B. N. Goswami, J. C. S. Kataky and J. N. Baruah*

Regional Research Laboratory,
Jorhat 785 006, India

Received November 22, 1985

The reaction of 3-(2,4-dichlorophenyl)-5-mercapto 1,2,4-1*H*-triazole with α-haloketones and with 1,2-dibromoethane leading to the formation of fused heterocycles were carried out and the orientation of cyclization was studied. The reaction of 3-(2,4-dichlorophenyl)-5-mercapto-4-amino-1,2,4-*s*-triazole with α-haloketones

J. Heterocyclic Chem., **23**, 1439 (1986).

Triazoles and their fused heterocyclic products are reported to possess significant antifungal and antibacterial properties [1,2]. In continuation of search for biologically active new heterocycles, some bridgehead nitrogen heterocycles were synthesized from 3-(2,4-dichlorophenyl)-5-mercapto-1,2,4--1*H*-triazole (**3**) and 3-(2,4-dichlorophenyl)-5-mercapto-4-amino-1,2,4-*s*-triazole (**6**) by the reaction of α haloketones and 1,2-dibromoethane on **3** and α-haloketones and cyanogen bromide on **6**.

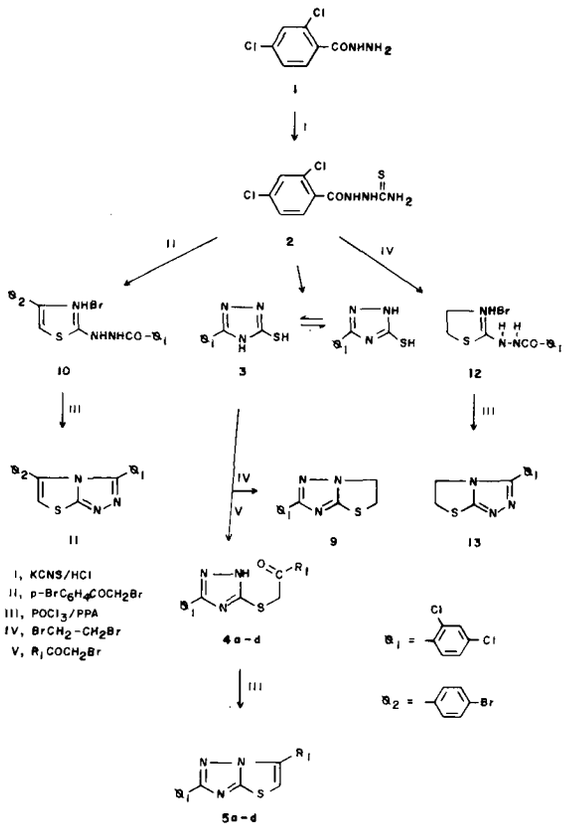
Potts and Hussain [3] observed that 3-methyl-5-mercapto-*s*-triazole with α-haloketones in anhydrous ethanol gave first an uncyclized ketone which on treatment with phosphorus oxychloride underwent cyclizatoin to furnish a thiazolo[2,3-*c*]-*s*-triazole. On the other hand ketones, bearing any aryl substituents obtained by the reaction of 3-aryl-5-mercapto-*s*-triazole with α-haloketones on cyclization with phosphorus oxychloride or PPA gave thiazolo[3,2-*b*]-*s*-triazoles [4]. This view was further supported by Jag Mohan [5] who reported that condensation of 5-mercapto-3-tolyl-*s*-triazole with α-haloketones in one step gave only one product which was characterized to be a thiazolo-[3,2-*b*]-*s*-triazole.

The work of Jain and Handa [6] showed that condensation of 5-mercapto-3-(4-pyridyl)-*s*-triazole with α-haloketones in anhydrous ethanol gave a ketone which on PPA cyclization furnished the 5-aryl-3-(4-pyridyl)thiazolo[2,3-*c*]-*s*-triazoles.

In view of these observations that different substituted triazoles on reaction with α-haloketones and subsequent cyclization with phosphorus oxychloride/PPA gave different fused heterocyclic systems with different mode of cyclizations, it was thought worthwhile to study the orientation of cyclization of 3-(2,4-dichlorophenyl)-1,2,4-*s*-triazole (**3**) with α-haloketones and subsequent cyclization with phosphorus oxychloride.

The reaction of 3-(2,4-dichlorophenyl)-1,2,4-*s*-triazole (**3**) with α-haloketone first gave an uncyclized ketone **4a-d** and not the thiazolo[2,3-*c*]-*s*-triazole (**11**), Scheme 1. The ketones **4a-d** in their ir spectra (potassium bromide ν cm^{-1}) exhibited bands in the region 1760-1685 (C = O). Absence of this band in the ir spectr of **5a-d** suggested the cyclic structure which was further supported by pmr (deu-

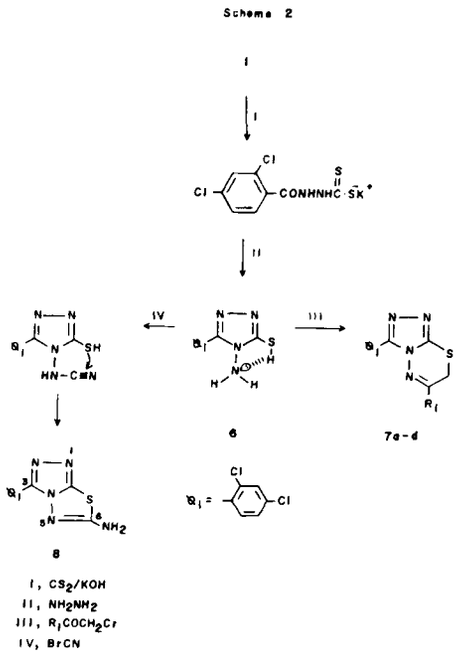
Scheme I



teriochloroform) data of the compounds obtained from **4a** [pmr δ 6.90 (1H, s, C_6-H, 7.12-8.2 (8H, m, Ar-H)]. The mass spectra of the compounds showed a cluster of ions as expected in their molecular ion due to the presence of nitrogen and chlorine in the molecule.

The ketones **4a-d** being unsymmetrical [6], there is the possibility of giving two isomeric traizoles *i.e.* 3-(2,4-dichlorophenyl)-thiazolo[3,2-*b*]-*s*-triazole or 3-(2,4-dichlorophenyl)thiazolo[2,3-*c*]-*s*-triazole. It is not possible to distinguish the structures for these two compounds on the basis of pmr spectra. Hence, unequivocal synthesis of the compound with the alternative structure thiazolo[2,3-*c*]triazole (**11**) was carried out.

Treatment of 1-(2,4-dichlorobenzoyl)-3-thiosemicarba-



zide (**2**) with *p*-bromophenacylbromide yielded 2-benzoylhydrazino-4-*p*-bromophenylthiazolo hyrobromide (**10**) which on phosphorus oxychloride cyclization gave 3-(2,4-dichlorophenyl)-2-*p*-bromophenylthiazolo[2,3-*c*]-*s*-triazole (**11**) which is not identical with **5b**. This suggested that the cyclized product obtained from **4** have structure **5**. The physical properties, yield and spectral data of the compounds **4a-d** and **5a-d** are given in Table 1.

Mercaptotriazole **3** when refluxed with 1,2-dibromoethane in absolute ethanol for 6 hours yielded a single product (tlc) which was assigned the structure **9** and not **13**. This assignment was based on the unequivocal synthesis of 3-(2,4-dichlorophenyl)-5,6-dihydrothiazolo[2,3-*c*]-*s*-triazole (**13**) by phosphorus oxychloride cyclization of 2-(2,4-dichlorobenzoyl)hydrazino-Δ^2-thiazoline hydrobromide (**13**) obtained from **2** and 1,2-dibromoethane. This was not identical with the structure **9**. This suggested the structure **9** for the product obtained from 3-(2,4-dichlorophenyl)-1,2,4-triazole and 1,2-dibromoethane and ruled out the alternative structure **13**.

Table 1

Characterization Data of the Compounds **4a-d** and **5a-d**

Compound No.	R_1	mp (°C)	Yield (%)	Molecular Formulae (M^+)	Microanalysis Calcd. (Found) C	H	N	IR (Potassium bromide ν cm^{-1})	PMR (δ TMS = 0 ppm) (Deuteriochloroform)
4a	C_6H_5	140	73	$C_{16}H_{11}Cl_2N_3OS$ (363)	52.89 (52.68	3.03 3.09	11.57 11.60)	3400, 1675, 1590	4.4 (s, S-CH_2), 6.9-8.2 (m, Ar-H)
4b	*p*-BrC_6H_4	158	65	$C_{16}H_{10}BrCl_2N_3OS$ (443)	43.34 (43.30	2.25 2.34	9.48 9.49)	3400, 1675, 1595	4.45 (s, S-CH_2), 7-8.2 (m, Ar-H)
4c	2,4-$Cl_2C_6H_3$	156	60	$C_{16}H_9Cl_4N_3OS$ (433)	44.34 (44.42	2.07 2.11	9.69 9.73)	3400, 1675, 1595	4.6 (s, S-CH_2), 7-8.3 (m, Ar-H)
4d	*p*-ClC_6H_4	149	55	$C_{16}H_{10}Cl_3N_3OS$ (399)	48.12 (48.20	2.50 2.60	10.53 10.64)	3400, 1675, 1590	4.52 (s, S-CH_2), 7-8.0 (m, Ar-H)
5a	C_6H_5	189	48	$C_{16}H_9Cl_2N_3S$ (345)	55.65 (56.01	2.60 2.58	12.17 12.19)	1610 (C=N), 1595 (C=C)	6.9-8.2 H_6 and Ar-H
5b	*p*-BrC_6H_4	205	51	$C_{16}H_8BrCl_2N_3S$ (425)	45.17 (45.22	1.88 1.80	9.88 9.98)	1600, 1590 (C=N), (C=C)	6.9-8.25 H_6 and Ar-H
5c	2,4-$Cl_2C_6H_3$	178	46	$C_{16}H_7Cl_4N_3S$ (415)	46.26 (46.10	1.68 1.76	10.12 10.51)	1610, 1595 (C=N), (C=C)	6.7-8.2 H_6 and Ar-H
5d	*p*-ClC_6H_4	165	45	$C_{16}H_8Cl_3N_3S$ (381)	50.39 (50.45	2.09 2.18	11.02 11.35)	1610, 1590 (C=N), (C=C)	6.8-8.1 H_6 and Ar-H

Table 2

Characterization Data of the Compounds **7a-d**

Compound No.	R_1	mp (°C)	Yield (%)	Molecular Formulae (M^+)		Microanalysis Calcd. (Found) C	H	N	IR (Potassium bromide ν cm^{-1})	PMR (Solvent TMS = 0 ppm)
7a	C_6H_5	190	77	$C_{16}H_{10}Cl_2N_4S$	(360)	53.33 (53.45	2.77 2.68	15.55 15.40)	1600 (C=N) 1570 (C-N)	(DMSO-d_6), 4.5 (s, $-CH_2$), 7.5-8 (m, Ar-H)
7b	*p*-BrC_6H_4	245 (d)	75	$C_{16}H_9BrCl_2N_4S$	(440)	43.63 (43.82	2.04 2.11	12.72 12.84)	1610 (C=N) 1575 (C-N)	(DMSO-d_6), 4.62 (s, $-CH_2$ 7.6-8.1 (m, Ar-H)
7c	2,4-$Cl_2C_6H_3$	240	65	$C_{16}H_8Cl_4N_4S$	(430)	44.65 (44.42	1.86 1.73	13.02 13.05)	1610 (C=N) 1570 (C-N)	(DMSO-d_6), 4.65 (s, $-CH_2$), 7.6-8 (m, Ar-H)
7d	*p*-Cl-C_6H_4	248	68	$C_{16}H_9Cl_3N_4S$	(396)	48.48 (49.02	2.27 2.36	14.14 14.38)	1605 (C=N), 1570 (C-N)	(DMSO-d_6), 4.42 (s, $-CH_2$), 7.6-8.2 (m, Ar-H)

Table 3

Antibacterial Acitivity of the Compounds **5a-d**, **6**, **7a-d**, **8** and **9**

Compound No.	*B. cereus*	*B. substilis*	*Esch. coli*	*P. solanarium*
5a	+	—	+	—
5b	+	+	+ +	—
5c	—	—	+	—
5d	+ +	+	+	—
6	+ + +	+ + +	+ + +	+ + +
7a	+	+	+	—
7b	+	+	—	—
7c	+	+	+ +	—
7d	+	—	+	—
8	+	+	+ +	+
9	—	—	—	—

Diameter of zone of inhibition: + = 5-7 mm, + + = 8-14 nm, + + + = 14-20 mm, — = No inhibition.

Reaction of 3-(2,4-dichlorophenyl)-5-mercapto-4-amino-1,2,4-triazole with α-haloketone and cyanogenbromide under reflux in ethanol gave 3-(2,4-dichlorophenyl)-6-aryl-7H-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines **7a-d** and 3-(2,4-dichlorophenyl)-6-amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (**8**). Physical properties and characterization data of the compounds **7a-d** are given in Table 2.

Biologicla Activity.

The compounds **5a-d**, **6**, **7a-d**, **8** and **9** were screened for their antibacterial activity against 24 hours old culture of *B. cereus*, *B. substilis*, *E. coli* and *P. solanarium* using agar diffusion technique [7].

The antibacterial activity of these condensed heterocycles were found to be less than that of the aminotriazole **6**. The screening results are shown in Table 3.

EXPERIMENTAL

General.

The melting points were determined on a Buchi oil-heated apparatus and are uncorrected. The ir spectra (ν max cm^{-1}) were recorded on a Perkin-Elmer 237B spectrophotometer in potassium bromide discs. The pmr spectra were recorded on a Varian T-60 instrument using TMS as internal reference. Mass Spectra were recorded on an AEIMS-30 instrument at 70 eV.

The compounds 1-(2,4-dichlorobenzoyl)thiosemicarbazide (**2**), 3-(2,4-dichlorophenyl)-5-mercapto-1,2,4-1*H*-triazole (**3**) and 3-(2,4-dichlorophenyl)-5-mercapto-4-amino-1,2,4-triazole (**6**) were prepared according to the method reported earlier [8].

5-Benzoylmethylmercapto-3-(2,4-dichlorophenyl)-*s*-triazole (**4a**).

To a mixture of 0.245 g (1 mmole) of **3** in 20 ml of anhydrous ethanol, 0.199 g (1 mmole) of phenacylbromide was added and refluxed for 6 hours. After cooling to room temperature the reaction mixture was neutralised with ammonia solution. The colourless solid after filtration was recrystallized from aqueus ethanol giving 0.266 g (73%) of pale yellow crystals, mp 140°. The compounds **4b-d** were prepared in a similar manner.

5-Phenylthiazolo[3,2-*b*]-2-(2,4-dichlorophenyl)-1,2,4-triazole (**5a**).

A mixture of 0.200 g (0.55 mmole) of **4a** (R_1 = C_6H_5), 0.8 g of phosphorus pentoxide, 0.6 ml of orthophosphoric acid was heated on an oilbath at 150° for 3 hours. The reaction mixture was then poured into cold water, neutralised with potassium carbonate. The resulting solid after washing with cold water was filtered. Recrystallization from ethanol gave 0.096 g (48%) of colourless crystals, mp 189°. The other compounds of this series, **5b-d** were prepared in a similar manner. The physical properties and spectroscopic data of the compounds **4a-d** and **5a-d** are shown in Table 1.

2-(2,4-Dichlorophenyl)-5,6-dihydrothiazolo[3,2-*b*]-*s*-triazole **9**.

A mixture of 0.245 g (1 mmole) of **3** and 0.188 g (1 mmole) of 1,2-dibromoethane in 20 ml of anhydrous ethanol was refluxed for 6 hours. After cooling to room temperature the reaction mixture was neutralized with ammonia solution. The solid was filtered and recrystallized from ethanol giving 0.216 g (80%) of needle like crystals, mp 216°; ir (potassium bromide): 1600 cm^{-1} (C=N), 1480 cm^{-1} (C-N); pmr (deuteriochloroform): δ 3.70 (s, S-CH_2-2H), 3.86 (s, N-CH_2, 2H), 7.2-8.0 (m, ArH, 3H); ms: 271/273 (M^+, 100), 245/247 (90), 212 (80), 173 (90), 99 (90), 57 (40).

Anal. Calcd. for $C_{10}H_7Cl_2N_3S$: C, 44.11; H, 2.57; N, 15.44. Found: C, 44.01; H, 2.60; N, 15.39.

2-(2,4-Dichlorobenzoylhydrazino)-Δ^2-thiadiazoline Hydrobromide (**12**).

A mixture of 0.264 g (1 mmole) of 1-(2-dichlorbenzoyl)-3-thiosemicarbazide (**2**) and 0.188 g (1 mmole) of 1,2-dibromoethane in 20 ml of anhydrous ethanol was refluxed for 5 hours. On cooling the reaction mixture a white solid appeared. This was recrystallized from ethanol giving 0.189 g (50%) as light yellow crystals, mp 260° dec; ir (potassium bromide): 3300 cm^{-1} (−NH), 1675 cm^{-1} (−NHCO).

Anal. Calcd. for $C_{10}H_{10}BrCl_2N_3OS$: C, 32.34; H, 2.69; N, 11.32. Found: C, 32.40; H, 2.73; N, 11.41.

3-(2,4-Dichlorophenyl)-5,6-dihydrothiazolo[2,3-*d*]-*s*-triazole (**13**).

Compound **12** (0.185 g, 0.5 mmole) and 0.2 ml of phosphorus oxychloride were refluxed in an oil bath at 140°-145° for 4 hours. The reaction mixture was cooled to room temperature and poured in water. Neutralization with potasium carbonate gave a pale yellow solid which was recrystallized from ethanol giving 0.105 g (78%) colourless crystals, mp 120°; ir (potassium bromide): 1615 cm^{-1} (C=N), 1535 cm^{-1} (C-N); pmr (deuteriochloroform): δ 3.75 (s, S-CH_2, 2H), 3.84 (s, N-CH_2, 2H), 7.00-8.1 (m, ArH).

Anal. Calcd. for $C_{10}H_7Cl_2N_3S$: C, 44.11; H, 2.57; N, 15.44. Found: C, 44.20; H, 2.50; N, 15.51.

3-(2,4-Dichlorophenyl)-6-aryl-7*H*-*s*-triazolo[3,4-*b*]thiadiazine (**7a**).

To a solution of 0.261 g (1 mmole) of **6** in a minimum quantity of ethanol was added 0.2 g (1 mmole) of phenacylbromide and the mixture was refluxed for 5 hours. Cooling to room temperature and subsequent neutralization with potassium carbonate gave a solid which was recyrstallized from ethanol giving 0.280 g (77%) of pale yellow crystals, mp 190°. The other thiadiazines **7b-d** were prepared in a similar manner. The physical properties and spectral data of the compounds **7a-d** are given in Table 2.

3-(2,4-Dichlorophenyl)-6-amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **8**.

A mixture of 0.652 g (2.5 mmoles) of **6** and 0.318 g (3 mmole) of cyanogen bromide in 30 ml of ethanol (75%) was refluxed for 3 hours. The reaction mixture was evaporated to a small volume and neutralized it by the addition of saturated aqueous solution of sodium acetate. The solid separated was filtered and recrystallized from ethanol giving 0.552 g (78%) of **8**; ir (potassium bromide): ν 3290-3150 cm^{-1} (broad, N-H stretching), 1620 cm^{-1} (C=N), 1575 cm^{-1} (C-N); pmr (deuteriodimethylsulfoxide): δ 7.0-8.2 (m, ArH and $-NH_2$); ms: 285/287 (M^+, 10), 173 (90), 188 (70), 137 (100), 58 (90), 42 (50).

Anal. Calcd. for $C_9H_5Cl_2N_3S$: C, 37.76; H, 1.74; N, 24.74. Found: C, 37.81; H, 1.80; N, 24.53.

Acknowledgement.

The authors are grateful to the analytical division of this laboratory for providing pmr, ir and ms spectral data. They are also grateful to Dr. R. P. Singh of Biochemistry Division for antibacterial screening of the compounds.

REFERENCES AND NOTES

[1] K. S. Dhaka, J. Mohan, V. K. Chadha and H. K. Pujari, *Indian, J. Chem.*, **12**, 287 (1974).

[2] S. Bala, R. P. Gupta, M. L. Sachedeva, A. Singh and H. K. Pujari, *Indian J. Chem.*, **16B**, 481 (1978).

[3] K. T. Potts and S. Hussain, *J. Org. Chem.*, **36**, 10 (1971).

[4] R. P. Gupta, M. L. Sachedeva and H. K. Pujari, *Indian J. Chem.*, **15B**, 1143 (1977).

[5] J. Mohan, *Indian J. Chem.*, **21B**, 243 (1982).

[6] (Miss) Kiran Jain and R. N. Handa, *Indian J. Chem.*, **21B**, 732 (1982).

[7] R. S. Verma, S. A. Iman and W. L. Nobbles, *J. Pharm. Sci.*, **62**, 140 (1973).

[8] B. N. Goswami, J. C. S. Kataky and J. N. Baruah, *J. Heterocyclic Chem.*, **21**, 1225 (1984).