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BRIDGEHEAD NITROGEN HETEROCYCLES. PART-II*: SYNTHESIS OF SOME FUSED HETEROCYCLIC SYSTEMS FROM 4-AMINO-3-(2,4-DICHLOROPHENYL)-5-MERCAPTO-1,2,4-*s*-TRIAZOLES

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Abstract - The condensation reaction of 4-amino-3-(2,4-dichlorophenyl)-5-mercapto-1,2,4-*s*-triazole with aromatic carboxylic acids, aromatic aldehydes, ketones, diketones and α-haloketones leading to the formation of fused heterocycles was carried out.

The synthesis of condensed *s*-triazole heterocycles has been receiving much attention during recent years.[1,11] Triazoles and their condensed products are reported to possess significant antifungal and antibacterial properties.[2,3] Condensed triazole systems have found considerable use in the photographic industry,[4] and possess strong CNS depressant, mild to moderate antiinflammatory and mild hypocholesteremic and hypotensive activities.[5,6]

In continuation of our interest in the chemistry of heterocycles[7] the results obtained from these studies prompted us to synthesize some new bridgehead nitrogen heterocycles from 4-amino-3-(2,4-dichlorophenyl)-5-mercapto-1,2,4-*s*-triazole (1) by reactions with aromatic carboxylic acids, aromatic aldehydes, ketones, diketones and α-haloketones and to investigate these products. Exploration of the studies is principally directed towards the synthesis of new heterocyclic products. The results obtained during this attempt are reported in this paper.

The *compound (1) underwent facile condensation* with various aromatic carboxylic acids in the presence of phosphorus oxychloride,[8] giving 6-aryl-3-(2,4-dichlorophenyl)- *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (2a-j). The ir spectra of compounds (2a-j) showed a sharp band near 1600 cm^{-1} due to the C=N group. The bands appeared at 3290 (NH_2), 1328, and 1095 cm^{-1} (C=S) for the starting triazole (1) were absent in the newly formed compounds (2a-j). The ^{1}H nmr spectra of the compounds (2a-j) lacked the peaks due to the SH proton of the original triazoles.

The triazole (1) when condensed with aromatic aldehydes in the presence of *p*-toluenesulphonic acid[9] as catalyst gave compounds 6-aryl-3-(2,4-dichlorophenyl)-5,6-dihydro[3,4-*b*][1,3,4]thiadiazoles (3a-g). The ir spectra exhibited a band at 3000-3250 cm^{-1} due to the NH group. The sharp band that appeared around 1600 cm^{-1} was due to C=N group. The ^{1}H nmr exhibited a broad peak at δ6.0-6.4 exchangeable with D_2O due to NH proton. The aromatic protons showed a multiplet at δ 6.8-7.4.

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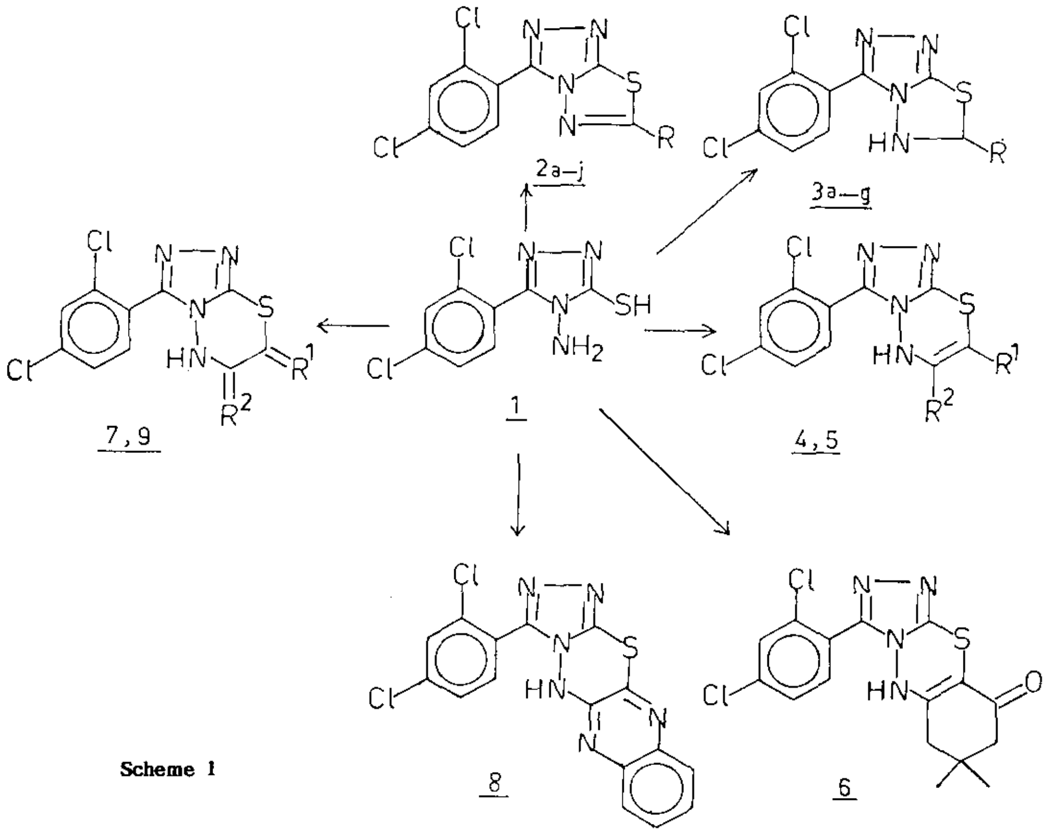
* Part I, B. N. Goswami, J. C. S. Kataky, and J. N. Baruah, J. Heterocycl. Chem., 1986, 23, 1439.

The reaction of compound (1) with benzoin and furoin in ethanolic solution in the presence of potassium hydroxide[3] yielded 3-(2,4-dichlorophenyl)-6,7-diphenyl/difuryl-5*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (4,5), whereas with dimedone by oxidative cyclization in the presence of DMSO[10] gave 3-(2,4-dichlorophenyl)-7,7-dimethyl-6,7,8,9-tetrahydro-*s*-triazolo[4,3-*b*][2,3,4]benzothiadiazin-9-one (6). The ir spectra of the compounds (4,5,6) showed a band in the region 3350-3340 cm^{-1} due to the NH group. In the ^1H nmr spectra a singlet appeared in the region δ 6.0, 6.2 and 8.6 for compounds (4,5,6) respectively due to NH proton (Table 1).

Triazole (1) reacted with chloroacetic acid and then cyclized with fused sodium acetate[11] in dry methanol to yield the fused 3-(2,4-dichlorophenyl)-7H-*s*-triazolo[3,4-*b*][1,3,4]thiadiazin-6(5H)-one (7). Reaction of the triazole (1) with 2,3-dichloroquinoxaline[11] in ethanol resulted in the formation of 3-(2,4-dichlorophenyl)-*s*-triazolo[3',4',2,3][1,3,4]thiadiazin[5,6-*b*]quinoxaline (8).

Reaction of the triazole (1) dimethyl acetylenedicarboxylate[12] afforded (E)-7-methoxycarbonylmethylene-3-(2,4-dichlorophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazin-6-one(9). These compounds (7,8,9) showed the bands (νcm^{-1}) at 3300-3200(NH), 1700-1690 (CONN, except for 8) and 1610(C=N, only for 8) in the ir spectra. The ^1H nmr spectra of compound (7) showed peaks at δ 4.6 (CH_2), 7.0-7.8(Ar-H), 12.0(NH), (8) δ 6.8-7.8 (Ar-H) and 9.0(NH) and (9) δ 3.8 ($COOCH_3$), 7.2-7.8 (Ar-H), 8.1(=CH) and 12.0(NH) respectively.



Scheme 1

EXPERIMENTAL

Melting points were determined with a Büchi oil heated apparatus in open capillaries and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 580B spectrophotometer using potassium bromide discs, unless otherwise *stated* (ν_{max} *in cm*$^{-1}$). ^{1}H Nmr *spectra* were recorded in solutions stated with TMS as the internal reference in 90 MHz on a Zeol-FX-90 spectrometer (chemical shifts in δ ppm). 3-(2,4-Dichlorophenyl)-4-amino-5-mercapto-1,2,4-*s*-triazole (1) was prepared following the method of *Goswami* et al.[12a]

3-(2,4-Dichlorophenyl)-6-aryl/substituted aryl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (2a-j)

General Procedure

A mixture of (1) (0.01 mol), aromatic carboxylic *acid (0.01 mol) and phosphorus oxychloride* (10 ml) was refluxed for 1 h. The reaction mixture was then cooled and poured over crushed ice (100 g). The solid thus separated was filtered, then treated with 2% aq. sodium hydroxide solution (50 ml). The solid was *filtered, washed* 3 *times with* water (30 ml) and then recrystallized from CH_3COOH. The physical data of the compounds (2a-j) are given in Table 1.

3-(2,4-Dichlorophenyl)-6-aryl/substituted aryl-5,6-dihydro-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (3a-g)

General Procedure

A equimolar mixture of (1) (0.01 mol), aldehyde (0.01 mol) and *p*-toluenesulphonic acid (20 mg) in dry benzene (100 ml) was refluxed for 10 h using Dean-Stark apparatus for continuous removal of liberated water from the reaction mixture. The mixture was then cooled and treated with water (100 ml). The organic layer thus separated was washed 2 times with water (50 ml) and dried over anhydrous sodium sulfate. Benzene was then removed under reduced pressure. The *solid thus obtained was recrystallized* from C_2H_5OH to give compounds (3a-g). The physical data of the compounds are given in Table 1.

3(2,4-Dichlorophenyl)-6,7-diphenyl/difuryl-5H-*s*-triazolo[3,4-*b*][1,3,4]thiadizines (4,5)

General Procedure

A mixture of (1) (0.01 mol) and benzoin (0.01 mol) in ethanol (25 ml) was heated to give a clear solution. To this hot solution 2N aq. potassium hydroxide solution (2 ml) was added and then the whole was refluxed for 1 h. On *cooling the mixture a light yellow* precipitate separated out. It was filtered, dried and recrystallized from hot C_2H_5OH to afford dazzling white needles of compound (4). Similar procedure was adopted for the synthesis of 5 using furoin in place of benzoin.

3-(2,4-Dichlorophenyl)-7,7-dimethyl-6,7,8,9-tetrahydro-*s*-triazolo[3,4-*b*][1,3,4]benzothiadiazin-9-one (6)

A solution of (1) (0.01 mol) and dimedone (0.01 mol) in DMSO (100 ml) was heated under reflux for 1 h. The solvent was removed under reduced pressure. The solid thus obtained was purified by column chromatography (silica gel, petroleum ether, bp 40-60°C as *eluent) to give the product* 6 as a light yellow crystalline product.

Table - 1

Physical and spectral data of compounds(2a-j, 3a-g).

Cmpd No	R	mp (°C)	Yield (%)	ir (KBr) νcm^{-1}	^1H nmr (δ ppm, DMSO-d_6)	Analysis (%) Found (Calcd)		
						C	H	N
2a	$C_6H_4(OCH_3)$(-p)	205	79	1600(C=N)	3.8(s, 3H) 6.8-7.8(m, 7H)	50.90 (50.93	2.60 2.65	14.80 14.85)
2b	$C_6H_4(NH_2)$(-p)	225	93	1600(C=N)	6.8-7.4(m, 7H)	49.70 (49.72	2.50 2.49	19.45 19.34)
2c	$C_6H_3(Cl)_2$(-o,-p)	250	93	1600(C=N)	6.9-7.2(m, 6H)	43.37 (43.27	1.35 1.45	13.46 13.46)
2d	$C_6H_4(OH)$(-o)	245	93	1600(C=N) 3000 (OH)	6.8-7.6(m, 7H)	49.69 (49.59	2.10 2.20	15.30 15.43)
2e	$C_6H_4(CH_3)$(-p)	216	76	1600(C=N)	1.8(s, 3H) 7.0-7.6(m, 7H)	53.00 (53.19	2.65 2.77	15.45 15.51)
2f	$C_6H_5CH_2CH_2$	103	85	1600(C=N)	3.6(s,2H),3.8(s,2H) 6.8-7.2(m,8H)	54.35 (54.40	3.09 3.20	14.85 14.93)
2g	$C_6H_3(OH)_2$(-o,-p)	106(d)	98	1600(C=N) 3000 (OH)	7.0-7.4(m,6H)	47.50 (47.49	2.00 2.11	14.70 14.78)
2h	$C_6H_4(OH)$(-p)	193	94	1600(C=N) 3500 (OH)	6.8-7.6(m,7H)	49.50 (49.59	2.15 2.20	15.40 15.43)
2i	$C_6H_4(NH_2)$(-o)	249	91	1600(C=N) 3300 (NH_2)	6.8-7.4(m,7H)	49.65 (49.72	2.50 2.49	19.30 19.34)
2j	C_6H_5	226	77	1600(C=N)	6.8-7.2(m,8H)	51.19 (51.29	2.36 2.30	16.00 16.14)
3a	$C_6H_4N(CH_3)_2$(-p)	162	79	1600(C=N) 3075 (NH)	2.4(s,6H),6.2(br s, 1H),6.8-7.2(m,7H)	50.00 (50.04	3.79 3.83	17.80 17.85)
3b	C_6H_5	193	83	1610(C=N) 3050 (NH)	1.6(s,1H),7.4-8.4 (br s,1H),6.8-7.2 (m, 8H)	52.00 (52.14	2.90 2.87	16.30 16.33)
3c	$C_6H_5CH{=}CH$	128	65	1610(C=N) 3000(NH)	1.6(s,1H),4.8(s,2H) 6.8-7.4(m,8H)	54.39 (54.41	3.00 3.20	14.85 14.94)
3d	$C_6H_4(Cl)$(-m)	173	95	1600(C=N) 3100 (NH)	1.3(s,1H), 6.2(br s, 1H), 7.0-7.2(m,7H)	46.83 (46.93	2.30 2.35	14.55 14.60)
3e	$C_6H_4(Cl)$(-p)	223	90	1610(C=N) 3100 (NH)	1.3(s,1H), 6.2(br s, 1H),6.8-7.2(m,7H)	46.90 (46.93	2.25 2.35	14.75 14.60)
3f	$C_6H_4(OCH_3)$(-p)	125	76	1610(C=N) 3050 (NH)	1.6(s,1H),3.4(s,3H) 6.6(br s,1H),7.0-7.2 (m,7H)	50.61 (50.66	3.10 3.17	14.65 14.78)
3g	$C_6H_3(OH,OCH_3)$(-p,-m)	175	65	1600(C=N) 3250 (NH)	1.6(s,1H),3.2(s,3H) 6.4(br s,1H),6.8-7.2(m, 6H)	48.50 (48.61	3.75 3.82	14.09 14.18)

Table - 2

Physical and spectral data of compounds (4-9)

Compd No	R^1	R^2	mp (°C)	Yield (%)	ir (KBr) $\nu_{cm^{-1}}$	^1H nmr (δppm,DMSO-d_6)	Analysis		
							Compd (Calcd)		
							C	H	N
4	C_6H_5	C_6H_5	75	30	1620(C=N) 3340 (NH)	6.0(s, 1H) 7.0-8.0(m,13H)	60.20 (60.41	3.20 3.29	12.56 12.81)
5	Furyl	Furyl	145	50	1615(C=N) 3350 (NH)	6.2(s, 1H) 7.0-8.0(m,11H)	50.90 (50.97	2.81 2.90	13.35 13.28)
6			Gummy	67	1620(C=N) 1690(C=O) 3350 (NH)	1.8(s, 6H) 4.2-4.5(m,4H) 7.2-8.0(m,3H) 8.6(s, 1H)	50.32 (50.39	3.62 3.67	14.75 14.70)
7	H_2	O	185	83	1620(C=N) 1690(C=O) 3200 (NH)	4.6(s, 2H) 7.0-7.8(m,3H) 12.0(br s,1H)	39.82 (39.87	1.89 1.99	18.67 18.60)
8			110	90	1610(C=N) 3200 (NH)	6.8-7.8(m,7H) 9.0 (br s, 1H)	49.65 (49.61	2.00 2.06	21.65 21.70)
9	CH-$COOCH_3$	O	195	39	1610(C=N) 1700(C=O) 3300 (NH)	3.8(s,3H) 7.2-7.8(m,3H) 8.1(s,1H), 12.0(br s,1H)	42.00 (42.05	2.24 2.16	14.85 14.96)

3-(2,4-Dichlorophenyl)-7H-*s*-triazolo[3,4-*b*][1,3,4]thiadiazin-6-one (7)

A mixture of (1) (0.01 mol), chloroacetic acid (0.01 mol) and fused sodium acetate (0.01 mol) in dry methanol (50 ml) was refluxed on a steam bath for 6 h, cooled and the separated solid was recrystallized from C_2H_5OH to give the compound (7). Compound (8) was also prepared in a similar manner using 2,3-dichloroquinoxaline in place of chloroacetic acid.

(E)-3-(2,4-Dichlorophenyl)-7-methoxycarbonylmethylene-*s*-triazolo[3,4-*b*][1,3,4]thiadiazin-6-one (9)

A mixture of triazole (1) (0.01 mol), dimethyl acetylenedicarboxylate (0.01 mol), methanol (100 ml) and a few drops of glacial acetic acid, was refluxed for 6 h. On cooling a white crystalline solid was obtained, filtered, washed with water, dried and recrystallized from CH_3OH to get the compound (9).

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