

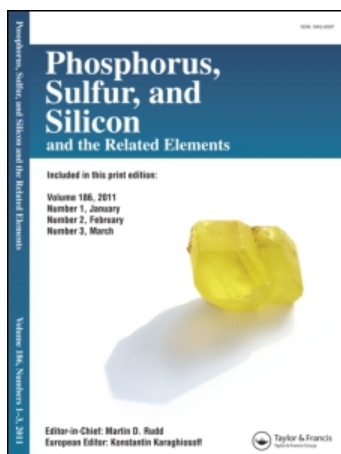
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Studies on Thiazolopyridines. Part 4: Synthesis of Hitherto Unknown 1,4-Bis(thiazolopyridine)benzene Derivatives

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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 heterocyclic compounds.⁵ Some thiazolo[3,2-a]pyridines have been reported to possess antibacterial,⁶ bactericide,⁷ coronary dilator, antihypertensive, and muscle relaxant⁸ 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

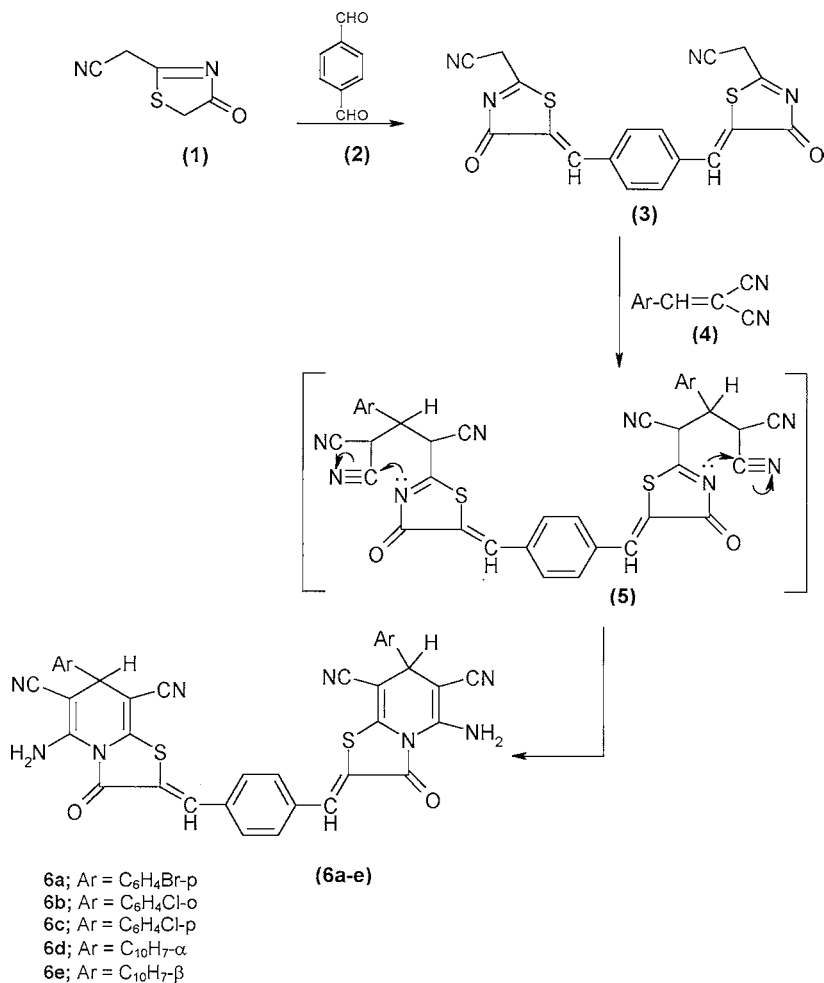
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the synthesis of heterocyclic compounds for antimicrobial activity, we report here the synthesis of novel bisthiazolo[3,2-a] pyridine derivatives.

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. Its ^1H 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. ^1H 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).

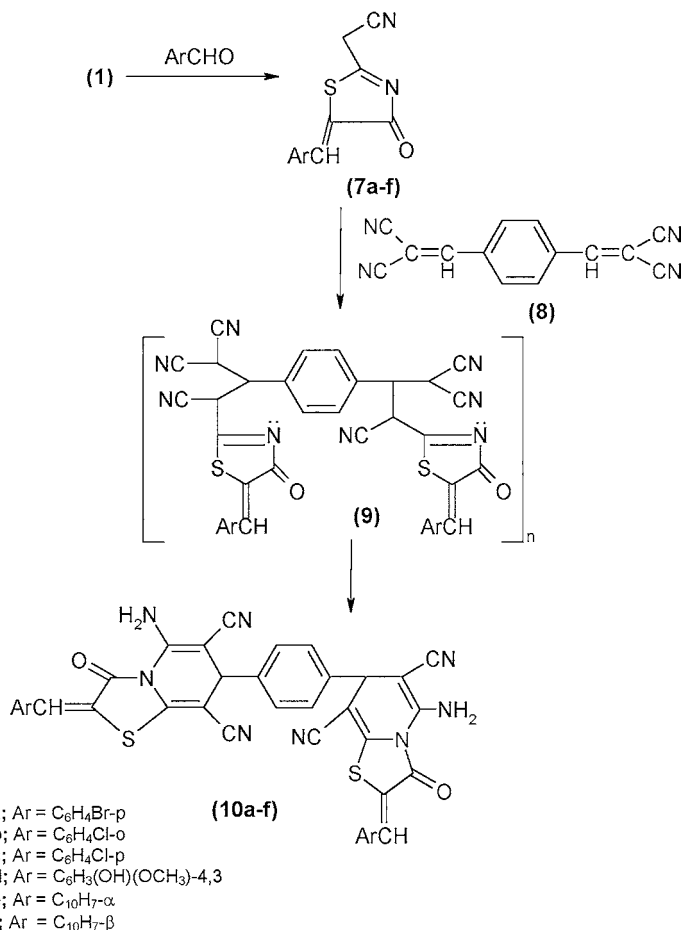
5-Arylmethylidene-2-cyanomethyl-4,5-dihydro-4-thiazolinones (**7a–f**) were obtained by condensation of 2-cyanomethyl-4-thiazolinone (**1**) with aromatic aldehydes in ethanol containing piperidine as catalyst under reflux. Reaction of benzylidene derivative (**8**) with excess of (**1**) in absolute 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 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). ¹HNMR spectra were recorded in DMSO-d₆ 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



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 ₄ O ₂ S ₂ (378.43)	57.13 57.20	2.66 2.60	14.80 14.10
6a	>300	72	D	C ₃₈ H ₂₀ Br ₂ N ₈ O ₂ S ₂ (844.58)	54.04 54.10	2.39 2.20	13.27 13.30
6b	>300	65	D	C ₃₈ H ₂₀ Cl ₂ N ₈ O ₂ S ₂ (755.67)	60.40 60.40	2.67 2.70	14.83 14.70
6c	>300	60	D	C ₃₈ H ₂₀ Cl ₂ N ₈ O ₂ S ₂ (755.67)	60.40 60.30	2.64 2.60	14.83 14.80
6d	>300	53	D	C ₄₆ H ₂₆ N ₈ O ₂ S ₂ (786.90)	70.21 70.21	3.33 3.29	14.24 14.20
6e	>300	80	D	C ₄₆ H ₂₆ N ₈ O ₂ S ₂ (786.90)	70.21 70.20	3.33 3.20	14.24 14.20
7a	167–168	56	E	C ₁₂ H ₇ BrN ₂ OS (307.18)	46.92 46.80	2.30 2.10	9.12 9.30
7b	160–162	63	E	C ₁₂ H ₇ Cl N ₂ OS (262.72)	54.86 54.80	2.69 2.50	10.66 10.40
7c	162–164	69	E	C ₁₂ H ₇ Cl N ₂ OS (262.72)	54.86 54.90	2.69 2.60	10.66 10.50
7d	166–165	60	E	C ₁₃ H ₁₀ N ₂ O ₃ S (274.30)	56.92 56.70	3.67 3.60	10.21 10.20
7e	167–168	63	E	C ₁₆ H ₁₀ N ₂ OS (278.33)	69.05 69.10	3.62 3.60	10.06 10.10
7f	155	64	E	C ₁₆ H ₁₀ N ₂ OS (278.33)	69.05 69.10	3.62 3.60	10.06 10.20
10a	>300	67	D	C ₃₈ H ₂₀ Br ₂ N ₈ O ₂ S ₂ (844.58)	54.04 54.20	2.39 2.10	13.27 13.20
10b	>300	70	D	C ₃₈ H ₂₀ Cl ₂ N ₈ O ₂ S ₂ (755.67)	60.40 60.30	2.67 2.60	14.83 14.80
10c	>300	82	D	C ₃₈ H ₂₀ Cl ₂ N ₈ O ₂ S ₂ (755.67)	60.40 60.40	2.67 2.60	14.83 14.80
10d	>300	86	D	C ₄₀ H ₂₆ N ₈ O ₆ S ₂ (778.83)	61.69 61.70	3.36 3.20	14.39 14.70
10e	>300	62	D	C ₄₆ H ₂₆ N ₈ O ₂ S ₂ (786.90)	70.21 70.10	3.33 3.30	14.24 14.25
10f	>300	59	D	C ₄₆ H ₂₆ N ₈ O ₂ S ₂ (786.90)	70.21 70.20	3.33 3.30	14.24 14.30

D = dioxane; E = ethanol.

1,4-Bis{5-amino-7-aryl-2-methyldene-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 ($\nu_{\max}$, cm^{-1})	$^1\text{H-NMR}$ (δ , ppm) (DMSO- d_6)
3	2950 (CH-aliph), 2200 (C $\equiv$ 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 $\equiv$ 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 $\equiv$ 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 $\equiv$ N), 1713 (C=O)	
6d	3464, 3323, 3264 (NH ₂), 2928 (CH-aliph), 2198 (C $\equiv$ 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 $\equiv$ 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 $\equiv$ 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 $\equiv$ N), 1720 (C=O)	
7c	2934 (CH-aliph), 2200 (C $\equiv$ N), 1718 (C=O)	
7d	3483–2985 (broad, OH), 2200 (C $\equiv$ 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 $\equiv$ N), 1711 (C=O)	
7f	2971 (CH-aliph), 2202 (C $\equiv$ N), 1713 (C=O)	
10a	3446, 3336, 3266 (NH ₂), 2198 (C $\equiv$ 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 $\equiv$ 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 $\equiv$ 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 $\equiv$ N), 1709 (C=O)	
10e	3397, 3363, 3337 (NH ₂), 2924 (CH-aliph), 2199 (C $\equiv$ 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 $\equiv$ N), 1715 (C=O)	

for 3 h. The solid product which was produced on heating was collected and recrystallized from 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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