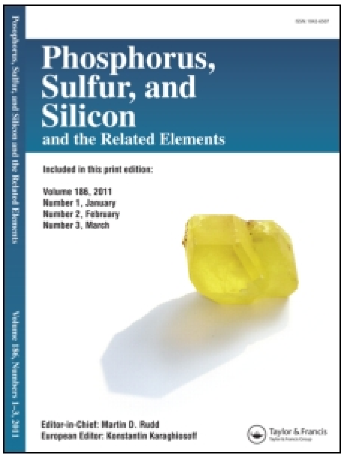

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SYNTHESIS OF SOME FUSED HETEROCYCLES CONTAINING 2,5-DISUBSTITUTED-1,3,4-THIADIAZOLES

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SYNTHESIS OF SOME FUSED HETEROCYCLES CONTAINING 2,5-DISUBSTITUTED-1,3,4-THIADIAZOLES

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The synthesis of some novel fused heteracyclic compounds such as 1,3,4-thiadiazolo[3,2-*b*]diazepine, indenothiadiazolopyrimidine, indenocyclopentathiadiazole and naphthoquinoimidazolothiadiazole derivatives containing 1,3,4-thiadiazole ring system have been reparted.

Keywords: 2,5-Disubstituted-1,3,4-thiadiazoles; π-acceptors; fused heterocyclic compounds

Numerous reports have appeared in the literature describing the biological activities[1–14] and medicinal[15,16] as well as industrial[17,18] applications of 1,3,4-thiadiazoles, when positions 2- and 5 are substituted.

Because of the above-mentioned useful applications of 1,3,4-thiadiazole derivatives, several reports have described the synthesis of 2,5-disubstituted-1,3,4-thiadiazoles[19–24].

Recently the synthesis of 2-amino-5-aryl-, and 2-amino-5-methylthio-1,3,4-thiadiazoles by cyclization of azomethine derivatives of thiosemicarbazide[25], and S-methyldithiocarbazate[26,27] with some π-acceptors has been reported.

In the present contribution, the results of our studies on the reactivity of 5-amino-3H-1,3,4-thiadiazole-2-thione(1a) and 5-methyl-3H-1,3,4-thiadiazole-2-thione(1b) towards some π-acceptors, are reported.

Treatment of 1a with tetracyanoethylene (TCNE) gave 1,3,4-thiadiazolo[3,2-*b*]diazepine derivative 2 (Scheme 1) which has been assigned on the basis of the

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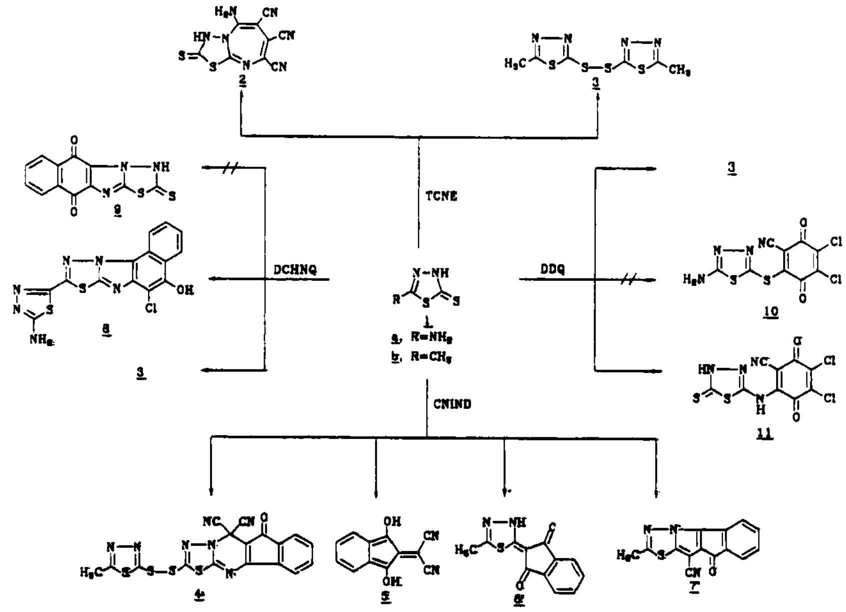

SCHEME 1

results of combustion analysis and spectral data (Tables I and II). From the elemental analysis the gross formula $C_9H_3N_7S_2$ was deduced. This was confirmed also by the mass spectrum which exhibited a molecular ion at m/z 273 (23%). The IR spectrum showed absorptions at 3350–3140 and 2220 cm^{-1} (NH_2 and CN respectively). The ^{1}H-NMR (DMSO-d_6) spectrum had a broad singlet at 7.70 ppm (NH_2) and 1-H resonance at 13.20 ppm for thiadiazole-NH. These results suggested that compound 2 was formed as a result of the reaction between 2-amino-1,3,4-thiadiazole 1a and the intermediate pentacyanopropene with the loss of HCN. It is worth noting that the intermediate pentacyanopropene was formed during the interaction of two molecules of TCNEH in the presence of H_2[28] with elimination of one molecule of malononitrile and of HCN.

Addition of one mole each of thiadiazoles 1a and 1b to twofold molar amount of 2-(dicyanomethyleneindane-1,3-dione)(CNIND) in ethyl acetate and DMF at room temperature afforded the predominant products, 2-substituted-indenothiadiazolopyrimidine derivative 4 and 2-(indane-1,3-dionyl)-3H-5-methyl-1,3,4-thiadiazole 6, in addition to two minor compounds, 1,3-dihydroxy-2H-(inden-2-ylidene) malonodinitrile 5 and indenocyclopentathiadiazole 7 (Scheme 1).

TABLE I The ^{1}H-NMR, IR and mass spectra of compounds 2–4, 6–8 and 11

Compound	*H-NMR(δ, TMS) ([D$_6$]DMSO)*	*IR(KBr, Cm^{-1})*	*MS m/z (rel. intensity %)*
2	7.70(br, 2H, NH$_2$); 13.20(br, 1H, thiadiazole-NH).	3350, 3260, 3140(NH, NH$_2$), 2220(CN), 1485, 1475, 1365, 1325(C=S).	273(23, M$^+$), 247(41), 181(76), 167(22), 133(92), 120(48), 92(100).
3	2.50(s, 6H, 2CH$_3$).	2190(Ali-CH), 1610(C=N).	264(10, M^{+2}), 232(24), 189(33), 131 (100), 99(71).
4	7.00–8.20(m, 6H, Ar-H and NH$_2$).	3390–3200(NH$_2$), 2210(CN), 1720, 1700, 1680(CO), 1620 (Ar-C=C).	455(4, M^{+1}), 389(11), 354(100), 327 (61), 326(82). 299(36), 271(38), 243 (36), 210(94), 104(88), 76(79).
6	2.50(s, 3H, CH$_3$), 7.30–8.22 (m, 4H, Ar-H), 11.50(br, 1H, thiadiazole-NH).	3380–3190(NH$_2$), 1710, 1680(CO), 1620(Ar-C=C).	244(100, M$^+$), 210(32), 154(24), 104 (36), 76(38).
7	2.48(s, 3H, CH$_3$), 7.50–8.26 (m, 4H, Ar-H).	2210(CN), 1710(CO), 1620 (Ar-C=C).	265(5, M$^+$), 262(18), 230(54), 189(37), 132(76), 104(33), 99(100).
8	7.10–7.90(m, 6H, Ar-H and NH$_2$), 8.64(br, 1H, OH).	3460–3170(OH, NH$_2$), 1640, 1590(Ar-C=C).	375/377(66, M$^+$), 348(12), 284(31), 247(81), 230(49), 220(54), 188(79), 104(100).
11	8.67(br, 1H, NH), 13.20(br, 1H, thiadiazole-NH).	3440–3210(NH), 2220(CN), 1690(CO).	333/337(17, M$^+$), 256(32), 224(22), 192(34), 132(100).

Compounds 1a,b were treated with 2,3-dichloro-1,4-naphthoquinone (DCHNQ) in presence of DMF aiming to synthesize naphthoquinoimidazothiadiazole derivative 9 (Scheme 1). To our great surprise, however, we isolated 2-aminothiadiazolo-(naphthoquinoimidazothiadiazole) derivative 8. Whereas the reaction between DDQ and 2-amino-1,3,4-thiadiazole 1a gave a product of the molecular formula $C_9H_2Cl_2N_4S_2O_2$(m/z 333/337). Structures 10 and 11 are suggested for the reaction product. Structure 10 was readily excluded due to the presence of thiadiazole-NH and NH-attached to 1,4-benzoquinone system at 13.20 and 8.78 ppm respectively (see Tables I and II). These signals are difficult to interpret in terms of NH_2 attached to thiadiazole ring[29].

The formation of 2,4,8 and 11 in the reaction of 1a with TCNE, CNIND, DCHNQ and DDQ respectively, reveals the participation of the amino group in 1a in the course of the reaction. On the other hand, 1b can dimerizes in the

TABLE II Physical and Analytical Data for Compounds 2–4, 6–8 and 11

Compound	*m.p. 0°C*	*Yield (%)*	*Colour of crystals*	*Solvent of recrystallization*	*Mol. Formula (M. Wt.)*	*Analysis C*	*% Found H*	*(Calcd.) N*	*S*	*Cl*
2	252–254	64	Pale yellow	Acetonitrile	$C_9H_3N_7S_2$	39.38	1.27	36.11	23.61	
					(273.302)	(39.55	1.11	35.87	23.47)	
3	>360	71	Pale Yellow	Acetonitrile	$C_6H_6N_4S_4$	27.21	2.52	21.51	49.12	
					(262.404)	(27.46	2.30	21.35	48.88)	
4	323–325	61	Yellow	DMF/EtOH	$C_{16}H_6N_8S_4O$	42.11	1.46	24.53	28.38	
					(454.540)	(42.28	1.33	24.65	28.22)	
6	264–266	56	Pale yellow	Ethanol	$C_{12}H_8N_2O_2S$	58.81	3.48	11.28	12.96	
					(244.273)	(59.00	3.30	11.47	13.13)	
7	305–307	11	Pale Yellow	Methanol	$C_{14}H_7N_3OS$	63.24	2.76	16.11	11.84	
					(265.295)	(63.38	2.66	15.84	12.09)	
8	272–274	63	Blue	DMF/EtOH	$C_{14}H_7ClN_6OS_2$	45.12	1.63	22.61	16.92	9.59
					(374.834)	(44.86	1.88	22.42	17.11	9.46)
11	205–207	55	Yellow	Methanol	$C_9H_2Cl_2N_4S_2O_2$	32.58	0.69	17.12	19.39	21.44
					(333.178)	(32.44	0.61	16.82	19.25	21.28)

presence of TCNE, DDQ and DCHNQ, or dimerization and extrusion of sulphur took place easily to react with CNIND with elimination of a molecule of HCN or $H_2C(CN)_2$.

Experimental

All melting points are uncorrected. The IR spectra were recorded on Shimadzu 470 spectrophotometer. The ^{1}H-NMR spectra were obtained with a Bruker AC 200 (200 MHz) spectrometer using TMS as an internal standard, chemical shifts are expressed in ppm. Mass spectra were scanned on a Finnigan MAT 8430 spectrometer at 70 eV. Microanalyses were carried out by the Microanalytical centre at Cairo University. The purity of the compounds was monitered by thin layer chromatography (TLC) performed on silica gel plates (PF 254, Merck) using toluene/ethyl acetate as the eluent.

Materials

5-Amino-3H-1,3,4-thiadiazole-2-thione 1a was prepared according to the literature[23]. 5-Methyl-3H-1,3,4-thiadiazole-2-thione 1b (Merck). Tetracyanoethylene (TCNE, Merck); 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, Aldrich); 2,3-dichloro-1,4-naphthoquinone (DCHNQ, Merck) and dicyanomethylene-indane-1,3-dione prepared according to the literature[30].

1- Synthesis of 1,3,4-thiadiazolo[3,2-*b*]diazepine derivative 2

To a stirred solution of 256 mg TCNE (0.002 mol) in 10 ml of dry ethyl acetate, a solution of 133 mg of 1a (0.001 mol) in 15 ml of dry ethyl acetate was added at room temperature. The mixture was stirred for 5h., and then allowed to stand for 72 h., during which time, pale yellow crystals were separated. The resulting solid material was filtered, washed with cold ethanol, dried and recrystallized from suitable solvent to give 1,3,4-thiadiazolo-[3,2-*b*]diazepine 2.

2- Synthesis of 2,2-(5-methyl-1,3,4-thiadizole) disulphide 3

A solution of 132 mg of 1b (0.001 mol) in 10 ml of DMF was added to a solution of TCNE, 256 mg (0.002 mol) in 5 ml DMF. The reaction mixture was stirred for 48 h. at room temperature, concentrated and the residue was then chromatographed on TLC using toluene/ethyl acetate (3:1) as eluent to give only one zone contained the disulfide 3.

3- Synthesis of 2-substituted indenothiadiazolopyrimidine derivative 4, 2-(indane-1,3-dionyl)-3H-5-methyl-1,3,4-thiadiazole 6 and indenocyclopentathiadiazole derivative 7

To a stirred solution of 416 mg (0.002 mol) of CNIND in 10 ml of DMF, 1a,b (0.001 mol) in 5 ml of DMF were added at room temperature, and the stirring was continued for 48h. In case of the reaction of 1a, yellow crystals of indenothiadiazolopyrimidine derivative 4 were precipitated. Concentration of the filtrate and chromatographic purification of the residue using toluene/ethyl acetate (5 : 1) gave 1,3-dihydroxy-2H-(inden-2-ylidene) malonodinitrile 5 (13%)[31]. In the case of the reaction with 1b, concentration and chramatographic purification of the reaction mixture on TLC using toluene/ethyl acetate (3 : 1) afforded two zones, the fastest migrating one contained indan-1,3-dionyl-1,3,4-thiadiazole 6. The second zone contained indencyclopentathiadiazole derivative 7.

4- Synthesis of naphthoquinoimidazolothiadiazole derivative 8

To a stirred solution of 454 mg (0.002 mol) of DCHNQ in 10 ml DMF, the thiadiazoles 1a,b (0.001 mol) in 5 ml DMF were added at room temperature. After standing 48h., the crystals of naphthoquinoimidazolothiadiazole were precipitated, in the case of the reaction with 1a. In the case of the reaction with 1b, concentration and chromatographic separation of the reaction mixture on TLC using toluene/ethyl acetate (3 : 1) gave the disulfide 3.

5- Synthesis of 2-thiadiazoloamino-3-cyano-5,6-dichloro-1,4-benzoquinone derivative 11

To a solution of DDQ, 340.5 mg (0.0015 mol) in 15 ml of dry ethyl acetate, a solution of 1a–b (0.001 mol) in 20 ml of dry ethyl acetate was added, and the reaction mixture was stirred for 24h. at room temperature. In the case of the reaction between 1a and DDQ, the reaction mixture was concentrated and the residue was then chromatographed on TLC using toluene/ethyl acetate (4 : 1) as eluent, only one zone was well separated, containing compound 11. In the case of 1b, pale yellow crystals were precipitated containing the disulfide 3 (66%).

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