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A FACILE SYNTHESIS OF 4, 5-DIARYL-5, 1-DIHYDRO-s-TRIAZOL-3- THIOL. *Part-III*

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4,5-Diaryl-5, 1-dihydro-s-triazol-3-thiols have been synthesized via cyclization of 1-arylaminomethylthio-semicarbazide derivatives using concentrated hydrochloric acid or from the reaction of arylaminomethylhydrazine derivatives with carbon disulphide in alkaline medium. Some heterocyclic system *viz*, pyrazolidinyltriazoline, thiazolidinylaminotriazoline, triazinotriazolidine and tetrazinyltriazoline, have been derived from 3-hydrazinotriazoline derivative, obtained from reaction of the title compound with hydrazine. The structures of the new compounds have been established by elemental analyses and spectral data.

Key words: Hydrobromic acid, Schiff bases, Carbon tetrachloride, Anilines, Triazole derivatives, Thiosemicarbazide, Hydrazine.

Introduction

Among a wide variety of nitrogen-heterocycles, triazoles have played an important role in pharmaceutical chemistry [1 - 5]. The present work is a continuous of our current research work in synthesis and reactions of 4,5-diaryl-1,2,4-triazoles [6,7].

Experimental

Melting points are uncorrected. The infrared spectra (KBr) were recorded on a Pye-Unicam SP-1200 infrared spectrophotometer and ^{1}H NMR spectra were determined on a Varian EM 360 (60 MHz) NMR spectrometer, using TMS as internal standard and DMSO-d_6 as solvent. Microanalyses were performed by the Microanalytical Centre, Cairo University.

N-(p-Substituted phenyl) bromomethyl-p-substituted anilines (2a,b). To a suspension of the Schiff bases **1a, b** (0.01 mole) in CCl_4 (10 ml), hydrobromic acid (0.01 mole) was added with vigorous shaking, the reaction mixture was stirred well for 2 hr and then the solvent was distilled off in vacuum. The residue was washed with cold water and cold methanol, then dried and crystallized affording **2a,** b. IR (**2b**): υ_{max}3200 (NH), 2980-2940 (CH aliph),1050 (C-O-C) and 670-660cm^{-1} (C-Br).

1-(p-Substituted phenylamino) (P-substituted phenyl) methylthiosemicarbazides (3a, b). A mixture of compounds **2a,b** (0.01 mole) and thiosemicarbazide (0.012 mole) in absolute ethanol (10 ml) were refluxed for 2 hr, cooled and poured into cold water. The solid separated were filtered, washed with hot water and crystallized affording compounds **3a, b.** IR (**3b**): υ_{max} 3390-3180 (NH_2 and NH groups), 2980-2940 (CH aliph), 1615 (def. NH), 1370 (C=S) and 1040 cm^{-1} (C-O-C).

(p-Substituted phenylamino) (p-substituted phenyl) methylhydrazines (4a, b). A mixture of **2a, b** (0.01 mole) and hydrazine hydrate (0.013 mole) in absolute ethanol (20 ml) were heated under reflux for 2 hr, cooled, filtered off and the solid obtained were crystallized to yield **4a, b.** IR (**4b**): υ_{max} 3390-3170 (NH_2, NH groups), 2995-2960 (CH aliph), 1610 (def. NH), 1600 (C=C) and 1050 (C-O-C).

4,5-Diaryl-5,1-dihydro-1,2,4-triazol-3-thiols (5a,b). Method (A): A suspension of compounds **3a, b** (2 g) in ethanol (10 ml) were treated with conc. hydrochloric acid (15 ml) and the mixture was refluxed for 12 hr, then cooled and poured into ice-cold water. The solid so obtained was filtered and recrystallized to give **5a, b.** IR (**5a**):υ_{max} 3300 (NH), 2980-2925 (CH aliph), 2560 (SH), 1370 (C=S) and 710-635 cm^{-1} (C-Cl). ^{1}H NMR (**5a**): δ 2.5 (s, 1H, 5-CH), 6.8-7.4 (m, 8H, Ar-H), 9.5 (br, 1H, SH) and 10.2-10.8 ppm (br, 2H, 1-NH and NHC=S).

Method (B): To a mixture of **4a,b** (0.01 mole) and carbon disulphide (15 ml) was added an ethanolic potassium hydroxide solution (0.02 mole) in ethanol (35 ml, 85%) and the mixture was refluxed for 6 hr. The excess CS_2 was distilled off in vacuum and the solid residue was dissolved in water, filtered from insoluble materials and acidified with glacial acetic acid. The yellow precipitate formed was filtered and crystallized to give **5a,b** (m.p., mixed m.p. and spectra).

4,5-Di-p-chlorophenyl-3-hydrazino/phenylhydrazino-5,1-dihyro-1,2,4 triazoles (6a, b). To a solution of **5a,** (0.01 mole) in ethanol, was added hydrazine hydrate/ or phenylhydrazine (0.01 mole) and the mixture was refluxed for 4 hr, cooled and poured into water. The solid separated was filtered off and crystallized to yield **6a,** b. IR (**6a**) : υ_{max} 3400-3200 (NH_2, NH), 1615 (C=N) and 710 cm^{-1} (C-Cl). IR (6b): υ_{max} 3360-3210 (NH groups), 1620 (C=N) and 715 cm^{-1} (C-Cl). ^{1}H-NMR (**6a**): δ 2.6 (s, 1H, 5-CH), 4.5 (bs, 2H, NH_2), 6.9-7.3 (m, 8H, Ar-H, 8.5 (bs, 1H, NH) and 10.3 (bs, 1H, NH).

4,5-Di-p-chlorophenyl-3-(p-nitrobenzal/m-hydroxybenzal) hydrazino-Δ^2 -1,2,4-triazolidine (7a, b). A mixture of **6a** (0.01 mole) and *p*-nitrobenzaldehyde and/or *m*-hydroxyben-

zaldehyde (0.01 mole) in ethanol (30 ml) and piperidine (1 ml) was refluxed for 6 hr, cooled and poured into water. The solid formed was filtered, washed with water and crystallized to afford **7a, b**. IR (**7a**): υ_{max} 3200-2500 (H-bonded NH groups), 1610 (C=N), 1560-1350 (NO_2) and 690 cm^{-1} (C-Cl). ^1H NMR (**7a**): δ 2.5 (s, 1H, 5-CH), 6.6-8.3 (m, 13H, Ar-H and N=CH) and 9.8-10.4 ppm (br, 2H, 2NH).

4,5-Di-p-chlorophenyl-3-(4'-chloro-3'-p-nitrophenyl-5'-oxo-1'- pyrazolidinyl)-Δ^2-1,2,4-triazoline (8). To a stirred mixture of **7a** (0.01 mole) and triethylamine (0.1 mole) in dry benzene, was added chloroacetyl chloride (0.1 mole) dropwise at room temperature. The mixture was stirred for 8 hr and left to stand overnight, then the precipitated $Et_3N.HCl$ filtered off, shaked with dil. HCl (5%), and washed with water. The benzene layer was separated and dried over anhydrous Na_2SO_4. The residue so obtained on evaporation of the solvent was triturated with methanol and crystallized to give **8.** IR: υ_{max} 3245 (NH), 2985-2940) (CH aliph.), 1640 (C=O), 1560, 1350

TABLE 1. PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS **2-13**.

Com-pound	Melting point (°C)	Crystn. solvent (yield%)	Mol. formula (mol. weight)	Microanalysis Calcd. /Found (%) C	H	N	S
2a	158	Ethanol	$C_{13}H_{10}NCl_2Br$	47.13	3.02	4.23	
		(78)	(331)	47.20	3.00	4.40	
2b	145	Ethanol	$C_{15}H_{16}NO_2Br$	55.90	4.97	4.35	
		(70)	(322)	56.10	5.00	4.50	
3a	182	Acetic acid	$C_{14}H_{14}N_4Cl_2S$	49.27	4.11	16.42	9.38
		(85)	(341)	50.00	4.10	16.70	9.40
3b	125	Acetic Acid	$C_{16}H_{20}N_4SO_2$	57.83	6.02	16.87	9.64
		(80)	(332)	58.00	6.00	16.80	10.00
4a	163	Ethanol	$C_{13}H_{13}N_3Cl_2$	55.32	4.61	14.89	
		(75)	(282)	55.10	4.30	14.50	
4b	159	Acetic acid	$C_{15}H_{19}N_3O_2$	65.93	6.96	15.38	
		(70)	(273)	65.80	7.00	15.10	
5a	190	Ethanol	$C_{14}H_{11}N_3Cl_2S$	51.85	3.40	12.96	9.88
		(40)	(324)	51.80	3.30	12.70	9.80
5b	165	Methanol	$C_{16}H_{17}N_3SO_2$	60.95	5.40	13.33	10.16
		(35)	(315)	60.60	5.20	13.30	10.20
6a	203	Acetone	$C_{14}H_{13}N_5Cl_2$	52.17	4.04	21.74	
		(60)	(322)	52.30	4.00	21.90	
6b	107	Ethanol	$C_{20}H_{17}N_5Cl_2$	60.30	4.27	17.59	
		(55)	(398)	60.20	4.10	17.30	
7a	210	Acetic acid	$C_{21}H_{16}N_6Cl_2O_2$	55.38	3.52	18.46	
		(80)	(455)	55.30	3.50	18.30	
7b	205	Acetic acid	$C_{21}H_{17}N_5Cl_2O$	59.15	3.99	16.43	
		(90)	(426)	59.00	4.10	16.50	
8	225	DMF	$C_{23}H_{17}N_6Cl_3O_3$	51.93	3.19	15.80	
		(15)	(531.5)	51.50	3.20	15.40	
9	>300	DMF	$C_{23}H_{18}N_6Cl_2O_3S$	52.17	3.40	15.88	
		(10)	(529)	51.20	3.40	15.70	
10	170	Ethanol	$C_{28}H_{23}N_5Cl_2O$	65.12	4.46	13.57	
		(90)	(516)	65.30	3.90	13.60	
11	188	Ethanol	$C_{28}H_{21}N_5Cl_2$	67.47	4.22	14.06	
		(95)	(498)	67.40	4.20	14.10	
12	195	Methanol	$C_{17}H_{16}N_8Cl_2$	50.62	3.97	27.79	
		(70)	(403)	50.50	4.00	27.60	
13	170	Acetic acid	$C_{19}H_{16}N_8Cl_2$	53.40	3.75	26.23	
		(80)	(427)	53.30	3.80	26.10	

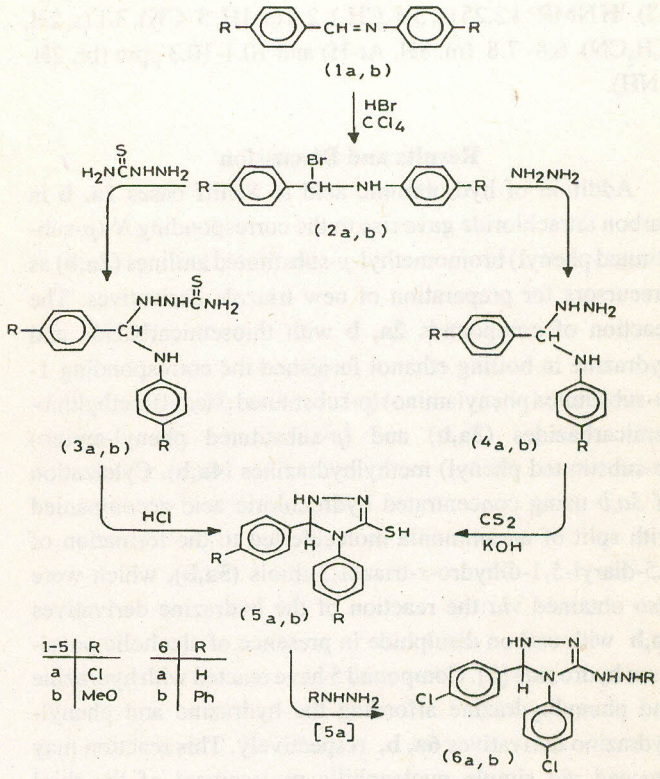
(NO_2), 700-630 cm^{-1} (C-Cl). ^1H NMR; δ 2.5 (s, 1H, 5-CH), 2.8 (dd,IH, 3'-CH), 3.5, (d, 1H, 4' -CH), 6.8-7.8 (m, 12H, Ar-H) and 10.3-10.8 (br, 2H, 2NH).

4,5-Di-p-chlorophenyl-3-(2'-p-nitophenyl-5'-oxo-3'-thiazolidinyl) amino -Δ²-1,2,4-triazoline (9). To a stirred solution of **7a** (0.01 mole) in dry benzene (50 ml), was added thioglycolic acid(0.15 mole) and the mixture was stirred for 5 hr, then refluxed for additional 5 hr, in presence of anhydrous Na_2SO_4 (20 g) and the mixture was filtered while hot. On concentration of the filterate to one third of its volume and recrystallization of the precipitate formed, compound **9** was afforded. IR : υ_{max} 3300-3280 (NH), 2960-2880 (CH aliph.), 1680-1660 (C=O), 1440 (def.CH_2), and 1040 cm^{-1} (C-S-C cyclic). ^1H NMR : δ 2.5 (s, 1H, 5-CH), 3.2 (s, 2H, CH_2), 3.6 (s, 1H, 2'-CH), 6.8-7.7 (m, 12H, Ar-H), 8.5 (s, 1H, NH) and 10.35 ppm (s, 1H, NH).

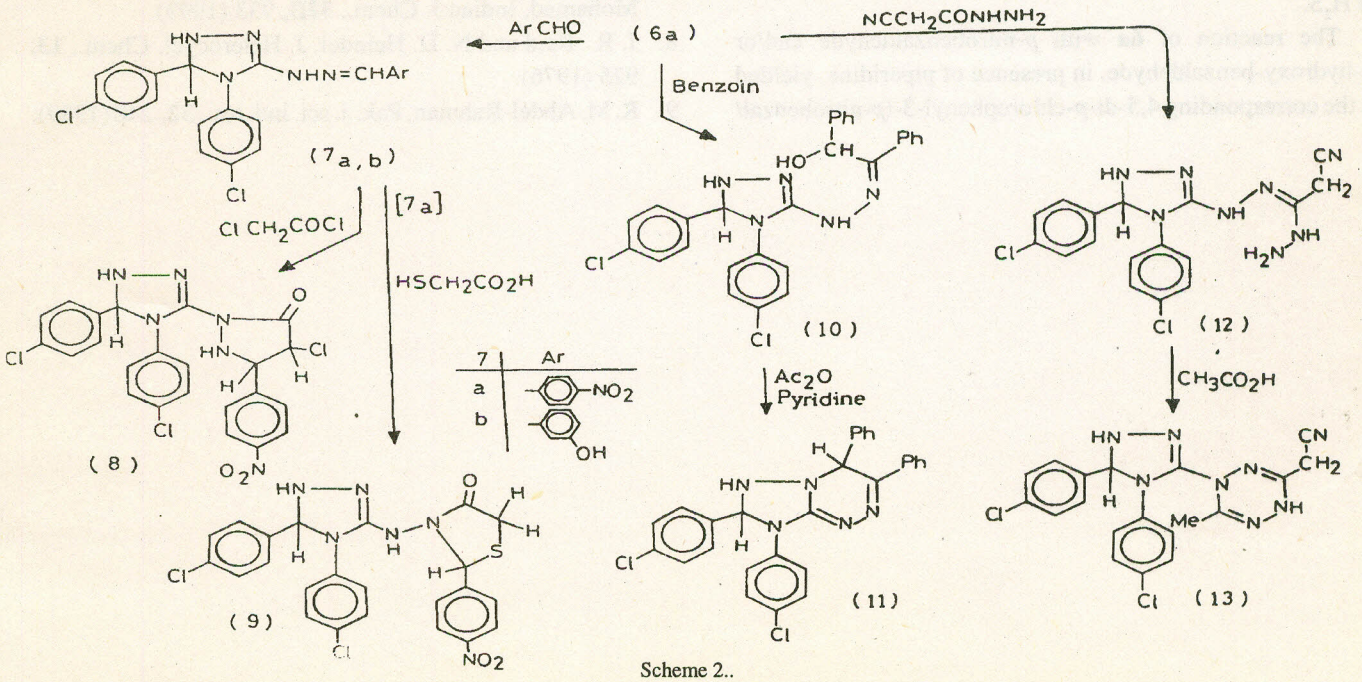
Benzoin 4, 5-di-p-chlorophenyl-Δ²-1, 2, 4-triazolin-3-ylhydrazone (10). A mixture of **6a** (0.01 mole), benzoin (0.015 mole) in ethanol (20 ml) was heated under reflux for 1 hr and diluted with cold water. The solid so obtained was filtered and crystallized to produce **10**. IR: υ_{max} 3450-2500 (H-bonded NH and OH groups), 1615 (C=N) and 710, 630 cm^{-1} (C-Cl).

2,3-Di-p-chlorophenyl-6, 7-diphenyl-1,2,3,7-tetrahydro-1, 2,4-triazolo (3,2-c)-1, 2,4-triazine (11). A mixutre of **10** (1 g), acetic anhydride (5 ml) and pyridine (5 ml) was refluxed for 2 hr, then cooled and poured into ice-dil. HCl (50 ml, 10%). The solid obtained was filtered and crystallized to produce **11.** IR: υ_{max} 3270 (NH), 1615 (C=N) and 710, 630 cm^{-1} (C-Cl). ^1H NMR: k 2.6 (s, 1H, 2-CH), 4.5 (s, 1H, 7-CH), 6.7-7.9 (m, 18H, Ar-H) and 8.7 ppm (s, 1H, NH).

Cyanoacetohyrazide 4, 5-di-p-chlorophenyl- Δ²-1, 2,4-triazolin-3-yl- hydrazone(12). A mixture of **6a** (0.01 mole) and cyanoacetohydrazide (0.01 mole) using the method des-cribed for synthesis of **10.** IR: υ_{max} 3390, 3200-3175 (NH_2 and NH groups), 2255 (CpN), 1620-1615 (C=N) and 710- 630 cm^{-1} (C-Cl).



Scheme 1.



Scheme 2..

1-[4',5'-p-Chlorophenyl-1',2'4'-triazolin-3'-yl]-3-cyano-methyl-6-methyl-1H,4H,-1,2,4,5-tetrazine (13). Compound **12** (0.01 mole) was heated under reflux with glacial acetic acid (50 ml) for 8 hr, then cooled and diluted with cold water. The solid so obtained was crystallized to give **13**. IR: υ_{max} 3250-3180 (NH), 2250 (C*p*N), 1615 (C=N) and 700-*p*-660 cm^{-1} (C-Cl). ^1H NMR : k2.25 (s, 3H, CH_3), 2.6 (s, 1H, 5'-CH), 3.1 (s, 2H, CH_2CN), 6.8- 7.8 (m, 8H, Ar-H) and 10.1-10.3 ppm (br, 2H, 2NH).

Results and Discussion

Addition of hydrobromic acid to Schiff bases **1a, b** in carbon tetrachloride gave rise to the corresponding *N*-(*p*-substituted phenyl) bromomethyl-*p*-substituted anilines **(2a,b)** as precursors for preparation of new triazole derivatives. The reaction of compounds **2a, b** with thiosemicarbazide and hydrazine in boiling ethanol furnished the corresponding 1-(*p*-substituted phenylamino) (p-substituted phenyl) methylthio-semicarbazides **(3a,b)** and (*p*-substituted phenyl-amino) (*p*-substituted phenyl) methylhydrazines **(4a,b).** Cylcization of *3a,b* using concentrated hydrochloric acid accompanied with split of an ammonia molecule led to the formation of 4,5-diaryl-5,1-dihydro-*s*-triazol-3-thiols **(5a,b),** which were also obtained *via* the reaction of the hydrazine derivatives **4a,b** with carbon disulphide in presence of alcoholic potassium hydroxide [8]. Compound 5 have reacted with hydrazine and phenylhydrazine affording the hydrazino and phenyl-hydrazino derivatives **6a, b,** respectively. This reaction may proceed *via* simple nucleophilic replacement of the thiol functional group at position-3 accomplished by evolution of H_2S.

The reaction of **6a** with *p*-nitrobenzaldehyde and/or *m*-hydroxy-benzaldehyde, in presence of piperidine, yielded in the corresponding 4,5-di-*p*-chlorophenyl-3-(*p*-nitrobenzal/*m*-hydroxybenzal) hydrazino-Δ^2-1,2,4-triazolines **(7a,b).** Compound **7a** reacted with chloroacetyl-chloride in presence of triethylamine, in benzene, giving rise to the pyrazolidinyltriazoline **8** [9], while the reaction of **7a** with thioglycolic acid, in dry benzene, afforded the thiazolidinyl-aminotriazoline derivative **9**. The condensation of **6a** with benzoin in presence of glacial acetic acid, using ethanol as medium, gave the hydrazone **(10)** which when refluxed in a mixture of acetic anhydride and pyridine, furnished 2,3-di-*p*-chlorophenyl-6,7-diphenyl-1,2,3,7-tetrahydro-1,2,4-triazolo [3,2-c]-1,2,4,-triazine **(11),** while the condensation of **6a** with cyanoaceto-hydrazide in boiling ethanol afforded the acetohydrazide hydrazone **(12)** [9], which readily cyclized in boiling glacial acetic acid to produce 1-(4',5'-diaryl-1', 2', 4'- triazolin-3'-yl)-3-cyanomethyl-6-methyl-1H, 4H-1, 2,4,5-tetrazine **(13).**

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