Novel Syntheses of Thiazolo[3,2-*b*]-*s*-triazoles

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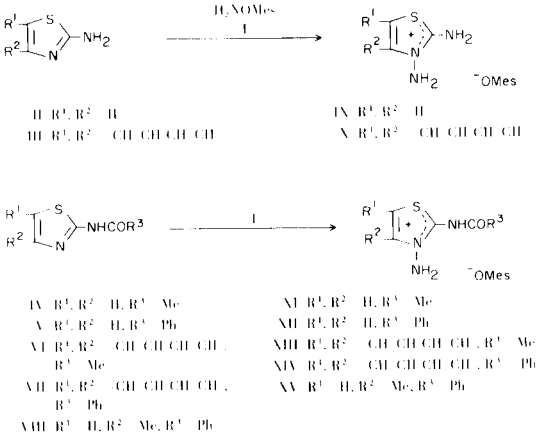
The reaction of 2-amino- and 2-acylaminothiazoles with *O*-mesitylenesulfonylhydroxylamine resulted in the ready formation of the corresponding 3-aminium salts, which were converted into thiazolo[3,2-*b*]-*s*-triazoles in high yields.

The preparation of 5-substituted thiazolo[3,2-*b*]-*s*-triazoles by reaction of *s*-triazole-3-thiol with α-haloketones or propargyl bromide has been reported previously (1,2). It has been claimed that the parent ring system has been synthesized by cyclization of 2-(*N*-methylimino)-3-nitroso-2,3-dihydrothiazole (3), although this structural assignment has been questioned (4). We now wish to described novel and general methods for this ring system, which involve (i) the reaction of 2,3-diaminothiazolium salts with acylating agents and (ii) cyclodehydration of the 2-acylamino-3-aminothiazolium salts. The former route



has been successfully applied to the pyridine congeners (5,6).

Syntheses of the starting 2,3-diamino- (IX, X) and 2-acylamino-3-amino(XI-XV)thiazolium salts were readily accomplished by treatment of the parent heterocycles (II-VIII) with *O*-mesitylenesulfonylhydroxylamine (MSH) (1) (7-9). The results are summarized in Table I. It has been reported that hydroxylamine-*O*-sulfonic acid fails to react with 2-aminothiazoles (1). Alkaline treatment of these 3-aminium salts (IX-XIV) gave the corresponding crystalline 3-amino-2-iminothiazolines (XVI, XVII) and 2-acylimino-3-aminothiazolines (XVIII-XXI) (see Tables II and III).

In contrast to the reported facile transformation of the 1,2-diaminopyridinium salts or 1-amino-2-iminopyridines into the *s*-triazolo[1,5-*a*]pyridines (5,6), treatment of 2,3-diaminothiazolium salts (IX, X) with acetyl chloride at room temperature gave recovery of the starting material. Treatment of IX in acetic anhydride under refluxing conditions (*ca.* 140-150°) led to a mixture of *N,N'*-diacetyl derivative (XXII) and 2-methylthiazolo[3,2-*b*]-*s*-triazole (XXIV) in 25 and 40% yields, respectively. When compound XVI was refluxed with acetic anhydride, again a mixture of XXII and XXIV was obtained in *ca.* 9:1

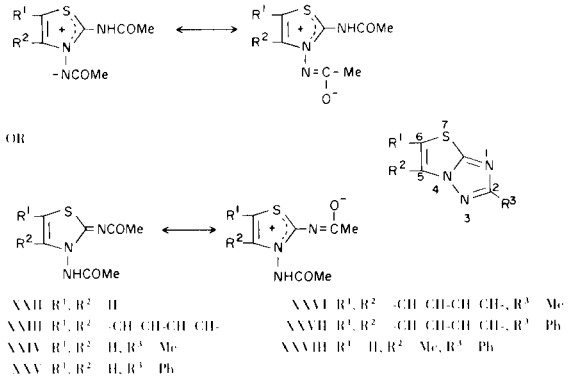


TABLE I

2,3-Diamino- and 2-Acylamino-3-aminothiazolium Salts

Compound	M.p. °C	Recrystallized from	Yield %	Formula	Anal.	C%	H%	N%
IX	178.5-179	EtOH-ether	70	$C_{12}H_{17}N_3O_3S_2$	Calcd.	45.71	5.44	13.33
					Found	45.76	5.62	13.43
X	218-220	EtOH-ether	75	$C_{16}H_{19}N_3O_3S_2$	Calcd.	52.60	5.24	11.50
					Found	52.70	5.35	11.49
XI	188-189	EtOH-ether	80	$C_{14}H_{19}N_3O_4S_2$	Calcd.	47.06	5.36	11.78
					Found	46.93	5.29	11.61
XII	216-217	MeOH	60	$C_{19}H_{21}N_3O_4S_2$	Calcd.	54.41	5.05	10.02
					Found	54.69	5.11	9.90
XIII	188-189	EtOH-ether	50	$C_{18}H_{21}N_3O_4S_2$	Calcd.	53.07	5.20	10.32
					Found	52.83	5.31	9.98
XIV	183-185	EtOH-ether	33	$C_{23}H_{23}N_3O_4S_2$	Calcd.	58.84	4.94	8.95
					Found	58.59	4.66	8.94
XV	207-208	EtOH-ether	50	$C_{20}H_{23}N_3O_4S_2$	Calcd.	55.42	5.35	9.70
					Found	55.58	5.51	9.52

TABLE II

3-Amino-2-imino- and 2-Acylimino-3-aminothiazolines

Compound	M.p. °C	Recrystallized from	Yield %	Formula	Anal.	C%	H%	N%
XVI	108-109	Me_2CO-pet. ether	50	$C_3H_5N_3S$	Calcd.	31.31	4.38	36.51
					Found	31.10	4.36	36.10
XVII	132-134	$CHCl_3$-pet. ether	90	$C_7H_7N_3S$	Calcd.	50.91	4.27	25.45
					Found	50.76	4.48	25.15
XVIII	129-130	Me_2CO-pet. ether	68	$C_5H_7N_3OS$	Calcd.	38.22	4.49	26.74
					Found	38.22	4.48	26.26
XIX	141-142	Me_2CO-pet. ether	66	$C_{10}H_9N_3OS$	Calcd.	54.79	4.14	19.17
					Found	54.76	4.18	19.47
XX	223-224	$CHCl_3$	66	$C_9H_9N_3OS$	Calcd.	52.17	4.38	20.28
					Found	52.39	4.54	20.15
XXI	216-217	$CHCl_3$-pet. ether	90	$C_{14}H_{11}N_3OS$	Calcd.	62.45	4.12	15.61
					Found	62.35	4.07	15.37

ratio. This route, however, proved to be efficient for the preparation of 2-phenyl derivatives (XXV, XXVII). For example, refluxing IX with benzoyl chloride (*ca.* 200°) produced 2-phenylthiazolo[3,2-*b*]-*s*-triazole (XXV) as the sole product in 68% yield. These results indicate that more drastic conditions are required for the cyclization of IX and X than in the pyridine case and that the cyclization reaction competes, in particular at low temperature, with the formation of diacyl derivatives, which do not cyclize even on prolonged heating.

Since the method mentioned above is limited in its application, an alternative synthetic route was sought. Suitable starting materials would be 2-acylimino-3-aminothiazolium salts (XI-XV) which are considered to be intermediates for cyclization of the 2,3-diaminium salts (IX, X). It was found that, when neat XI-XIV was heated at 20-30° above the melting point for 1 hour, cyclization occurred smoothly to give the thiazolo[3,2-*b*]-*s*-triazoles (XXIV-XXVII) in 35-90% yields. By contrast, compounds XVIII-XXI did not give the cyclized products under similar conditions. This may be attributed to the fact that the betaine forms are major contributors to the structures of XVIII-XXI, as supported by the ir spectra (Table III) which showed polarized carbonyl absorption bands (1600-1640 cm^{-1}).

As seen from Tables II and IV, the high-melting

TABLE III

Spectral data of 3-Amino-2-imino- and 2-Acylimino-3-aminothiazolines

Compound	IR (KCl) cm^{-1}	UV λ max (dioxane) nm (log ε)	NMR ($CDCl_3$) R^1 (or R^2)	NMR ($CDCl_3$) R^1 (or R^2) (a)	$COCH_3$	M^+ m/e
XVI	3200(s), 3100(s), 1605(s) 1590(s)	248sh(3.63), 265(3.79)	3.40(d) J = 5 Hz	4.41(d) J = 5 Hz		115
XVII	3300(w), 3170(s), 1605(s) 1580(s)	234(3.84), 265(3.84), 298(3.65)	2.80-3.10(m)			165
XVIII	3250(m), 3180(m), 1640(s) 1590(s), 1480(s)	296(4.11)	2.90(d) J = 5 Hz	3.51(d) J = 5 Hz	7.75(s)	157
XIX	3250(w), 3180(w), 1595(m) 1550(m), 1470(s)	240(4.08), 324(4.26)	2.89(d) J = 5 Hz	3.50(d) J = 5 Hz		219
XX	3260(w), 3150(w), 1630(w) 1590(s), 1480(s)	234(4.01), 255(3.60), 282sh (3.81), 307sh(4.34), 313(4.36)	2.19-2.90(m)		7.80(s)	207
XXI	3300(m), 1600(s), 1560(s)	242(4.28), 266sh(3.74), 275sh (3.66), 286sh(3.63), 334(4.46)	1.55-2.70(m)			269

(a) The units are in τ values.

TABLE IV

Thiazolo[3,2-*b*]-*s*-triazoles

Compound	M.p. °C	Recrystallized from	Yield % method (D) (c)	Yield % method (E) (c)	Formula	Anal.	C%	H%	N%
XXIV	49.5-51	(a), (b)	57	95	$C_5H_5N_3S$	Calcd.	43.17	3.62	30.21
						Found	42.90	3.59	29.98
XXV	118-119	Me_2CO	35	97	$C_{10}H_7N_3S$	Calcd.	59.70	3.51	20.89
						Found	60.02	3.45	20.50
XXVI	78.5-80	ether-pet. ether	90	97	$C_9H_7N_3S$	Calcd.	57.14	3.73	22.21
						Found	57.39	3.88	22.00
XXVII	176-177	Me_2CO	56	97	$C_{14}H_9N_3S$	Calcd.	66.92	3.61	16.73
						Found	66.87	3.76	16.53
XXVIII	125-126 (d)	Me_2CO	—	97	$C_{11}H_9N_3S$	Calcd.	61.39	4.22	19.53
						Found	61.69	4.43	19.20

(a) Hygroscopic. (b) Analytical sample was prepared by purification with preparative tlc using chloroform. (c) See Experimental. (d) Lit. (1), m.p. 124-125°.

starting materials XII and XIV gave low yields on cyclization, presumably due to thermal decomposition of either the starting material or the product. Much better results were obtained by using polyphosphoric acid. Generally, yields higher than 90% of thiazolo[3,2-*b*]-*s*-triazoles (XXIV-XXVIII) were obtained by heating XI-XV with PPA at 100-110° for 1.5 hours (Table IV).

Analytical and physical data of the thiazolo[3,2-*b*]-*s*-traizoles are summarized in Tables IV and V. In particular, the melting point and spectra of compound XXVIII were essentially identical with reported values (1), thus confirming the structure of the thiazolo[3,2-*b*]-*s*-triazole system (10).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Hitachi EPI G-2 spectrophotometer, and uv spectra on a Hitachi 124 spectrophotometer. Nmr spectra were determined with a Hitachi R-20A spectrometer (tetramethylsilane as internal standard) and mass spectra were obtained with a Hitachi RMU-6D instrument with a direct inlet system operating at 70 ev. Preparative thin layer chromatography was carried out on Merck Alumina PF_{254}.

TABLE V

Spectral Data of Thiazolo[3,2-*b*]-*s*-triazoles

Compound	IR (KCl) cm^{-1}	UV λ max (MeOH) nm (log ε)	Nmr ($CDCl_3$) R^3	R^2	R^1 (b)	Mass m/e (rel. intensity)
XXIV	3100(m), 1540(m) 1510(w), 1470(s) 1430(s), 1300(s)	206 (a), 242	7.53(s)	2.31(d) J = 5 Hz	3.09(d) J = 5 Hz	140(9), 139(100), 98(62) 71(37), 45(40)
XXV	3100(w), 2900(w) 1530(w), 1460(m) 1440(s), 1330(m)	210(4.20), 256(4.33)	1.78-2.65 (m)	2.26(d) J = 5 Hz	3.09(d) J = 5 Hz	202(15), 201(80), 103(44) 98(12), 77(40), 58(100)
XXVI	3050(w), 2900(w) 1600(w), 1490(s) 1450(m), 1300(s)	208(4.18), 225(4.43) 280(3.45), 288(3.50)	7.47(s)	2.05-2.75(m)		190(13), 189(87), 148(100) 78(53), 69(50)
XXVII	3050(w), 1600(w) 1470(s), 1430(m) 1320(m)	213(4.47), 240(4.38) 267(4.33), 284sh(4.16) 296(4.02)		1.70-2.67(m)		252(14), 251(70), 148(60) 103(50), 77(83), 51(100)
XXVIII	3100(m), 1475(s) 1440(s), 1330(m)	203(4.28), 233(4.06) 258(4.34)	1.76-2.67 (m)	7.50(d) J = 1.5 Hz	3.50(q) J = 1.5 Hz	216(14), 215(100), 112(10) 103(20), 77(17), 72(62) 71(26)

(a) Exact intensity was not determined due to hygroscopic property. (b) Units are in τ values.

General Procedure for 2,3-Diamino (IX and X) and 2-Acylamino-3-amino-(XI-XV)thiazolium Mesitylenesulfonates.

To a solution of the thiazole (II-VIII) (0.02 mole) in methylene chloride (20 ml.) was added a solution of *O*-mesitylenesulfonylhydroxylamine (I) (0.02 mole) in methylene chloride (20 ml.) with ice-cooling and the reaction mixture was stirred for 30 minutes. Ether was added and the precipitated crystals were collected and recrystallized. The yields, melting points, and analytical data are summarized in Table I.

General Procedure for 3-Amino-2-imino- (XVI and XVII) and 2-Acylimino-3-amino-(XVIII-XXI)thiazolines.

The 2,3-diamino-(IX, X) or 2-acylamino-3-amino-(XI-XV)-thiazolium salt (1 mmole) was added to a mixture of 20% sodium hydroxide (1 ml.) and methylene chloride (10 ml.) and the suspension was stirred at room temperature until the solid disappeared. The organic layer was separated, washed with water, and dried over magnesium sulfate. Evaporation of the solvent gave a white solid which was purified by recrystallization. The results are summarized in Tables II and III.

General Procedures for Thiazolo[3,2-*b*]-*s*-triazoles (XXIV-XXVIII).

(A) By the Reaction of 2,3-Diaminothiazolium Salts (IX and X) with Acetic Anhydride.

Compound IX (1 mmole) was refluxed with acetic anhydride (2 ml.) for 1 hour. After evaporation of acetic anhydride under reduced pressure, the residue was treated with 10% sodium hydroxide and extracted with chloroform. The extract was dried over magnesium sulfate and concentrated to give a mixture of two products. The products were separated by preparative tlc using chloroform as solvent. The major product (40%) was identified as 2-methylthiazolo[3,2-*b*]-*s*-triazole (XXIV) (see Tables IV and V). The minor product (25%) was 2-acetylamino-3-acetyliminothiazolium betaine (XXII), m.p. 152-153° (from acetone-petroleum ether); ir (potassium chloride): cm^{-1} 1700 (s), 1690 (vs), and 1590 (m); uv λ max (dioxane): 235 nm (log ε 3.41) and 296 (4.10); nmr (deuteriochloroform): τ 2.98 (1H, d, J = 5 Hz, H_4 or H_5), 3.88 (1H, d, J = 5 Hz, H_5 or H_4), 7.80 (6H, s, 2 x CH_3). The mass spectrum showed the parent ion at m/e 199 (Calcd. 199).

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.31; H, 4.53; N, 20.90.

Using a similar procedure, compound X provided 2-methylbenzothiazolo[3,2-*b*]-*s*-triazole (XXVI) (80%) (see Tables IV and V) and 2-acetylamino-3-acetyliminobenzothiazolium betaine (XXIII) (9%). The latter compound was recrystallized from 2-propanol-petroleum ether, m.p. 227-228°; ir (potassium chloride): cm^{-1} 3200 (s), 1700 (s), 1670 (s) and 1590 (vs); uv λ max (dioxane): 234 nm (log ε 4.30), 276 (3.73), 305 (sh) (4.30) and 310 (4.34); nmr (deuteriochloroform): τ 2.1-2.8 (m) (4H, m, aromatic protons), 7.84, 7.86 (2 x 3H, 2 x s, 2 x CH_3). The mass spectrum showed the parent ion at m/e 249 (Calcd. 249).

(B) By the Reaction of 2,3-Diaminothiazolium Salts (IX and X) with Benzoyl Chloride.

Compound IX (1 mmole) was refluxed in benzoyl chloride (10 mmoles) for 10 minutes. Work-up described above gave 2-phenylthiazolo[3,2-*b*]-*s*-triazole (XXV) as the sole product in 68% yield (see Tables IV and V).

Similarly, compound X gave 2-phenylbenzothiazolo[3,2-*b*]-*s*-triazole (XXVII) in 49% yield (see Tables IV and V).

(C) By the Reaction of 3-Amino-2-iminothiazolines (XVI and XVII) with Acetic Anhydride.

By a procedure similar to that described in (A), treatment of compound XVI with acetic anhydride gave XXIV and XXII in 10 and 80% yields, respectively. Similarly, compound XVII gave XXVI and XXIII in 15 and 72% yields, respectively.

(D) By the Thermal Reaction of 2-Acylamino-3-aminothiazolium Salts (XI-XIV).

Neat 2-acylamino-3-aminothiazolium salt (XI-XIV) (1 mmole) was heated at 20-30° above the melting-point for 1 hour. After cooling, 10% sodium hydroxide was added and the reaction

mixture was extracted with chloroform. The dried extract was concentrated and the residue was purified by preparative tlc using chloroform as solvent. The results are summarized in Tables IV and V.

(E) By Cyclization of 2-Acylamino-3-aminothiazolium Salts (XI-XV) with Polyphosphoric Acid.

The compound (XI-XV) (1 mmole) was heated in PPA (1 g.) at 100-110° for 1.5 hours. After cooling, the reaction mixture was poured into ice-water, made alkaline with 10% sodium hydroxide and extracted with chloroform. The dried extract was concentrated to give colorless crystals, which were recrystallized. The results are summarized in Tables IV and V.

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(10) The differences in intensity of some peaks and the appearance of an additional peak at m/e 112 which corresponds to loss of benzonitrile radical may be attributed to the differences of the instrument or conditions used.