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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

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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**.

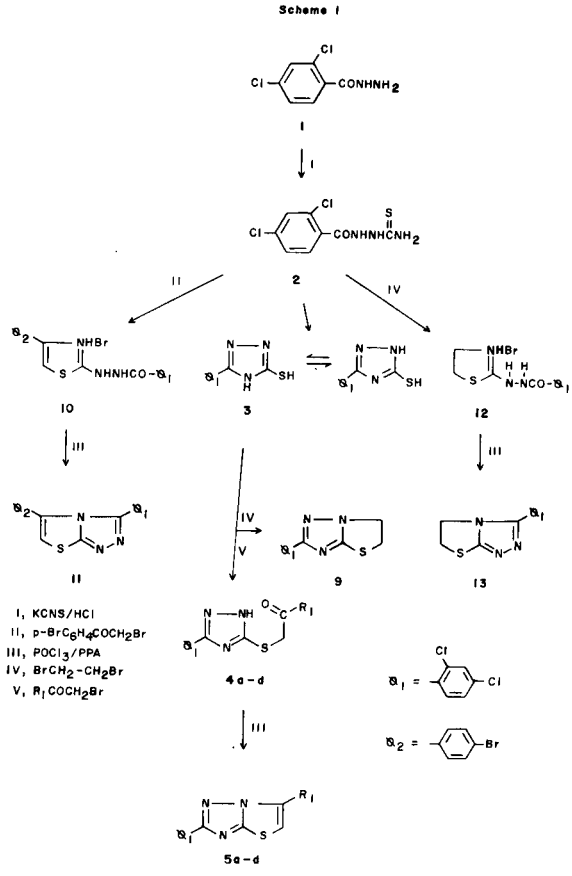
Potts and Hussain [3] observed that 3-methyl-5-mercapto-*s*-triazole with α-haloketones in anhydrous ethanol gave first an uncyclized ketone which on treatment with phosphorus oxychloride underwent cyclizatoin to furnish a thiazolo[2,3-*c*]-*s*-triazole. On the other hand ketones, bearing any aryl substituents 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

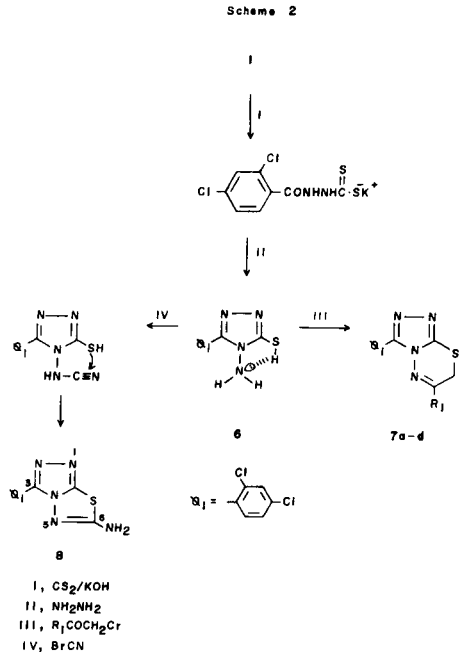


teriochloroform) data of the compounds obtained from **4a** [pmr δ 6.90 (1H, s, C_6-H, 7.12-8.2 (8H, m, Ar-H)]. The mass spectra of the compounds showed a cluster of ions as expected in their molecular ion due to the presence of nitrogen and chlorine in the molecule.

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-

Scheme 2



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)-Δ²-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 $C_9H_5Cl_2N_5S$: C, 37.76; H, 1.74; N, 24.74. Found: C, 37.81; H, 1.80; N, 24.53.

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