SYNTHESIS OF NEW TRIAZOLO[4',5':2,3]TRIAZINO-[5,6-B]QUINOXALINES

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ABSTRACT: Reaction of triazino[5,6-b]-3(4H)-quinoxalin one 2 with P_2S_5 and/or $pocl_3$ gave triazinoquinoxalin-3-thione 3 and/or the corresponding 3-chloro derivative 7. Treatment of 3 with alkyl (aralkyl) halides gave the corresponding 3-thioalkyl substituentes 4. Treatment of either 3 or 7 with hydrazine hydrate gaves the 2-hydrazino derivative 8. Reaction of 3 with ethyl chloroacetate gave thioester 5 which on treatment with hydrazine hydrate gave the corresponding thiocarbohydrazide derivative 6. Hydrazino derivative 8 was utilized as versatil to produce several of fused heterocyclic through ring closure reactions with chloroacetylchloride, ethyl chloroformate, carbon disulfide, benzoyl chloride, formic acid and/or nitrous acid to give substituted triazolo[4,3-b]triazinoquinoxaline(9-12,15) and/or tetrazolo[4,5-b]triazinoquinoxaline 13.

INTRODUCTION : Quinoxaline derivatives have long been known as a class of biologically active compounds(1), as antimicrobials, and as anticancers drug use(2,3). As a continuation of our earlier work on quinoxaline derivatives(4,5), the present investigation deals with the synthesis and chemistry of a series of new triazino quinoxalinone derivatives.

EXPERIMENTAL:

All melting points are uncorrected. ^{1}H-NMR spectra were measured using TMS as internal standard on EM 360-90 MHZ NMR spectrometer. IR spectra were determined with a Cat. No. pye unicam infrared spectrophotometer using KBr disc. Elemental analyses were determined on a perkin-Elmer 240 C microanalyzer.

2(1H)Quinoxalinone-3-carboazide 1 :

It was prepared according to literature (4) as yellow crystals m.p. > 320°C.

Triazino[5,6-b]3(4H)quinoxaline 2 :

It was prepared according to literature (4) as yellow crystals m.p. > 360°C.

Triazino[5,6-b]3(4H)quinoxalinthione 3 :

A mixture of 2 (1.99 g, 0.01 mol) and phosphorous pentasulphide (1.9 g, 0.01 mole) was refluxed in dry pyridine for four hours. After colling, the solid was filtered and recrystallized from proper solvent and anlaysed Table I.

3 Alkylthio Triazino[5,6-b]quinoxaline 4 :

A mixture of 3 (2.1 g, 0.01 mol) in ethanol (20 ml) and fused sodium acetate (2 g) was treated with methyl or ethyl iodide (3 ml) while stirring for 1 hr. The solid seperated on water addition (40 ml) was filtered, crystallized and analyzed (Table I).

3-Carboethoxymethylthio triazino[5,6-b]quinoxaline 5 :

A mixture of 3 (1.5 g, 0.005 mol), ethyl chloroacetate (0.6 g, 0.005 mol) and anhydrous sodium acetate (2 g) in ethanol (30 ml) was refluxed for 2 hr. The solid seperated on water addition (15 ml) was recrystallized and identifide as table 1.

3-Carbohydrazide triazino[5,6-b]quinoxaline 6 :

A mixture of 5 and hydrazine hydrate (3 ml) in absolute ethanol (20 ml) were refluxed for 2 hr. The seperated solid was recrystallized and identifide as in Table I.

3-Chloro triazino[5,6-b]quinoxaline 7 :

A mixture of 2 (2 g, 0.01 mol) and phosphorous pentachloride (2 g) and phosphorous oxychloride (4 ml) was refluxed for 3 hr. The solid seperated over ice was recrystallized and analyzed, Table I.

3-Hydrazino triazino[5,6-b]quinoxaline 8 :

The title compound was prepared by refluxing hydrazine hydrate (7 ml) with either 3 (4.2 g, 0.02 mol) in absolute ethanol (25 ml) for 3 hr. or with 7 (4.3 g, 0.02 mol) for 2 hr. The solid seperated in each case was washed with ethanol and analyzed as in table I.

3-Chloro acetyl hydrazino triazino[5,6-b]quinoxaline 9a :

A mixture of 8 (2,13 g, 0.01 mol) and chloro acetylchloride (5 ml) was refluxed in dry pyridine (30 ml) for 3 hr. The solid seperated on water addition was recrystallized and analyzed as in Table I.

Triazino[5',6':3,4]triazino[5,6,-b]quinoxaline 9b:

A solution of 9a (1.26 g, 0.005 mol) in alcoholic solution of KOH (10%, 40 ml) was refluxed for 2 hr. The solution was then filtered, cooled and acidified with dilute HCl (2 N). The resulting solid was washed with H_2O dried and recrystallized and analyzed.

Triazolo[4',5':2,3]triazino[5,6-b]-3(2H)-quinoxalinone 10 :

A mixture of 8 (4.26 g, 0.02 mol) and ethyl chloroformate (4 ml) in dry pyridine (20 ml) was refluxed for 4 hr. The solid seperated was recrystallized and analyzed as in table I.

Triazolo[4',5':2,3]triazino[5,6,-b]3-quinoxalinthione 11 :

A mixture of 8 (1.1 g, 0.005 mol) and carbon disulfide (8 ml) in dry pyridine (10 ml) was refluxed for 5 hr. -The solid seperated on water addition was recrystallized and analyzed. Table I.

Triazolo[4',5':2,3]Triazino[5,6-b]3-phenyl qyinoxaline 12 :

On refluxing benzoyl chloride (10 ml). with either of hydrazino compound 8 for 3hr, the seperated solid was washed several times with pet-ether 40-60°, recrystallized and analyzed as in table I.

Tetrazolo[4',5':2,3]Triazino[5,6-b]quinoxaline 13 :

Treatment of 8 (2.1 g, 0.01 mol) and hydrochloric acid while dropping with sodium nitrite solution (20 ml) at 0°C and stirring for 1 hr, the solid seperated was recrystallized and analyzed as in Table I.

Triazino[5,6-b]3-arylidine hydrazono quinoxalines 14a,b :

A mixture of 8 (0.56 g, 0.002 mol) and benzaldehyde, p-methoxy benzaldehyde (0.002 mol) in ethanol (25 ml) and drops of piperidine was refluxed for 3 hr. The seperated solid in each case was recrystallized from ethanol and analyzed as in Table I.

Triazolo[4',5':2,3]triazino[5,6-b]3H-quinoxaline 15 :

On refluxing 8 (4,20 g, 0.02 mol)with formic acid (15 ml) for 6 hr, gave a solid which was filtered off and recrystallized and analyzed as in Table I.

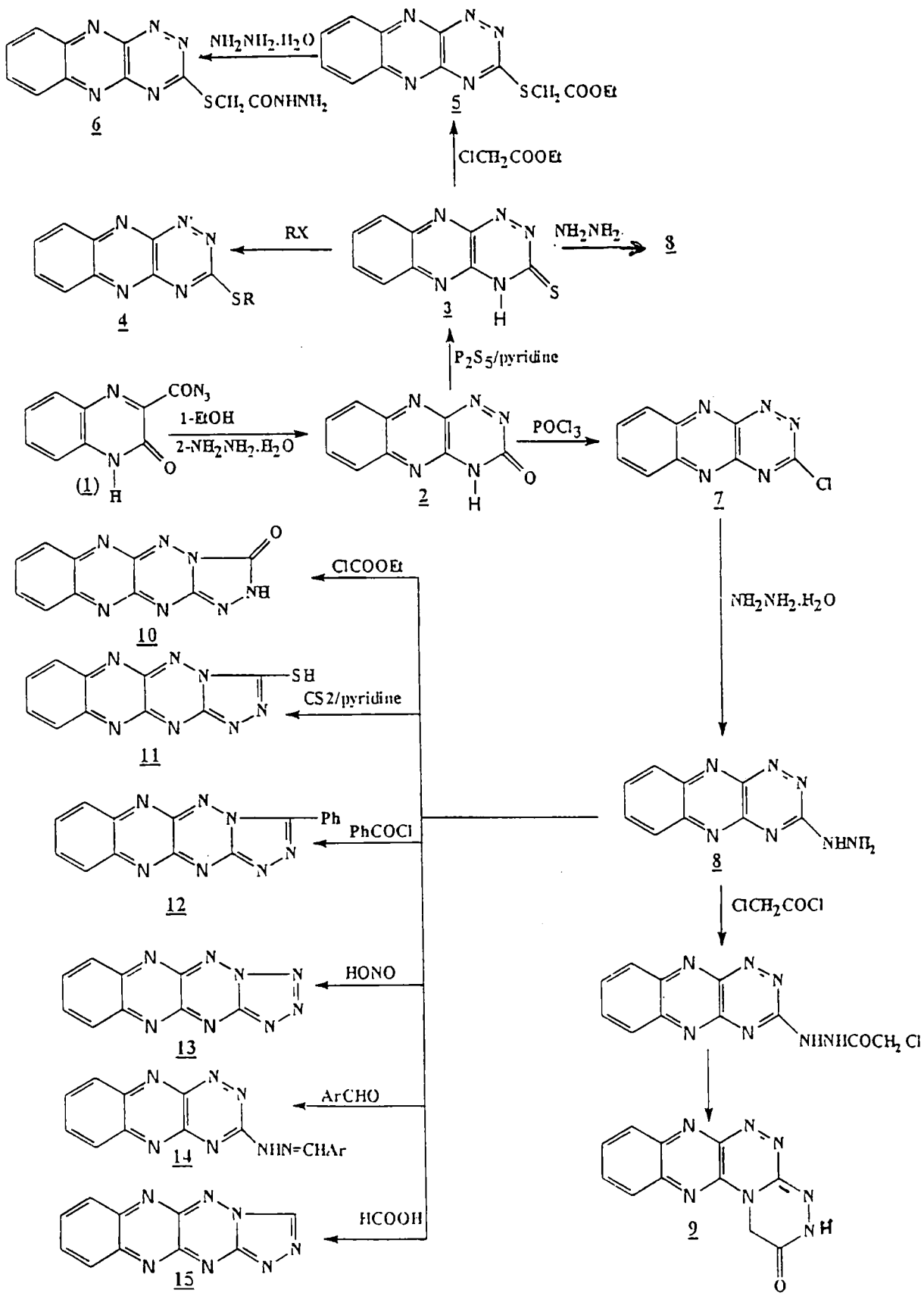
NH2NH2.H2O
SCH2 CONHNH2
6
5
SCH2 COOEt
ClCH2COOEt
RX
SR
4
3
NH2NH2
8
P2S5/pyridine
CON3
1-EtOH
2-NH2NH2.H2O
(1)
H
2
POCl3
7
Cl
ClCOOEt
10
NH2NH2.H2O
SH
CS2/pyridine
11
Ph
PhCOCl
12
NHNH2
8
ClCH2COCl
HONO
13
NHNHCOCH2 Cl
ArCHO
14
NHN=CHAr
9
HCOOH
15

Table (1): Physical and spectral data of compounds (1-15).

Comp. No.	M.P°C Solvent	Yield % Colour	Formula (M.W)	Analysis Calcd./Found C	H	N	S	Spectral data (ν)
1,2*								
3	330	82	$C_9H_5N_5S$	50.23	2.32	32.55	14.88	3260(NH), 1220(C=S)
	ethanol	orange	215	49.52	2.20	33.00	14.60	^{1}H NMR δ 9-1(S-H,NH), δ 7.5-8.1 (m, 4H, Ar.H).
4a	220	85	$C_{10}H_7N_5S$	52.40	3.05	30.56	13.97	1610 (C=N)
	ethanol	yellow	229	52.22	2.85	30.28	13.81	^{1}H NMR ($CDCl_3$) δ 2.7(s,3H, CH_3), δ 7.5-7.9(m, 4H, ArH).
4b	245	78	$C_{11}H_9N_5S$	54.32	3.70	28.80	13.16	2900(CH aliphatic), 1615(C=N)
	ethanol	yellowish	243	54.12	3.62	28.72	13.00	^{1}H-NMR($CDCl_3$) δ 1.4-1.7(t, 3H-CH_3), δ 3.4-3.7(q, 2H, CH_2), δ 7.6-8.1(m, 4H, ArH).
5	185	90	$C_{13}H_{11}N_5O_2S$	51.82	3.65	23.25	10.63	1730 (CO ester) 1630(C=N)
	ethanol	buff	301	51.51	3.57	23.41	10.58	^{1}H-NMR($CDCl_3$) δ 1.4-1.7(t, 3H-CH_3), δ 3.3-3.5(q, 2H, CH_2 ester), δ 4.1(s, 2H, CH_2) and 7.6-8.1(m, 4H, ArH).
6	265	70	$C_{11}H_9N_7OS$	45.99	3.10	34.14	11.14	3240-3420(NHNH$_2$), 1680(C=O)
	ethanol	redish	287	45.83	3.22	33.93	11.22	-
7**	173	75	$C_9H_4N_5Cl$	49.76	1.84	32.25	-	1590-1630 (C=N)
	ethanol	red	217	49.65	1.78	32.00		^{1}H-NMR($CDCl_3$) δ 7.9-8.4(m, 4H, Ar.H).
8	285	85	$C_9H_7N_7$	50.70	3.28	46.00	-	3100-3400 cm^{-1} (NHNH$_2$)
	ethanol	red	213	50.30	3.15	45.60		-
9a	273	82	$C_{11}H_8N_7Ocl$	45.67	2.76	33.91	-	3180-3500(NH), 1660(C=O)
	ethanol	pale yellow	289	45.41	2.57	33.69		^{1}H-NMR($CDCl_3$) δ 4.1(s,2H, CH_2), δ9.3(NH) and δ 7.8-8.3(m, 4H, ArH).
9b	275	55	$C_{11}H_7N_7O$	52.17	2.76	38.73	-	3260(NH), 1670(CO).
	acetic	yellow		51.93	2.62	38.42		^{1}H-NMR(DMSO) δ 4.75(s, 2H-CH_2), δ 10.3(s, 1H, NH). δ 7.5-8.2(m, 4H, ArH)
10	325	65	$C_{10}H_5N_7O$	50.20	2.09	41.00	-	3320(NH), 1685(CO)
	acetic	red	239	50.42	2.20	40.83		^{1}H-NMR (DMSO) δ 9.2(s,1H, NH).
11	305	71	$C_{10}H_5N_7S$	47.05	1.96	38.43	12.59	7.2-7.7(m, 4H, ArH).
	acetic	yellow	255	46.80	1.85	38.26	12.31	
12	340	68	$C_{16}H_9N_7$	64.12	3.01	32.77	-	1620(C=N), absence of NH, NH$_2$
	acetic	redish	299	64.13	2.95	32.54		^{1}H-NMR (TFA) δ 7.7-8.6(m, 9H, ArH).
13	> 360	70	$C_9H_4N_8$	48.21	1.78	45.90	-	1590(C=N).
	acetic	yellow	224	47.93	1.70	45.81		^{1}H-NMR (DMSO) δ 7.6-8.4(m, 4H, ArH).
14a	328	80	$C_{16}H_{11}N_7$	63.78	3.65	32.55	-	3360(NH), 1620(C=N)
	ethanol	red	301	63.64	3.62	32.36		^{1}H-NMR (DMSO) δ 8.2(s, 1H, CH), δ 9.5(s, 1H, NH), δ 7.2-7.8(m, 9H, ArH).
14b	345	85	$C_{17}H_{13}N_7O$	61.63	3.92	29.60	-	3340(NH), 1630(C=N)
	ethanol	redish	331	61.82	3.80	29.51		-
15	295	65	$C_{10}H_5N_7$	53.81	2.24	43.94	-	1630(C=N)
	acetic	brown	223	53.72	2.16	43.75		^{1}H-NMR (DMSO) δ 8.8(s, 1H, CH) and δ 7.3-7.9(m, 4H, ArH).

* Full analysis of 1, 2 are presented in Ref. (4).

** Cl (Calc. 16.32, Found 16.15%).

RESULTS AND DISCUSION

Treatment of triazino[5,6-b]3(4H)quinoxaline 2[4] with phosphorous pentasulfide in dry pyridine gave triazino[5,6-b]3-(4H)quinoxalinthione 3 which on reaction with alkyl halides and anhydrous sodium acetate in refluxing absolute ethanol gave the corresponding 3-alkyl thio products (4a,b). Refluxing 3 with ethyl chloroacetate and anhydrous sodium acetate in absolute ethanol gave triazino[5,6-b]-3-carboethyoxymethyl-thioquinoxaline 5 which on hydrazinolysis by refluxing with hydrazine hydrate produced the carbohydrazide derivative 6. Treatment of triazinone compound 2 by refluxing with phosphorus oxychloride gave triazino[5,6-b]-3-chloroquinoxaline 7, which in too reacted with hydrazine hydrate to give triazino[5,6-b]-3-hydrazino quinoxaline 8. The same product 8 was separated from fusion of 3 with hydrazine hydrate. Reaction of 8 with chloroacetylchloride gave 3-chloroacetyl hydrazino derivative 9a which cyclized to triazolo- triazinoquinoxalinone 9b.Compound 8 underwent several cyclization raction. Thus, treatment of 8 with ethyl chloroformate in pyridine gave triazolo[4',5':2,3]triazino[5,6-b]-3-quinoxalinone 10. Refluxing 8 with carbon disulfide in pyridine gave triazolo[4',5':2,3]triazino[5,6-b]-3-mercapto-quinoxaline 11. Reaction of 8 with benzoyl chloride gave triazolo[4',5':2,3]triazino[5,6-b]-3-phenyl-quinoxaline 12. Similarly, reaction of 8 with sodium nitrite in hydrochloric acid gave the cyclization product tetrazolo[4',5':2,3]triazino[5,6-b]quinoxaline 13. Condensation of 8 with benzaldehyde, p-methoxy benzaldehyde gave the corresponding triazino[5,6-b]-3-arylidine hydrazonoquinoxaline 14. Finally, reaction of 8 with formic acid gave triazolo[4',5':2,3] triazino[5,6-b]quinoxaline 15.

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