BROMONITRILES IN HETEROCYCLIC SYNTHESIS. SYNTHESIS AND REACTIONS OF THIAZOLO[3,2-*a*]PYRIMIDINES (III)

Ahmed A. GEIES

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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As a continuation of our previous work[1,2] about the synthesis and properties of thiazolopyrimidines, which are expected to be of biological and medicinal importance[3,4], the present work is aimed to synthesize new polyfunctional substituted thiazolo[3,2-*a*]-pyrimidines.

Pyrimidine derivatives *I* were reacted with bromomalononitrile or ethyl bromocyanoacetate at room temperature in ethanol in presence of potassium hydroxide as a basic catalyst followed by refluxing the reaction mixture to give thiazolo[3,2-*a*]pyrimidines *IIa – IId*.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr pellets. ^{1}H NMR spectra were measured with a 90 MHz Varian spectrometer using TMS as internal standard.

General Procedure for Preparation of Compounds *II*

To a solution of pyrimidine derivative *Ia* or *Ib* (0.01 mol) in ethanol (50ml) containing potassium hydroxide (0.12 mol), bromomalononitrile or ethyl bromocyanoacetate (0.01 mol) was added. The reaction mixture was stirred at room temperature for 30 min, after which was refluxed for 5 h, then allowed to cool. The precipitated product was collected by filtration and crystallized from the proper solvent. The results are summarized in Table I.

3-Acetamido-2,6-dicyano-7-phenylthiazolo[3,2-*a*]pyrimidin-5-one (*III*)

A mixture of *IIc* (0.01 mol) in acetic anhydride (20 ml) was refluxed for 2 h, then allowed to cool and poured into ice/water mixture. The remaining product was triturated with ethanol and the solid product so formed was collected by filtration.

4-Benzoylimino-8-cyano-2,7-diphenyloxazino[4',5' : 4,5]thiazolo[3,2-*a*]pyrimidin-9-one (*IV*)

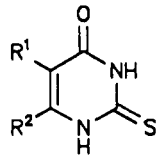
A mixture of *IIc* (0.01 mol) and benzoyl chloride (10 ml) was refluxed for 4 h, then allowed to cool and then triturated with excess light petroleum several times. The solid product precipitated was collected by filtration.

TABLE I
Physical and spectral data of compounds *II* – *XI*

Compound	M. p., °C (Solvent)	Yield, % (Colour)	Formula (M. w.)	Calculated/Found				Spectral data
				% C	% H	% N	% S	
IIa	318 (ethanol)	76 (pale yellow)	$C_7H_5N_5OS$ (207.2)	40.57 40.82	2.43 2.26	33.80 34.10	15.47 15.61	IR: 3 500, 3 400, 3 320 (NH_2), 2 220 (CN), 1 670 (C=O) ^{1}H NMR[a]: 6.1 s, 1 H (CH); 6.8 s, 2 H (NH_2); 8.1 s, 2 H (NH_2)
IIb	264 (ethanol)	64 (pale yellow)	$C_9H_{10}N_4O_3S$ (254.3)	42.50 42.31	3.96 4.13	22.03 22.26	12.60 12.84	IR: 3 480, 3 400, 3 320 (NH_2), 1 700, 1 670 (C=O)
IIc	270 (ethanol)	78 (yellow)	$C_{14}H_7N_5OS$ (293.3)	57.33 57.50	2.40 2.51	23.87 24.12	10.93 10.77	IR: 3 400, 3 300 (NH_2), 2 240, 2 220 (2CN), 1 680 (C=O)
IId	218 (ethanol)	58 (orange)	$C_{16}H_{12}N_4O_3S$ (340.3)	56.47 56.32	3.55 3.72	16.46 16.58	9.42 9.64	IR: 3 400, 3 300 (NH_2), 2 240 (CN), 1 700 (C=O) ^{1}H NMR[b]: 1.3 t, 3 H (CH_3); 4.3 q, 2 H (CH_2); 7.4 – 8.1 m, 7 H (NH_2 and arom.)
III	284 (ethanol)	74 (yellow)	$C_{16}H_9N_5O_2S$ (335.3)	57.31 57.12	2.70 2.84	20.88 21.62	9.56 9.70	IR: 3 220 (NH), 2 240 (CN), 1 710, 1 680 (C=O) ^{1}H NMR[a]: 2.3 s, 3 H (CH_3); 7.1 – 7.7 m, 5 H (arom.); 8.1 s, 1 H (NH)
IV	>360 (acetic acid)	74 (yellow)	$C_{28}H_{15}N_5O_3S$ (501.5)	67.06 67.32	3.01 2.88	13.96 14.22	6.39 6.62	IR: 2 200 (CN), 1 710, 1 680 (C=O)

V	>360 (DMF)	80 (yellow)	$C_{28}H_{26}N_6O_2S$ (500.5)	67.19 67.41	3.22 3.38	16.79 16.98	6.40 6.17	IR: 3 200 (NH), 2 220 (CN), 1 700, 1 680 (C=O)
VI	>360 (dioxane)	74 (red)	$C_{15}H_7N_5OS_3$ (369.4)	48.77 48.54	1.90 2.08	18.96 18.66	26.04 26.26	IR: 3 120, 3 100 (NH), 2 200 (CN), 1 680 (C=O)
VII	160 (ethanol)	66 (pale yellow)	$C_{17}H_{11}N_5OS_3$ (397.5)	51.36 51.14	2.79 2.94	17.61 17.87	24.20 24.37	IR: 2 200 (CN), 1 680 (C=O) ^{1}H NMR[b]: 2.3 s, 3 H (CH_3); 2.5 s, 3 H (CH_3); 7.3 – 8.1 m, 5 H (arom.)
VIII	226 (ethanol)	76 (yellow)	$C_{17}H_{11}N_5O_2S$ (349.3)	58.45 58.56	3.17 3.32	20.05 20.27	9.18 8.94	IR: 2 220 (CN), 1 680 (C=O) ^{1}H NMR[b]: 1.4 t, 3 H (CH_3); 4.5 q, 2 H (CH_2); 7.4 – 8.0 m, 5 H (arom.)
IX	265 (ethanol)	55 (orange)	$C_{21}H_{11}N_5OS$ (381.4)	66.13 65.90	2.90 2.78	18.36 18.21	8.40 8.27	IR: 2 220, 2 200 (CN), 1 680 (C=O) ^{1}H NMR[a]: 6.8 – 7.6 m, 10 H (arom.); 8.9 s, 1 H (CH)
X	262 (ethanol)	62 (pale yellow)	$C_{17}H_{10}N_4O_3S$ (350.3)	58.28 58.41	2.87 2.69	15.99 16.20	9.15 9.32	IR: 2 220, 2 200 (CN), 1 700, 1 680 (C=O) ^{1}H NMR[b]: 1.3 t, 3 H (CH_3); 4.3 q, 2 H (CH_2) 7.6 – 7.9 m, 5 H (arom.)
XI	160 (ethanol)	72 (yellow)	$C_{19}H_{16}N_4O_4S$ (396.4)	57.57 57.72	4.06 4.26	14.13 14.32	8.08 8.26	IR: 2 220 (CN), 1 710, 1 680 (C=O) ^{1}H NMR[b]: 1.2 – 1.6 m, 6 H (2 CH_3); 4.1 – 4.6 m, 4 H (2 CH_2); 7.3 – 8.0 m, 5 H (arom.)

[a] In $(CD_3)_2SO$; [b] in $CDCl_3$.



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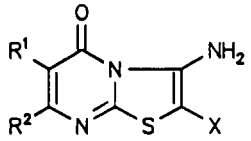
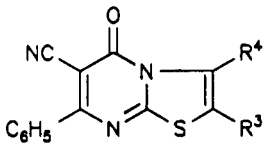
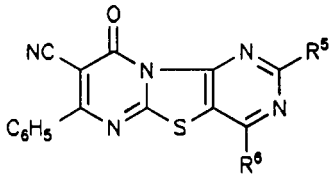


II

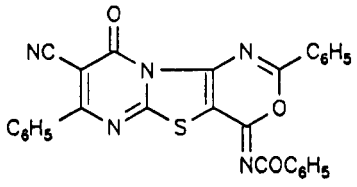
I, *II*	R^1	R^2	X
a	H	NH_2	CN
b	H	NH_2	$CO_2C_2H_5$
c	CN	C_6H_5	CN
d	CN	C_6H_5	$CO_2C_2H_5$





	R^3	R^4
III	CN	$NHCOCH_3$
VIII	CN	$N{=}CHOC_2H_5$
IX	CN	$N{=}CHC_6H_5$
X	$CO_2C_2H_5$	NC
XI	$CO_2C_2H_5$	$N{=}CHOC_2H_5$

	R^5	R^6
V	C_6H_5	$NHCOC_6H_5$
VI	SH	SH
VII	SCH_3	SCH_3



IV

4-Benzoylamino-8-cyano-2,7-diphenylthiazolo[3,2-*a*][4,5-*d'*]dipyrimidin-9-one (*V*)

A mixture of oxazino compound *IV* (0.01 mol) and ammonium acetate (10 g) in acetic acid (20 ml) was heated under reflux for 30 min. The solid product which precipitated from the hot solution was filtered off and crystallized from the proper solvent.

8-Cyano-2,4-dimercapto-7-phenylthiazolo[3,2-*a*][4,5-*d'*]dipyrimidin-9-one (*VI*)

A mixture of *IIc* (0.01 mol) and carbon disulfide (5 ml) in pyridine (15 ml) was heated on water bath for 20 h. The solid product which precipitated from the hot solution was collected by filtration, washed several times with water and crystallized from the proper solvent.

2,4-Bis(methylthio)-8-cyano-7-phenylthiazolo[3,2-*a*][4,5-*d'*]dipyrimidin-9-one (*VII*)

A mixture of dithio derivative *VI* (0.01 mol) and methyl iodide (2 ml) in presence of anhydrous sodium acetate in ethanol (30 ml) was heated on water bath for 3 h. The reaction mixture was concentrated, poured on water and the solid precipitated was collected by filtration.

6-Cyano-3-ethoxymethyleneamino-7-phenylthiazolo[3,2-*a*]pyrimidin-5-one (*VIII*)

A mixture of thiazolopyrimidine *IIc* (0.01 mol) and ethyl orthoformate (5 ml) in acetic anhydride (20 ml) was refluxed for 3 h, then cooled and the crystalline product which precipitated was collected by filtration.

3-Benzylideneamino-6-cyano-7-phenylthiazolo[3,2-*a*]pyrimidin-5-one (*IX*)

A mixture of *IIc* (0.01 mol) and benzaldehyde (0.01 mol) was fused together in presence of few drops of piperidine for 5 min, the mixture then refluxed in ethanol (30 ml) for 2 h. The reaction mixture was then cooled and the solid product which precipitated was collected by filtration and recrystallized from the proper solvent.

Ethyl-6-cyano-3-isocyanide-5-oxo-7-phenylthiazolo[3,2-*a*]pyrimidin-2-carboxylate (*X*)

A solution of thiazolopyrimidine *IId* (0.01 mol) in formamide (20 ml) was refluxed for 1 h. The reaction mixture was then cooled, poured in water and acidifed by dilute hydrochloric acid. The solid product precipitated was collected by filtration and recrystallized from the proper solvent.

Ethyl-6-cyano-3-ethoxymethyleneamino-5-oxo-7-phenylthiazolo[3,2-*a*]pyrimidin-2-carboxylate (*XI*)

A mixture of *IId* (0.01 mol) and ethyl orthoformate (5 ml) in acetic anhydride (20 ml) was refluxed for 4 h, then cooled and the crystalline solid product was collected by filtration and recrystallized from the proper solvent.

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