO); 1190 (C=S).	2.73(s, 3H, CH_3); 5.93(s, 1H, CH=N); 7.34-7.53(m, 14H, aromatic protons); 8.36(s, 1H, NH).
5c	3420 (NH); 2220 (CN); 1685 (CO); 1200 (C=S).	2.79(s, 3H, CH_3); 5.90(s, 1H, CH=N); 7.32-7.55(m, 14H, aromatic protons); 8.40(s, 1H, NH).
5d	3440 (NH); 2215 (CN); 1680 (CO); 1200 (C=S).	3.82(s, 3H, OCH_3); 5.96(s, 1H, CH=N); 7.30-7.56(m, 14H aromatic protons); 8.38(s, 1H, NH).
5e	3430 (NH); 2220 (CN); 1690 (CO); 1200 (C=S).	6.01(s, 1H, CH=N); 7.32-7.50(m, 14H, aromatic protons) 8.40(s, 1H, NH).
6a	1690, 1680 (2 CO); 1200 (C=S).	7.21(s, 1H, pyridazine 3-H); 7.32-7.59(m, 15H, aromatic protons).

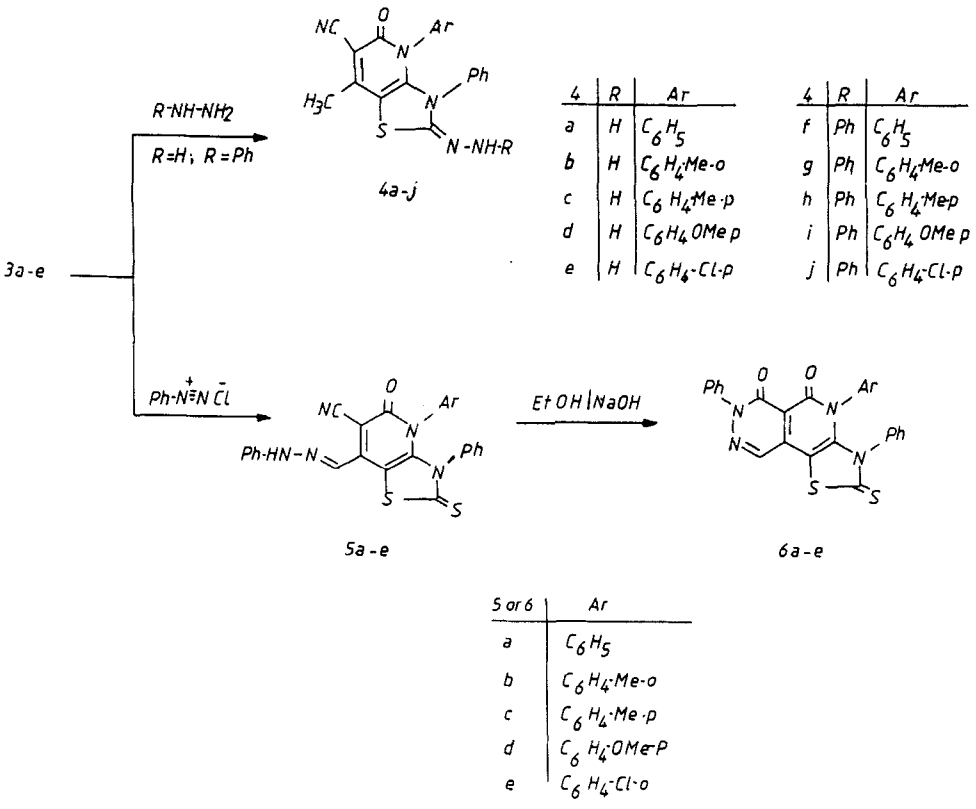
TABLE II (*Continued*)

Compd.	Ir (cm^{-1}) (Selected bands)	^1H nmr (δ ppm)
6b	1695, 1680 (2 CO). 1200 (C=S).	2.61(s, 3H, CH_3); 7.22(s, 1H, pyridazine 3-H); 7.32-7.59(m, 14H, aromatic protons).
6c	1690, 1670 (2 CO); 1160 (C=S).	2.64(s, 3H, CH_3); 7.25(s, 1H, pyridazine 3-H); 7.34-7.59(m, 14H, aromatic protons).
6d	1695-1680 (2 CO); 1195 (C=S).	3.89(s, 3H, OCH_3); 7.29(s, 1H, pyridazine 3-H); 7.32-7.53(m, 14H, aromatic protons).
6e	1695-1675 (2 CO); 1195 (C=S).	7.29(s, 1H, pyridazine 3-H); 7.31-7.58(m, 14H, aromatic protons).
8	3445-3415 (2 NH_2); 1695 (CO); 1205 (C=S).	3.49, 4.21(2s, 4H, $2NH_2$); 7.32-7.53(m, 11H, aromatic protons).
9	3460, 3420 (NH_2); 1690 (CO); 1200 (C=S).	3.78(s, 2H, NH_2); 6.92(s, 1H, thiophene 2-H); 7.33-7.52(m, 10H, aromatic protons).
11	3450, 3425 (NH_2); 2220 (CN); 1685 (CO); 1190 (C=S).	3.49(s, 2H, NH_2); 7.32-7.45(m, 12H, aromatic protons).
12	3430, 3415 (NH_2); 1700-1680 (3 CO); 1190 (C=S).	4.52(s, 2H, NH_2); 7.32-7.45(m, 11H, aromatic protons).

the mass spectrum of **3a** showed the molecular ion at m/z 375. It is believed that the formation of compounds **3a–e** proceed via the intermediacy of **2** followed by intramolecular cyclization via loss of ethanol. Further confirmation of structure **3** was obtained by studying the reactivity of compounds **3a–e** towards chemical reagents.

Thus, it was found that compounds **3a–e** reacted with hydrazine hydrate and phenylhydrazine to afford the corresponding hydrazone derivatives, **4a–j**, respectively (Scheme II). Structure **4** was established on the basis of analytical and spectral data. The IR spectrum of compound **4b**, for example, showed amino absorption at ν 3455 and 3420 cm^{-1}, cyano absorption at ν 2225 cm^{-1} and carbonyl absorption at ν 1685 cm^{-1}. Its ^1H nmr spectrum revealed, besides the aromatic multiplet at δ 7.33–7.48 ppm, the presence of three singlets at δ 2.22, 2.79 and 3.79 ppm corresponding to the methyl, methoxy and amino protons, respectively. Also compounds **3a–e** readily coupled, at the active methyl function, with benzenediazonium chloride at 0°C to afford the phenylhydrazono derivatives **5a–e**.

The latter compounds readily cyclized in ethanolic sodium hydroxide solution to afford the thiazolo[4′,5′:2,3]pyridino[4,3-*d*]pyridazine derivatives **6a-e**. It is believed that such cyclization took place through the addition of the phenylhydrazono NH group to the ortho-cyano group,[15] followed by hydrolysis of the so formed imino group by the sodium hydroxide.[16] Evidence for the assigned structure **6** was provided by analytical and spectral data. The Ir spectrum of compound **6a**, for example, showed two carbonyl absorption bands at ν 1690 and 1680 cm^{-1}. Its ^1H nmr spectrum revealed the presence of a singlet at δ 7.21 ppm due to the pyridazine



4	R	Ar
a	H	C_6H_5
b	H	C_6H_4-Me-o
c	H	C_6H_4-Me-p
d	H	C_6H_4-OMe-p
e	H	C_6H_4-Cl-p

4	R	Ar
f	Ph	C_6H_5
g	Ph	C_6H_4-Me-o
h	Ph	C_6H_4-Me-p
i	Ph	C_6H_4-OMe-p
j	Ph	C_6H_4-Cl-p

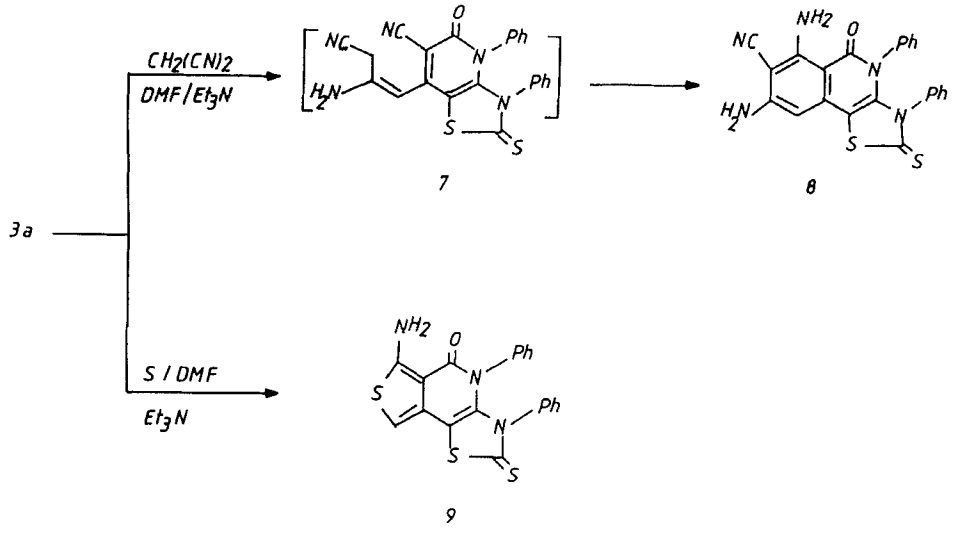
5 or 6	Ar
a	C_6H_5
b	C_6H_4-Me-o
c	C_6H_4-Me-p
d	C_6H_4-OMe-p
e	C_6H_4-Cl-o

SCHEME II

H-3 and a multiplet at δ 7.32–7.59 ppm corresponding to the three phenyl protons. Its mass spectrum showed the molecular ion at m/z 480.

On the other hand, compound **3a** reacted with malononitrile in refluxing dimethylformamide containing a catalytic amount of triethylamine to afford the thiazolo[4,5-*b*]isoquinoline derivative **8** (Scheme III). The formation of the latter compound is assumed to proceed via the intermediacy of **7**, followed by the addition of the active methylene protons to the cyano group. Evidence for the assigned structure **8** was provided on the basis of analytical and spectral data. Its Ir spectrum showed amino absorption at ν 3445–3415 cm^{-1}, cyano absorption at ν 2220 cm^{-1} and carbonyl absorption at ν 1695 cm^{-1}. Its ^1H nmr spectrum revealed the presence of two D_2O exchangeable singlets at δ 3.49 and 4.21 ppm due to the two amino groups, and a multiplet at 7.32–7.53 ppm corresponding to the eleven aromatic protons.

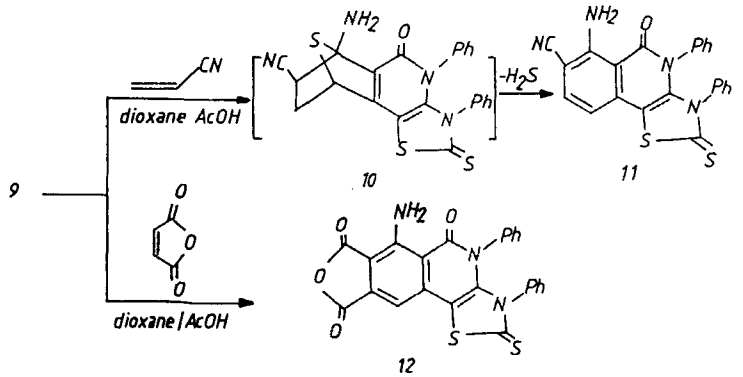
The reactivity of the o-methylnitrilo group present in **3a** towards the formation of thiophene derivatives[17,18] was explored. Thus, **3a** reacted with elemental sulfur in dimethylformamide solution containing a catalytic amount of triethylamine afforded the thieno[3′,4′:4,5]pyridino[2,3-*d*]thiazole derivative **9**, (Scheme III). Evidence for structure **9** was provided by analytical and spectral data. The Ir spectrum of **9** showed absorption bands at ν 3460, 3420 cm^{-1} due to the amino group and



SCHEME III

a carbonyl absorption band at ν 1690 cm^{-1}; moreover, it revealed the absence of any absorption due to the cyano function. The ^1H nmr spectrum revealed the presence of a D_2O exchangeable singlet at δ 3.78 ppm due to the amino protons, a singlet at δ 6.92 ppm for the thiophene H-2 and a multiplet at δ 7.33–7.52 ppm corresponding to ten aromatic protons.

Compound **9** underwent (4 + 2) intermolecular cycloaddition with dienophiles (Scheme IV). Thus, compound **9** reacted with each of acrylonitrile or maleic anhydride in dioxane/acetic acid solution to yield the thiazolo[4,5-*b*]isoquinoline derivative **11** and furo[3″,4″:5′,6′]isoquinolino[2′,3′:4,5]thiazole derivative **12**, respectively. Evidence for structures **11** and **12** was provided by elemental analyses and spectral data. Thus, the Ir spectrum of compound **11** showed absorption bands



SCHEME IV

at ν 3450, 3425 cm^{-1} due to the amino group, a cyano absorption band at ν 2220 cm^{-1} and a carbonyl absorption band at ν 1685 cm^{-1}. The ^1H nmr spectrum revealed a D_2O exchangeable singlet at δ 3.49 ppm due to the amino protons and a multiplet at δ 7.32–7.47 ppm corresponding to the twelve aromatic protons. The formation of compound **11** is assumed to proceed via cycloaddition of acrylonitrile to the thiophene ring in **9** to afford the non-isolable intermediate **10**, which spontaneously aromatized via loss of H_2S to afford the final product.[19]

EXPERIMENTAL

All melting points were uncorrected. Ir spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^1H nmr spectra were recorded on a Varian EM-390 MHz spectrometer with DMSO-d_6 as solvent and chemical shifts are expressed in δ (ppm) units using TMS as internal reference. Ms spectra were recorded on an AEI MS 30 mass spectrometer operating at 70 eV. Microanalytical data were obtained from the Microanalytical Data Centre, Institut für Organische Chemie der Universität Erlangen, Nürnberg, Germany.

1-Aryl-3-cyano-4-methyl-7-phenyl-2-oxo-pyridino[2,3-d]thiazonle-6-thione **3a–e**. To a solution of the appropriate Knoevenagel adducts **1a–e** (10 mmol) in dimethylformamide (30 ml) containing triethylamine (0.5 ml), phenyl isothiocyanate (1.3 g, 10 mmol) and elemental sulfur (0.32 g, 10 mmol) were added. The reaction mixture was heated under reflux for 6 h, then left at room temperature for 24 h with stirring. The solid product formed in each case, upon dilution with water, was collected by filtration and crystallized from the proper solvent.

1-Aryl-3-cyano-6-hydrazone-4-methyl-7-phenyl-2-oxo-pyridino[2,3-d]thiazole **4a–j.** To a solution of the appropriate pyridino[2,3-*d*]thiazole derivative **3a–e** (10 mmol) in dimethylformamide (50 ml), hydrazine hydrate (0.5 g, 10 mmol) or phenylhydrazine (1.1 g, 10 mmol) was added. The reaction mixture, in each case, was heated under reflux for 8 h, then poured into ice-cold water containing few drops of hydrochloric acid. The produced solid, in each case, was collected by filtration and crystallized from the proper solvent.

1-Aryl-3-cyano-2-oxo-7-phenylhydrazonomethylpyridino[2,3-d]thiazole-6-thione **5a–e**. To a cold solution of the appropriate pyridino[2,3-*d*]thiazole derivative **3a–e** (10 mmol) in ethanol (30 ml) containing sodium hydroxide (10 ml, 10%), a cold solution of benzenediazonium chloride (10 mmol) was added with stirring. The reaction mixture was kept at 0–5°C for 4 h and the precipitated solid product was collected by filtration and crystallized from the proper solvent.

7-Aryl-8,9-dioxo-1,6-diphenyl-5-thioxothiazolo[4',5':2,3]pyridino[4,3-d] pyridazine **6a–e**. A solution of each of the appropriate **5a–e** (10 mmol) in ethanol (30 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 8 h. The reaction mixture, in each case, was then poured into ice-cold water and acidified with few drops of hydrochloric acid (pH 6). The produced solid, in each case, was collected by filtration and crystallized from the proper solvent.

4-Cyano-3,5-diamino-1,9-diphenyl-2-oxo-8-thioxothiazolo[4,5-b]isoquinoline (**8**). To a solution of **3a** (3.7 g, 10 mmol) in dimethylformamide (30 ml) containing triethylamine (0.5 ml), malononitrile (0.7 g, 10 mmol) was added. The reaction mixture was heated under reflux for 5 h, then poured into ice-cold water. The so formed product was then collected by filtration, dried and crystallized from dioxane.

8-Amino-5,6-diphenyl-7-oxothieno[3',4':4,5]pryidino[2,3-d]thiazol-5-thione (**9**). To a solution of **3a** (3.7 g, 10 mmol) in dimethylformamide (30 ml) containing triethylamine (0.5 ml), elemental sulfur (0.35 g, 10 mmol) was added. The reaction mixture was heated under reflux for 3 h, then evaporated *in vacuo*. The solid product formed, upon triturating the remainder oily product with diethyl ether, was collected by filtration, dried and crystallized from dioxane.

Reaction of compound **9** *with dienophiles.* To a solution of **9** (4.1 g, 10 mmol) in dioxane (30 ml) containing acetic acid (8 ml), acrylonitrile or maleic anhydride (10 mmol each) was added. The reaction mixture, was heated under reflux for 10 h (until the evolution of H_2S has ceased). The solid product, formed upon cooling to room temperature, in each case, was collected by filtration, to afford **11** and **12**, respectively.

REFERENCES

1. J. Thomas and J. Kant, *Synthesis*, 293 (1993).
2. H. Wamhoff, R. Berressem and S. Herrman, *Synthesis*, 107 (1993).
3. M. T. Cocco and V. Onnis, *Synthesis*, 199 (1993).
4. A. Dondoni and P. Merino, *Synthesis*, 903 (1993).
5. O. Ates, A. Salmow, N. Cesur and G. Otuk, *Die Pharmazie*, **48,** 143 (1993).
6. P. N. Bhagava and S. C. Shama, *Bull. Chem. Soc. Jpn.*, **35,** (1962).
7. W. H. Buton, W. L. Budde and C. C. Cheng, *J. Med. Chem.*, **13,** 1009 (1970).
8. S. R. Singh, *J. Indian Chem.*, **52,** 734 (1975).
9. R. M. Mohareb, H. F. Zohdi, S. M. Sherif and W. W. Wardkhan, *Tetrahedron*, **50,** 5807 (1994).
10. K. A. Maier and O. Hromatke, *Monatsh. Chem.*, **102,** 1010 (1971).
11. K. Gewald and R. Schindler, *J. Prakt. Chem.*, **332,** 223 (1990).
12. R. M. Mohareb, H. Z. Shams and Y. M. El-Kholy, *Phosph., Sulf. and Silic.*, **70,** 317 (1992).
13. A. Habashi, N. S. Ibrahim, R. M. Mohareb and S. M. Fahmy, *Liebigs Ann. Chem.*, 1632 (1986).
14. A. Habashi, N. S. Ibrahim, S. M. Sherif, H. Z. Shams and R. M. Mohareb, *Heterocycles*, **24,** 2463 (1986).
15. K. Sato and T. Amakasu, *J. Org. Chem.*, **33,** 2446 (1968).
16. R. M. Mohareb and S. M. Fahmy, *Z. Naturforsch.*, **40B,** 1537 (1985).
17. R. M. Mohareb, A. M. El-Torgoman, S. I. Aziz, S. M. El-Kousy and M. Riad, *Gazz. Chim. Ital.*, **122,** 503 (1992).
18. M. H. Elnagdi, R. M. Mohareb, F. A. Abdel-Aal and H. A. Mohamed, *Phosph., Sulf. and Silic.*, **82,** 195 (1993).
19. M. H. Elnagdi and A. W. Erian, *Liebigs Ann. Chem.*, 1215 (1990).