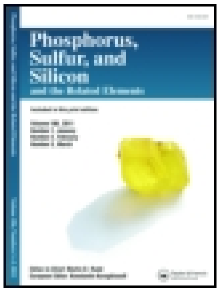

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Studies on Thiazolopyridines. Part 4: Synthesis of Hitherto Unknown 1,4-Bis(thiazolopyridine)benzene Derivatives

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Version of record first published: 27 Oct 2010.

To cite this article: Mohamed S. A. El-Gaby , Moustafa M. Khafagy , Gameel A. M. El-Hag Ali , Hassan A. Eyada , Ahmed A. El-Maghraby & Mohamed H. M. Helal (2003): Studies on Thiazolopyridines. Part 4: Synthesis of Hitherto Unknown 1,4-Bis(thiazolopyridine)benzene Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 178:8, 1681-1688

To link to this article: http://dx.doi.org/10.1080/10426500307827

Phosphorus, Sulfur, and Silicon, 178:1681–1688, 2003
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ISSN: 1042-6507 print
DOI: 10.1080/10426500390200729

STUDIES ON THIAZOLOPYRIDINES. PART 4: SYNTHESIS OF HITHERTO UNKNOWN 1,4-BIS(THIAZOLOPYRIDINE)BENZENE DERIVATIVES

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*2-Cyanomethyl-4-thiazolinone (**1**) was condensed with terephthalaldehyde (**2**) (2:1 molar ratio) and produced 1,4-bis(2-cyanomethyl-4,5-dihydro-5-methylidene-4-thiazolinone-5-yl) benzene (**3**). Treatment of compound (**3**) with benzylidenemalononitrile (**4**) (1:2 molar ratio) furnished the novel bisthiazolopyridines (**6a–e**). Condensation of compound (**1**) with aromatic aldehyde yielded the benzylidene derivatives (**7a–f**), which on treatment with compound (**8**) (2:1 molar ratio) afforded the novel bisthiazolopyridines (**10a–f**). Structures of the synthesized compounds have been established by elemental analyses and spectral data.*

Keywords: Bisthiazolopyridines; thiazolinones

A considerable number of bisheterocyclic compounds exhibited various biological activities including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties.[1–4] It also was reported that bisheterocyclic compounds display much better antibacterial activity than heterocyelic compounds.[5] Some thiazolo[3,2-a] pyridines have been reported to possess antibacterial,[6] bactericide,[7] coronary dilator, antihypertensive, and muscle relaxant[8] activities. It is observed from the literature that 7H-thiazolo[3,2-a] pyridines have been prepared from 2-alkoxycarbonylmethylidene-5-(arylmethylidene)-1,3-thiazolidin-4-one and arylmethylidenemalononitriles.[9–12] On this basis and in continuation of our research[13–17] program on

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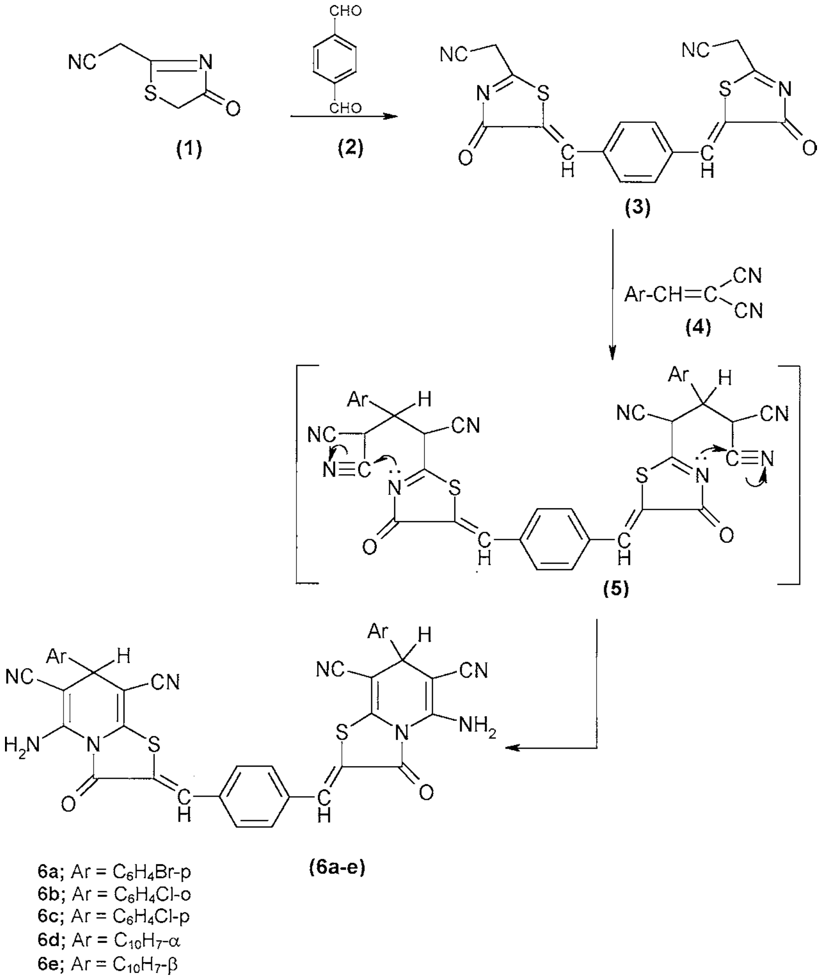
the synthesis of heterocyclic compounds for antimicrobial activity, we report here the synthesis of novel bisthiazolo[3,2-a] pyridine derivatives.

RESULTS AND DISCUSSION

The reaction of 2–cyanomethyl-4-thiazolinone (**1**) with terephthalaldehyde (**2**) (2:1 equivalents) in refluxing ethanol using piperidine as base yielded the corresponding 1,4-bis(2-cyanomethyl-4,5-dihydro-5-methylidene-4-thiazolinone-5-yl) benzene (**3**). The IR spectrum of this product exhibited the presence of the absorption band of the nitrile function and a band for C=O (thiazolinone) was observed. It's ^{1}H NMR spectrum recorded in DMSO-d_6 revealed the presence of signals of methylene and aromatic protons. When a solution of (**3**) and benzylidenemalononitrile (**4**) (1:2 molar ratio) was heated to reflux in absolute ethanol, in the presence of catalytic amounts of piperidine for 3 h the 1,4-bis[5-amino 7-aryl-2-methylidene-2,3-dihydro-7H-3-oxo thiazolo[3,2-a] pyridin-6,8-dicarbonitrile-2-yl] benzene derivatives **6a–e** were isolated. The novel compounds **6** were synthesized in good yields as stable crystalline solids and easily recrystallized from dioxane. The structure of compounds **6a–e** were characterized by elemental and spectroscopic analysis. Thus, IR spectra of compounds **6** revealed the presence of characteristic bands for amino, cyano and carbonyl functional groups. ^{1}H NMR spectrum of compound **6a** showed signal in the region δ 4.26 ppm, attributed to the pyridine-H. The formation of **6** is assumed to proceed via Michael addition of nucleophilic carbon atom of cyanomethyl in **3** to the benzylidene (**4**) to form Michael intermediate[18,19] **5** followed by intramolecular nucleophilic attack at the cyano group to form bisthiazolopyridines (**6**) (Scheme 1).

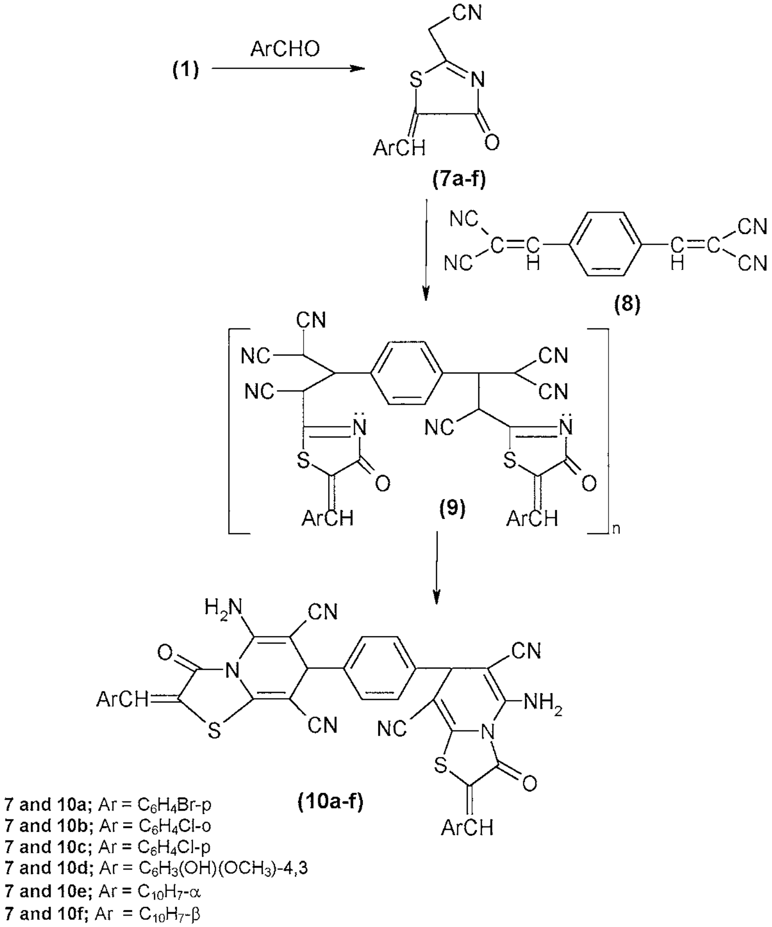
5-Arylmethylidene-2-cyanomethyl-4,5-dihydro-4-thiazolinones **(7a–f)** were obtained by condensation of 2-cyanomethyl-4-thiazolinone **(1)** with aromatic aldehydes in ethanol containing piperidine as catalyst under reflux. Reaction of benzylidene derivative **(8)** with excess of **(1)** in absolute ethanol in the presence of triethylamine gave 1,4-bis[5-amino-2-arylmethylidene-2,3-dihydro-7H-3-oxo-thiazolo[3,2-a]pyridin-6,8-dicarbonitrile-7-yl] benzene derivatives **(10a–f)** in good yields (Scheme 2). The formation of **10** is a assumed to proceed via initial formation of Michael adduct **9** followed by intramolecular cyclization at the cyano group to form compounds **10** (Scheme 2).



SCHEME 1

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Shimadzu-440 infrared spectrophotometer (ν; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}HNMR spectra were recorded in DMSO-d$_6$ at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo



7 and 10a; Ar = C_6H_4Br-p
7 and 10b; Ar = C_6H_4Cl-o
7 and 10c; Ar = C_6H_4Cl-p
7 and 10d; Ar = $C_6H_3(OH)(OCH_3)$-4,3
7 and 10e; Ar = $C_{10}H_7$-α
7 and 10f; Ar = $C_{10}H_7$-β

SCHEME 2

University. The characteristics data for the prepared compounds are given in Table I.

1,4-Bis(2-cyanomethyl-4,5-dihydro-5-methylidene-4-thiazolinone-5-yl) Benzene (3)

A mixture of thiazolinone **1**[20] (0.02 mmol), terephthalaldehyde **2** (0.01 mmol), and piperidine (0.5 mL) in absolute ethanol (50 mL) was heated under reflux for 3 h. The product obtained after cooling was filtered, dried, and recrystallized from ethanol to give **3** (Table I).

TABLE I Physical and Analytical Data for the Synthesized Compounds

Compd. no.	m.p. (°C)	Yield (%)	Solvent cryst.	Mol. formula (mol. wt.)	Calculated/found (%)		
					C	H	N
3	204–205	78	E	$C_{18}H_{10}N_4O_2S_2$	57.13	2.66	14.80
				(378.43)	57.20	2.60	14.10
6a	>300	72	D	$C_{38}H_{20}Br_2N_8O_2S_2$	54.04	2.39	13.27
				(844.58)	54.10	2.20	13.30
6b	>300	65	D	$C_{38}H_{20}Cl_2N_8O_2S_2$	60.40	2.67	14.83
				(755.67)	60.40	2.70	14.70
6c	>300	60	D	$C_{38}H_{20}Cl_2N_8O_2S_2$	60.40	2.64	14.83
				(755.67)	60.30	2.60	14.80
6d	>300	53	D	$C_{46}H_{26}N_8O_2S_2$	70.21	3.33	14.24
				(786.90)	70.21	3.29	14.20
6e	>300	80	D	$C_{46}H_{26}N_8O_2S_2$	70.21	3.33	14.24
				(786.90)	70.20	3.20	14.20
7a	167–168	56	E	$C_{12}H_7BrN_2OS$	46.92	2.30	9.12
				(307.18)	46.80	2.10	9.30
7b	160–162	63	E	$C_{12}H_7Cl\ N_2OS$	54.86	2.69	10.66
				(262.72)	54.80	2.50	10.40
7c	162–164	69	E	$C_{12}H_7Cl\ N_2OS$	54.86	2.69	10.66
				(262.72)	54.90	2.60	10.50
7d	166–165	60	E	$C_{13}H_{10}\ N_2O_3S$	56.92	3.67	10.21
				(274.30)	56.70	3.60	10.20
7e	167–168	63	E	$C_{16}H_{10}\ N_2OS$	69.05	3.62	10.06
				(278.33)	69.10	3.60	10.10
7f	155	64	E	$C_{16}H_{10}N_2OS$	69.05	3.62	10.06
				(278.33)	69.10	3.60	10.20
10a	>300	67	D	$C_{38}H_{20}Br_2N_8O_2S_2$	54.04	2.39	13.27
				(844.58)	54.20	2.10	13.20
10b	>300	70	D	$C_{38}H_{20}Cl_2N_8O_2S_2$	60.40	2.67	14.83
				(755.67)	60.30	2.60	14.80
10c	>300	82	D	$C_{38}H_{20}Cl_2N_8O_2S_2$	60.40	2.67	14.83
				(755.67)	60.40	2.60	14.80
10d	>300	86	D	$C_{40}H_{26}N_8O_6S_2$	61.69	3.36	14.39
				(778.83)	61.70	3.20	14.70
10e	>300	62	D	$C_{46}H_{26}N_8O_2S_2$	70.21	3.33	14.24
				(786.90)	70.10	3.30	14.25
10f	>300	59	D	$C_{46}H_{26}N_8O_2S_2$	70.21	3.33	14.24
				(786.90)	70.20	3.30	14.30

D = dioxane; E = ethanol.

1,4-Bis{5-amino-7-aryl-2-methylidene-2,3-dihydro-7H-3-oxo thiazolo[3,2-a] pyridin-6,8-dicarbonitrile-2-yl} Benzene Derivatives (6a–e)

A mixture of **3** (0.01 mmol), arylidenemalononitrile **4** (0.02 mmol), and piperidine (0.5 mL) in absolute ethanol (50 mL) was heated under reflux

TABLE II Spectral Data of the Synthesized Compounds

Compd. no.	IR (ν_{max}, cm^{-1})	^{1}H-NMR (δ, ppm) (DMSO-d$_6$)
3	2950 (CH-aliph), 2200 (C≡N), 1695 (C=O)	4.02 (s, 4H, 2 CH$_2$ CN), 7.31–8.11 (m, 6H, 4H-Ar and 2H-methine)
6a	3468, 3433, 3267 (NH$_2$), 2928 (CH-aliph), 2200 (C≡N), 1713 (C=O)	4.26 (s, 2H, pyridine-H), 4.98 (s, 2H, NH$_2$), 7.29–8.17 (m, 14H, 12H-Ar and 2H-methine), 10.10 (Hump, 2H, NH$_2$)
6b	3472, 3330, 3250 (NH$_2$), 2922 (CH-aliph), 2199 (C≡N), 1714 (C=O)	4.80 (s, 2H, pyridine-H), 5.07 (s, 2H, NH$_2$), 7.39–8.09 (m, 14H, 12H-Ar and 2H-methine), 8.59 (s, 2H, NH$_2$)
6c	3412, 3301, 3229(NH$_2$), 2929 (CH-aliph), 2197 (C≡N), 1713 (C=O)	
6d	3464, 3323, 3264 (NH$_2$), 2928 (CH-aliph), 2198 (C≡N), 1714 (C=O)	4.79 (s, 2H, pyridine-H), 4.89 (s, 2H, NH$_2$), 7.10–8.11 (m, 20H, 18H-Ar and 2H-methine), 10.05 (s, 2H, NH$_2$)
6e	3437, 3325, 3237 (NH$_2$), 2926 (CH-aliph), 2197 (C≡N), 1714 (C=O)	4.60 (s, 2H, pyridine-H), 5.30 (s, 2H, NH$_2$) 7.20–8.06 (m, 20H, 18 H-Ar-H and 2H-methine), 10.05 (s, 2H, NH$_2$)
7a	2950 (CH-aliph), 2199 (C≡N), 1715 (C=O)	4.04 (s, 2H, CH$_2$ CN), 7.12–7.85 (m, 5H, 4H-Ar and methine-H)
7b	2981 (CH-aliph), 2204 (C≡N), 1720 (C=O)	
7c	2934 (CH-aliph), 2200 (C≡N), 1718 (C=O)	
7d	3483–2985 (broad, OH), 2200 (C≡N), 1707 (C=O)	3.84 (s, 3H, OCH$_3$), 4.76 (s, 2H, CH$_2$, CN), 6.67–7.89 (m, 4H, 3H-Ar and methine-H), 10.00 (s, 1H, OH)
7e	2924 (CH-aliph), 2202 (C≡N), 1711 (C=O)	
7f	2971 (CH-aliph), 2202 (C≡N), 1713 (C=O)	
10a	3446, 3336, 3266 (NH$_2$), 2198 (C≡N), 1707 (C=O)	4.79 (s, 2H, pyridine-H), 7.45–8.14 (m, 14H, 12H-Ar and 2H-methine), 8.60, 10.20 (2s, 4H, 2 NH$_2$)
10b	3452, 3385, 3208 (NH$_2$), 2900 (CH-aliph), 2196 (C≡N), 1715 (C=O)	5.13 (s, 2H, pyridine-H), 7.44–8.16 (m, 14H, 12H-Ar and 2H-methine), 8.61, 10.10 (2s, 4H, 2 NH$_2$)
10c	3431, 3413, 3347 (NH$_2$), 2920 (CH-aliph), 2199 (C≡N), 1716 (C=O)	4.83, 4.85 (2s, 2H, pyridine-H), 7.49–8.17 (m, 14H, 12H-Ar and 2H-methine), 8.59, 10.09 (2s, 4H, 2 NH$_2$)
10d	3379, 3337, 3223 (NH$_2$), 2934 (CH-aliph), 2200 (C≡N), 1709 (C=O)	
10e	3397, 3363, 3337 (NH$_2$), 2924 (CH-aliph), 2199 (C≡N), 1712 (C=O)	4.83, 4.85 (2s, 2H, pyridine-H), 7.50–8.15 (m, 20H, 18H-Ar and 2H-methine), 8.59, 10.10 (2s, 4H, 2 NH$_2$)
10f	3339, 3214, 3170 (NH$_2$), 2199 (C≡N), 1715 (C=O)	

for 3 h. The solid product which was produced on heating was collected and recrystallized form dioxane to give **6a–e** (Table I).

5-Arylmethylidene-2-cyanomethyl-4,5-dihydro-4-thiazolinones (7a–f)

A mixture of **1** (0.01 mmol), aromatic aldehyde (0.01 mmol), and piperidine (0.5 mL) in absolute ethanol (30 mL) was heated under reflux for 1 h. then allowed to cool to room temperature. The precipitate was collected by filtration and recrystallized from ethanol/benzene to give **7a–f** (Table I).

1,4-Bis{5-amino-2-arylmethylidene-2,3-dihydro-7H-3-oxo-thiazolo[3,2-a] pyridin-6,8-dicarbonitrile-7-yl} Benzene Derivatives (10a–f)

A mixture of **7** (0.02 mmol), benzylidene **8** (0.01 mmol), and triethylamine (0.5 mL) in absolute ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture was then cooled, poured into crushed ice, and neutralized with dilute HCl to give **10a–f**, which were recrystallized from dioxane (Table I).

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