Synthesis of Bridgeheaded Nitrogen Systems. *s*-Triazolo[4,3-*b*]-*as*-triazine, *s*-Triazolo[4,3-*d*]-*as*-triazine and *s*-Triazolo[3,4-*b*]-1,3,4-Thiadiazole Ring Systems

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By the reactions of hydrazino-*as*-triazines (**1a-d** and **5**) with cyanogen bromide were synthesized *s*-triazolo-*as*-triazines (**2a-d**) and (**6**). Likewise, similar reactions of amino-*s*-triazolethiols (**7a-e**) gave *s*-triazolo-1,3,4-thiadiazoles (**8a-e**). Compound **2a** was brominated to **2g**.

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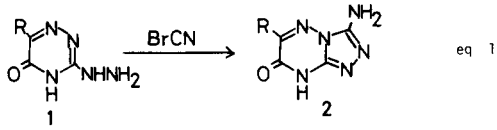
Results.

We have aimed at the synthesis of pharmacologically interesting fused *s*-triazoles by using cyanogen bromide, which is a well known cyclization reagent (1) in the formation of amino-substituted heterocyclic systems. In this paper we wish to report the reactions of hydrazino-*as*-triazine derivatives and amino-*s*-triazolethiol derivatives with cyanogen bromide, affording *s*-triazolo-*as*-triazine and *s*-triazolo-*as*-triazine and *s*-triazolo-1,3,4-thiadiazole derivatives.

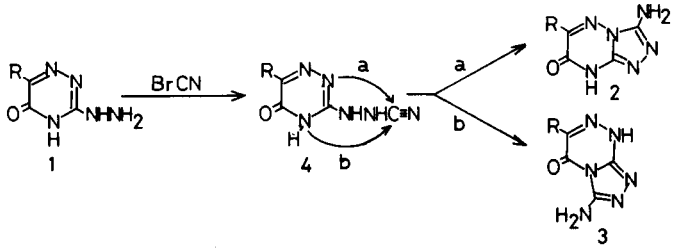
The starting 3-hydrazino-*as*-triazin-5-ones (**1a-f**) and 5-hydrazino-*as*-triazin-3-one (**5**) were prepared according to the reported procedures (2,3,4). Bromo derivative **2g**



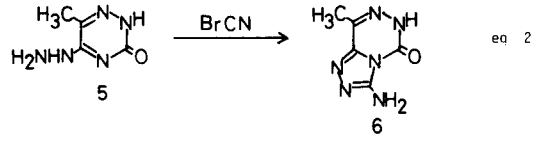
a, R=H
b, R=CH_3
c, R=Ph
d, R=4-FC_6H_4
e, R=4-ClC_6H_4
f, R=4-BrC_6H_4
g, R=Br

was synthesized by the reaction of *s*-triazolo-*as*-triazine (**2g**) with bromine in water. The reactions of 3-hydrazino-*as*-triazines (**1a-d**) with cyanogen bromide were carried out in a buffer solution (5) (AcOH-NaOAc, $pH = 5$) under reflux for a few hours to give *s*-triazolo[4,3-*b*]-*as*-triazines (**2a-d**). Similar treatment of 6-(4-chlorophenyl and 4-bromophenyl)-*as*-triazines (**1a** and **f**) were unsuccessful probably because of their insolubility in water; in all cases the use of ethanol as a solvent gave only decomposition products. The structural proofs were based on elemental and spectral analyses; for *s*-triazolo-*as*-triazine (**2b**), the ^1H nmr spectrum (DMSO-d_6) showed signals of amino protons at 6.40 ppm (s, 2H, $-NH_2$) and 3.50 ppm (br s, 1H, =NH). In these reactions there seems to be two possible courses to give two different ring systems, *s*-triazolo[4,3-*b*]-*as*-triazine system (**2**) and *s*-triazolo[3,4-*c*]-*as*-triazine system (**3**) depending on the direction of the cyclization (a and b in Scheme 1). In the intermediate, cyanohydrazine (**4**), the

Scheme 1

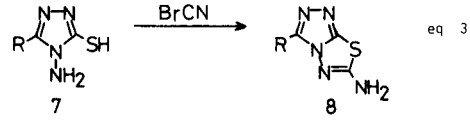


less nucleophilic N-4 nitrogen due to the electronic effect of the carbonyl group could cause preferential ring closure to *s*-triazolo[4,3-*b*]-*as*-triazine (**2**). Likewise, 5-hydrazino-*as*-triazine (**5**) (4) gave *s*-triazolo[4,3-*d*]-*as*-triazine (**6**). The



yields and the physical properties of *s*-triazolo-*as*-triazine derivatives (**2a-f** and **6**) are summarized in Table 1.

Next we synthesized 3-heteroaryl-*s*-triazolo-1,3,4-thiadiazoles by the reactions of amino-*s*-triazolethiols with cyanogen bromide. *s*-Triazoles (**7a-e**) as the starting material were prepared according to the reported procedure (6). The reactions of *s*-triazoles (**7a-d**) with cyano-



a, R=2-pyridyl
b, R=3-pyridyl
c, R=4-pyridyl
d, R=2-thienyl
e, R=2-furyl

gen bromide were carried out in ethanol under reflux for a few hours. After concentration of the reaction mixture, neutralization of it with saturated aqueous sodium acetate afforded *s*-triazolo-1,3,4-thiadiazoles (**8a-e**) in high yields. Potts (7) suggested that the thiocyanate might be involved as an intermediate in the reaction of 3-alkyl and phenyl-4-amino-*s*-triazole-5-thiols with cyanogen bromide.

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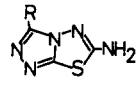
Table 1

Physical Properties of *s*-Triazolo-*as*-triazines (**2a-d,g** and **9**)

No.	Yield (%)	Solvent	Reaction Condition	mp (°C)	IR (cm^{-1})
2a	19	NaOAc-AcOH, *p*H = 5	reflux 2 hours	>300	3400, 3300, 1618, 1550
2b	24	NaOAc-AcOH, *p*H = 5	reflux 2 hours	>300	3410, 3300, 1615, 1550
2c	23	NaOAc-AcOH, *p*H = 5	reflux 4 hours	>300	3420, 3200, 1678, 1608, 1550
2d	87	NaOAc-AcOH, *p*H = 5	reflux 4 hours	>300	3420, 3210, 1682, 1622, 1603, 1560
2g	22	H_2O	rt 2 days	>300	1660, 1620, 1555
9	95	NaOAc-AcOH, *p*H = 5	reflux 4 hours	260 (dec)	3480, 3300, 3100, 1740, 1640

Table 2

Physical Properties of 3-Heteroaryl-6-amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles



No.	R	Yield (%)	mp (°C) (solvent)	IR (cm^{-1})	UV (MeOH) λ nm (log ε)	NMR (DMSO-d_6)
8a	2-pyridyl	92	283 (EtOH)	3400, 3310, 3090 1640, 1635, 1595	260 (4.10) 283 (4.19)	δ 8.02 (br, s, 2H, NH_2) δ 8.34-9.00 (m, 4H, Ar)
8b	3-pyridyl	55	285-287 ($EtOH-H_2O$)	3585, 3240, 3200 1615, 1565	258 (4.08) 284 (4.19)	δ 7.99 (br s, 2H, NH_2) δ7.21-8.96 (m, 4H, Ar)
8c	4-pyridyl	92	>300 (DMF)	3250, 3200, 3070 1655, 1615, 1580	278 (-) (a)	δ 8.07 (br s, 2H, NH_2) δ 7.90-8.97 (m, 4H, Ar)
8d	2-thienyl	100	247-250 (n-C_6H_{14}-AcOEt)	3300, 3120, 1620 1570	242 (4.02), 247 (4.01) 291 (4.27)	δ 8.10 (br s, 2H, NH_2) δ 7.12-8.04 (m, 3H, Ar)
8e	2-furyl	85	290-292 ($EtOH-H_2O$)	3400, 3300, 3060 1655, 1585, 1530	273 (4.33), 280 (4.36) 292 (4.14)	δ 8.06 (br s, 2H, NH_2) δ6.64-8.18 (m, 3H, Ar)

(a) Slightly soluble in methanol.

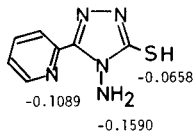
Table 3

Yields and Physical Properties of **7a,b** and **e**

No.	Yield (%)	mp (°C) (a)	IR (cm^{-1})	NMR (DMSO-d_6)
7a	56	215-216	3320, 3280, 3130	δ 14.00 (br s, 1H, SH deuterium oxide exchangeable)
			1630, 1595, 1580	δ 6.30 (br s, 2H, NH_2 deuterium oxide exchangeable)
			1650, 1500	δ 4.30-8.95 (m, 4H, Ar deuterium oxide exchangeable)
7b	62	206-207	3260, 3180, 2500 (br)	δ 14.04 (br s, 1H, SH deuterium oxide exchangeable)
			1650, 1610, 1595	δ5.83 (br s, 2H, NH_2 deuterium oxide exchangeable)
			1585, 1530	δ 7.40-9.41 (m, 4H, Ar)
7e	56	218-219	3340, 3150, 1635	δ 13.84 (br s, 1H, SH deuterium oxide exchangeable)
			1535, 1515	δ 5.84 (br s, 2H, NH_2 deuterium oxide exchangeable)
				δ 6.11-8.10 (m, 3H, Ar)

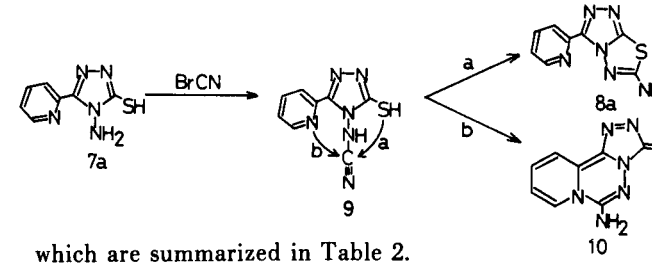
(a) All compounds were recrystallized from ethanol.

Chart 1. Atomic net charges of 7a calculated by CNDO/2



However, our CNDO/2 calculations of *s*-triazole (**7a**) (Chart 1) showed the cyanamide **9** would be a preferable intermediate. From this result we expected that *s*-triazole **7a** might give two different heterocyclic compounds; *s*-triazolo-1,3,4-thiadiazole (**8a**) and *s*-triazolobenzotriazine (**10**), *via* the cyanamide **9** as shown in Scheme 2, but *s*-triazolo--1,3,4-thiadazole (**8a**) was the sole product. The structural proofs were based on elemental and spectral analyses, which are summarized in Table 2.

Scheme 2



EXPERIMENTAL

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The uv spectra were determined with a Hitachi spectrophotometer (Model 200-10). The ^1H nmr spectra were taken at room temperature with a JEOL C-60-HL spectrometer with tetramethylsilane as an internal standard. The ir spectra were taken with a JASCO-IRA-1 spectrometer.

3-Hydrazino-*as*-triazin-5-one (**1a**).

This compound was prepared by a method described in a patent by F. Hoffmann-La Roche and Co (2).

6-Methyl-3-hydrazino-*as*-triazin-5-one (**1b**).

This compound was prepared by a method described by Dornow, Abele and Minzel (3).

6-Phenyl-3-hydrazino-*as*-triazin-5-one (**1c**).

To a solution of 500 mg (2.4 mmoles) of 6-phenyl-3-thioxo-*as*-triazin-5--one (8) in 10 ml of 2*N* aqueous sodium hydroxide was added 0.44 ml (7.0 mmoles) of methyl iodide at room temperature, and the solution was stirred until the mixture was homogeneous and then acidified with concentrated hydrochloric acid under cooling. Filtration gave 470 mg (89%) of 6-phenyl-3-methylmercapto-*as*-triazin-5-one, which was treated with hydrazine hydrate without further purification. A solution of 470 mg (2.1 mmoles) of methylmercapto derivative and 540 mg (10.5 mmoles) of hydrazine hydrate in 6 ml of isopropyl alcohol was heated under reflux for 5 hours. Filtration of the precipitates gave 150 mg (35%) of 6-phenyl--3-hydrazino-*as*-triazin-5-one as yellow crystals, mp 242° dec; ir (potassium bromide): 3240, 3090, 1620, 1588 cm^{-1}.

Similarly the following compounds were prepared from 6-(4-halophenyl)-3-thioxo-*as*-triazines (8).

6-(4-Fluorophenyl)-3-hydrazino-*as*-triazin-5-one (**1d**).

This compound was obtained in a yield of 19%, mp 270° dec (from water); ir (potassium bromide): 3200, 1655, 1600, 1520 cm^{-1}.

Anal. Calcd. for $C_9H_8FN_5O$: C, 48.87; H, 3.65; N, 31.66. Found: C, 48.91; H, 3.63; N, 31.79.

6-(4-Chlorophenyl)-3-hydrazino-*as*-triazin-5-one (**1e**).

This compound was obtained in a yield of 31%, mp 270° dec (from water); ir (potassium bromide): 3360, 1637, 1560, 1510 cm^{-1}.

Anal. Calcd. for $C_9H_8ClN_5O$: C, 45.49; H, 3.39; N, 29.47. Found: C, 45.75; H, 3.45; N, 29.15.

6-(4-Bromophenyl)-3-hydrazino-*as*-triazin-5-one (**1f**).

This compound was obtained in a yield of 19%, mp 280° dec (from water); ir (potassium bromide): 3350, 1637, 1560, 1518 cm^{-1}.

Anal. Calcd. for $C_9H_8BrN_5O$: C, 38.32; H, 2.86; N, 24.83. Found: C, 38.50; H, 2.87; N, 24.60.

6-Substituted-3-amino-*s*-triazolo[4,3-*b*]-*as*-triazin-7-ones (**2a-d**).

A general procedure is the following: A mixture of cyanogen bromide (0.06 mole) and the 6-substituted-3-hydrazino-*as*-triazin-5-one (0.05 mole) in buffer solution (AcOH-NaOAc, $pH = 5$) was refluxed for 2-4 hours. After cooling with ice, the precipitated *s*-triazolo-*as*-triazine was collected and purified by recrystallization from water. The yields and the physical properties are summarized in Table 1. Analytical data of **2a-d** are summarized below.

Compound **2a**.

Anal. Calcd. for $C_4H_4N_6O \cdot 3/8H_2O$: C, 30.24; H, 3.10; N, 52.90. Found: C, 30.08; H, 3.17; N, 53.14.

Compound **2b**.

Anal. Calcd. for $C_5H_6N_6O \cdot 1/2H_2O$: C, 34.29; H, 4.03; N, 47.98. Found: C, 34.25; H, 4.26; N, 47.94.

Compound **2c**.

Anal. Calcd. for $C_{10}H_8N_6O \cdot 1/2H_2O$: C, 50.63; H, 3.82; N, 35.43. Found: C, 50.50; H, 3.79; N, 35.68.

Compound **2d**.

Anal. Calcd. for $C_{10}H_7FN_6O \cdot 1/2H_2O$: C, 47.07; H, 3.16; N, 32.93. Found: C, 47.05; H, 2.90; N, 32.94.

6-Bromo-3-amino-*s*-triazolo[4,3-*b*]-*as*-triazin-7-one (**2g**).

A mixture of 450 mg (3.0 mmoles) of 3-amino-*s*-triazolo[4,3-*b*]-*as*-triazin-7-one and 480 mg (3.0 mmoles) of bromine in 15 ml of water was stirred at room temperature for 2 days. After filtration, the collected product was dissolved in 60 ml of hot methanol, followed by filtration. Methanol was removed *in vacuo* to give 150 mg (22%) of 6-bromo-*s*-triazolo[4,3-*b*]-*as*-triazin-7-one as yellow crystals. The physical properties are summarized in Table 1.

Anal. Calcd. for $C_4H_3BrN_6O \cdot 3/4H_2O$: C, 19.65; H, 1.86; N, 34.36. Found: C, 19.59; H, 1.72; N, 34.36.

6-Methyl-5-hydrazino-*as*-triazin-3-one (**5**).

This compound was prepared by a method described by Sasaki and Minamoto (5).

3-Amino-8-methyl-*s*-triazolo[4,3-*d*]-*as*-triazin-5-one (**6**).

This compound was synthesized from 6-methyl-5-hydrazino-*as*-triazin--3-one and cyanogen bromide in the similar manner to the synthesis of 6-substituted-3-amino-*s*-triazolo[4,3-*b*]-*as*-triazin-7-one as described above. The yield and the physical properties are shown in Table 1.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 35.88; H, 3.88; N, 50.53.

3-Heteroaryl-4-amino-*s*-triazole-5-thiols (**7a-e**).

3-(4-Pyridyl and 2-thienyl)-4-amino-*s*-triazole-5-thiols were prepared by a method of Reid and Heindel (6). 3-(3-Pyridyl, 2-pyridyl and 2-furyl)-4--amino-*s*-triazolethiols were prepared similarly from the reaction of the corresponding potassium 3-aroyldithiocarbazates and hydrazine hydrate. The yields and the physical properties of *s*-triazoles (**7a,b** and **e**) are summarized in Table 3.

Analytical data of **7a,b** and **e** are summarized below.

Compound **7a**.

Anal. Calcd. for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24. Found: C, 43.63; H, 3.96; N, 36.51.

Compound **7b**.

Anal. Calcd. for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24. Found: C, 43.47; H, 3.71; N, 36.45.

Compound **7e**.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75. Found: C, 39.45; H, 3.38; N, 30.59.

3-Heteroaryl-6-amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**8a-e**).

A general procedure was as follows. A solution of cyanogen bromide (0.06 mole) and the 3-heteroaryl-4-amino-*s*-triazole-5-thiol (0.05 mole) in 75% aqueous alcohol was refluxed for 2-3 hours. The reaction mixture was evaporated to one-fourth of the original volume and diluted with saturated aqueous sodium acetate. The precipitated *s*-triazolo-1,3,4-thiadiazole was collected and purified by recrystallization from the solvents listed in Table 2. The yields and the physical properties of *s*-triazolo--1,3,4-thiadiazoles (**8a-e**) are summarized in Table 2. Analytical data of **8a-e** are summarized below.

Compound **8a**.

Anal. Calcd. for $C_8H_6N_6S$: C, 44.03; H, 2.77; N, 38.51. Found: C, 44.15; H, 2.79; N, 38.59.

Compound **8b**.

Anal. Calcd. for $C_8H_6N_6S$: C, 44.03; H, 2.77; N, 38.51. Found: C, 44.02;

H, 2.82; N, 38.47.

Compound **8c**.

Anal. Calcd. for $C_6H_6N_6S$: C, 44.03; H, 2.77; N, 38.51. Found: C, 44.29; H, 2.98; N, 38.33.

Compound **8d**.

Anal. Calcd. for $C_7H_5N_5S_2$: C, 37.66; H, 2.26; N, 31.37. Found: C, 37.83; H, 2.35; N, 31.65.

Compound **8e**.

Anal. Calcd. for $C_7H_5N_5OS$: C, 40.57; H, 2.43; N, 33.80. Found: C, 40.64; H, 2.51; N, 33.64.

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