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SYNTHESIS OF SOME NEW FUSED AND POLYFUSED [1,2,4]TRIAZOLO-[3,4-*b*][1,3,4]THIADIAZEPINES

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7-[1,3-Dithiolan-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine-6,8-dione and 7-[5-oxo-1,3-dithiolan-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazepine-6,8-diones were obtained by treating 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazepine-6,8-diones with CS_2 and chloroacetyl chloride, respectively. Treatment of the above compounds with mercaptoacetic acid gave 1,2-dibromoethane or the corresponding spiro polyfused heterocycles. Some other triazolothiadiazepine derivatives including spiro polyfused compounds were also synthesized.

Keywords: 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines, spiro compounds.

The synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines had been thoroughly studied and developed because of their important characteristics as antimicrobial and antibacterial agents [1-3]. From this point and starting with 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione first prepared by the author in [3], the synthesis of new polyfused compounds was the objective of this research.

One-pot reaction of 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazepine-6,8-dione (**1**) [3] with equimolar ratios of CS_2, dihalo compounds (1,2-dibromoethane or chloroacetyl chloride), and a double molar amount of NaOH gave compounds **2** or **3**, respectively (Scheme 1). The reaction pathway was postulated to proceed through a nucleophilic addition of the active methylene group in compound **1** at the carbon disulfide molecule to get the intermediate disodium dithiocarbamate **A**, which in turn was cyclized with 1,2-dibromoethane or chloroacetyl chloride, yielding 7-[1,3-dithiolan-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**2**) and 7-[1,3-dithiolane-5-oxo-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**3**). With the same reaction mechanism and also in one-pot reaction under solid-liquid phase-transfer catalysis (PTC) [DMF–K_2CO_3–tetrabutylammonium bromide (TBAB)], compound **1** was treated with an equimolar ratio of phenylisothiocyanate or phenylisocyanate and 1,2-dibromoethane, affording compounds **4a**,**b**, respectively (Scheme 1, Table 1).

Spiro-polyfused derivatives **5** or **6** were prepared through nucleophilic addition of mercaptoacetic acid at the activated ethylenic double bond in compounds **2** or **4**, respectively. The reaction proceeds *via* a nucleophilic attack of the SH group of mercaptoacetic acid at the ethylenic double bond in compounds **2** or **3** followed by intramolecular cyclization through H_2O elimination to yield the condensed products **5** or **6**. The IR and ^1H NMR spectral data were consistent with the proposed structures (cf. Scheme 1). The

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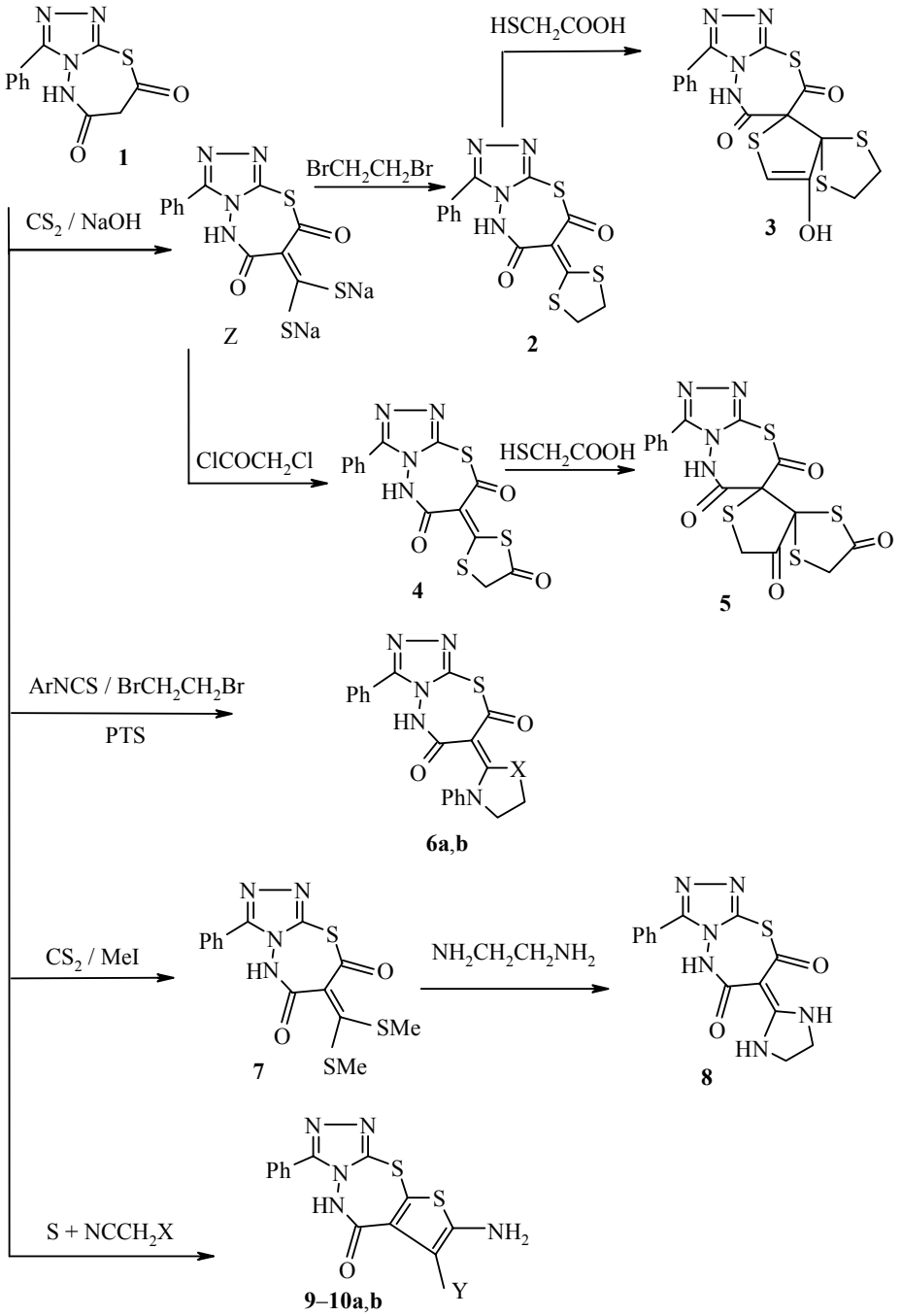
dithiomethylmethylene derivative **7** was prepared by the reaction of compound **1** with an equimolar ratio of CS_2 and with a double molar amount of both NaOH and methyl iodide. Compound **7** was used as a key intermediate in the preparation of heterocyclic system by the reaction with ethylenediamine to afford the corresponding 7-[1,3-imidazolo-2-ylidene-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione] (**8**) (cf. Scheme 1, Table 1).

Scheme 1



6 a X = S, **b** X = O; **9** X,Y = COOEt; **10 a** X,Y = CN, **b** X,Y = $CONH_2$

TABLE 1. Analytical and Spectral Data of the New Compounds

Compound	mp, °C* (cryst. solvent)	Empirical formula (M_w)	Found, %*[2] / Calculated, %				IR (KBr), ν (cm^{-1})*[3]	^{1}H NMR (DMSO-d_6)*[4], δ, ppm (*J*, Hz)	Yield, %
			C	H	N	S			
1	2	3	4	5	6	7	9	10	11
2	201 DMF–H_2O	$C_{14}H_{10}N_4O_2S_3$ (362.45)	46.50 / 46.39	2.87 / 2.78	15.37 / 15.46	26.60 / 26.54	3220 (NH); 3062, 2924 (CH); 1710, 1654 (2C=O)	8.00 (1H, s, NH); 7.50-6.65 (5H, m, arom.); 3.59-3.10 (2H, t, *J* = 6, CH_2); 2.86-2.53 (2H, t, *J* = 6, CH_2)	79
3	220 DMF–H_2O	$C_{14}H_8N_4O_3S_3$ (376.44)	44.60 / 44.67	2.23 / 2.14	14.80 / 14.88	25.63 / 25.55	3210 (NH); 3050, 2926 (CH); 1710, 1700, 1652 (3C=O)	8.15 (NH); 7.50-6.41 (5H, m, arom.); 2.81-2.52 (2H, d, *J* = 6, CH_2)	69
4a	160 DMF–H_2O	$C_{20}H_{15}N_5O_2S_2$ (421.51)	57.21 / 56.99	3.69 / 3.59	16.74 / 16.62	15.30 / 15.21	3260 (NH); 3030, 2932 (CH);1715, 1658 (2C=O)	7.88 (NH); 7.51-6.31 (10H, m, arom.); 2.80 (2H, t, *J* = 2.4, CH_2); 2.70-2.61 (2H, t, *J* = 1.2, CH_2)	60
4b	219 DMF–H_2O	$C_{20}H_{15}N_5O_3S$ (405.44)	59.37 / 59.25	3.80 / 3.73	17.30 / 17.27	7.80 / 7.91	3300 (NH); 3057, 2935 (CH); 1710, 1653 (2C=O)	7.75 (NH); 7.40-6.10 (10H, m, arom.); 2.81-2.70 (2H, t, *J* = 6, CH_2); 2.65-2.58 (2H, t, *J* = 6, CH_2)	53
5	142 DMF–H_2O	$C_{16}H_{12}N_4O_3S_4$ (640.83)	30.16 / 29.99	2.00 / 1.89	8.80 / 8.74	20.12 / 20.01	3421 (OH); 3200 (NH); 3030, 2924 (CH); 1710, 1632 (2C=O)	7.52 (NH); 7.20-6.65 (5H, m, arom.); 3.70 (1H, s, CH); 3.31-2.91 (3H, t, *J* = 8.4, CH_2); 2.90-2.41 (3H, t, *J* = 7.2, CH_2); 1.14 (1H, s, OH)	68
6	300 DMF–H_2O	$C_{16}H_{10}N_4O_4S_4$ (450.54)	42.85 / 42.66	2.20 / 2.24	12.40 / 12.44	28.60 / 28.47	3210 (NH); 3066, 2924 (CH); 1730, 1700, 1642 (4C=O)	7.85 (NH); 7.68-6.60 (5H, m, arom.); 3.00-2.58 (4H, d, *J* = 2.4, CH_2)	72
7	300 DMF–H_2O	$C_{14}H_{12}N_4O_2S_3$ (364.47)	46.15 / 46.14	3.25 / 3.32	15.41 / 15.37	26.30 / 26.39	3320 (NH); 3030, 2960 (CH); 1710, 1650 (2C=O)	7.62 (NH); 7.52-6.60 (5H, m, arom.); 2.76 (3H, s, CH_3); 2.58 (3H, s, CH_3)	81
8	>300 DMF	$C_{14}H_{12}N_6O_2S$ (328.35)	51.42 / 51.21	3.60 / 3.68	25.52 / 25.59	9.80 / 9.77	3423, 3270 (NH); 3033, 2926 (CH); 1725, 1637 (2C=O)	7.50 (1H, s, NH); 7.10-6.31 (5H, m, arom.); 4.21 (2H, s, 2NH), 2.30-2.50 (4H, t, *J* = 7.2, $2CH_2$)	78

TABLE 1 (continued)

1	2	3	4	5	6	7	9	10	11
9	244 dioxane	$C_{16}H_{13}N_5O_2S_2$ (387.44)	50.06 49.60	3.56 3.38	18.72 18.07	17.11 16.55	3480, 3400 (NH_2); 3225 (NH); 3080, 2941 (CH); 1725, 1634 (2C=O)	9.8 (1H, s, NH); 7.42-6.62 (5H, m, arom.); 4.45-3.61 (2H, br, NH_2); 3.30-2.61 (2H, q, CH_2); 1.43-0.70 (3H, t, CH_3)	83
10a	>300 dioxane	$C_{14}H_8N_6OS_2$ (340.39)	49.63 49.40	2.28 2.37	24.61 24.69	18.73 18.84	3439, 3330 (NH_2); 3230 (NH); 3033 (CH); 2203 (CN); 1641 (C=O)	8.80 (1H, s, NH); 8.00-6.95 (5H, m, arom.); 4.65-4.15 (2H, br, NH_2)	79
10b	>300 dioxane	$C_{14}H_{10}N_6O_2S_2$ (358.40)	46.75 46.92	2.80 2.81	23.51 23.45	17.98 17.89	3500, 3400 (NH_2, $CONH_2$); 3020 (CH); 1640, 1635 (2C=O)	8.12 (1H, s, NH); 7.75-6.65 (5H, m, arom.); 5.00-4.23 (4H, br, $2NH_2$)	85
11	310 dioxane	$C_{13}H_{12}N_6O_3S$ (332.36)	47.34 46.98	3.40 3.64	25.30 25.29	9.70 9.65	3420, 3332 (NH_2); 3239, 3191 (2NH); 1720, 1629 (3C=O)	8.10 (1H, s, NH); 8.00-7.00 (5H, m, arom.); 4.70-4.00 (3H, br, NH+NH_2); 2.80 (1H, s, CH); 2.71 (2H, s, CH_2)	68
12	320 DMF–H_2O	$C_{14}H_{10}N_6O_3S_2$ (374.40)	45.10 44.91	2.83 2.69	22.34 22.45	17.00 17.13	3322, 3300 (2NH); 3050, 2963 (CH); 1715, 1630 (2C=O); 1120 (C=S)	8.18-7.90 (1H, br, NH); 7.48-6.60 (5H, m, arom.); 5.53 (1H, s, NH); 2.71 (1H, s, CH_2); 2.41 (2H, s, CH_2)	59
13	>300 DMF	$C_{14}H_{12}N_4O_3S$ (316.34)	53.34 53.16	3.80 3.82	17.80 17.71	10.20 10.14	3439 (NH); 3130, 2990 (CH); 1720, 1645 (2C=O)	8.10 (1H, s, NH); 7.22-6.19 (5H, m, arom.); 4.00 (1H, s, CH); 3.92-3.09 (2H, q, J = 18, CH_2); 1.30-0.91 (3H, t, J = 7.2, CH_3)	56
14	230 DMSO	$C_{12}H_{10}N_6O_2S$ (292.32)	49.53 49.31	4.06 4.14	19.36 19.17	11.00 10.97	3317, 3217 (NH_2), 3195 (2NH); 1710, 1631 (2C=O)	8.59 (1H, s, NH); 7.32-6.90 (5H, m, arom.); 2.53 (1H, s, CH); 4.20-3.62 (2H, br, NH_2)	60
15	>300 DMSO	$C_{13}H_{10}N_6O_2S_3$ (378.46)	41.45 41.26	2.60 2.66	22.30 22.21	25.41 25.42	3419-3390 (3NH); 3050, 2992 (CH); 1700, 1631 (2C=O); 1060 (C=S)	8.00 (2H, s, 2NH); 7.41-6.80 (5H, m, arom.); 4.11 (1H, s, NH)	61

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
16	>300 DMF–H_2O	$C_{14}H_6N_6O_2S$ (322.31)	52.17 52.17	1.79 1.88	26.26 26.07	10.00 9.95	3441 (NH); 3080 (CH); 2197, 2189 (2CN); 1700, 1637 (C=O)	8.20 (1H, s, NH); 7.35-6.57 (5H, m, arom.)	57
17a	>300 DMF–H_2O	$C_{14}H_{10}N_8O_2S$ (354.36)	47.71 47.38	2.64 2.84	31.70 31.57	9.00 9.03	3427-3280 (4NH); 3060, 2910 (CH); 2189 (CN); 1700, 1650 (2C=O)	8.15 (1H, s, NH); 7.42-6.18 (5H, m, arom.); 3.92 (1H, s, NH); 3.11 (1H, s, NH); 2.88 (1H, s, CH); 2.18 (1H, s, NH)	70
17b	240 DMF–H_2O	$C_{20}H_{14}N_8O_2S$ (430.45)	55.83 55.81	3.15 3.28	26.00 26.03	7.60 7.45	3427, 3300, 3280 (3NH); 3048, 2928 (CH); 2193 (CN); 1710, 1655 (2C=O)	8.82 (1H, s, NH); 7.51-6.32 (10H, m, arom.); 2.90 (1H, s, NH); 2.76 (1H, s, NH); 2.57 (1H, s, CH)	68
18	216 DMF–H_2O	$C_{16}H_{10}N_6O_4S_2$ (414.42)	46.50 46.37	2.49 2.43	20.37 20.28	15.33 15.47	3510 (OH); 3427, 3360 (NH_2, NH); 3050, 2920 (CH); 2193 (CN); 1710, 1700, 1640 (3C=O)	8.30 (1H, s, NH); 7.41-6.65 (5H, m, arom.); 4.81-4.22 (2H, br, NH_2); 2.68 (1H, s, CH); 1.21 (1H, s, OH)	59
19	dec. 290 dioxane	$C_{22}H_{13}N_7O_3S$ (457.47)	58.00 57.76	3.00 2.86	21.45 21.43	7.00 7.01	3425, 3325 (NH_2, 2NH); 3060, 2991 (CH); 2187 (CN); 1630 (2C=O)	8.84 (1H, s, NH); 7.82-6.70 (9H, m, arom.); 5.10-4.22 (2H, br, NH_2); 3.85 (1H, s, NH)	76
20	300 dioxane	$C_{21}H_{13}N_7O_2S_2$ (459.51)	55.00 54.89	2.76 2.85	21.25 21.34	13.81 13.96	3445-3365 (3NH); 3060, 2936 (CH); 2199 (CN), 1629 (C=O)	8.45 (1H, s, NH); 7.78-6.72 (9H, m, arom.); 3.68 (1H, s, NH); 3.00 (1H, s, NH); 2.55 (1H, s, CH)	79
21	178 dioxane	$C_{21}H_{15}ClN_6O_3S$ (466.96)	54.15 54.02	3.35 3.24	18.00 18.00	6.69 6.87	3500 (2NH); 3448, 3348 (NH_2); 3150, 2950 (CH); 1685, 1640 (2C=O); 770 (C-Cl)	8.50 (1H, s, NH); 8.00-7.98 (9H, m, arom.); 6.00 (2H, br, NH_2); 4.00 (1H, s, NH); 3.55 (1H, d, J = 1.2, CH); 3.12 (1H, d, J = 6, CH)	81

* Uncorrected.

*[2] Satisfactory microanalyses; obtained C ± 0.35%; H ± 0.11%; N ± 0.40%; S ± 0.21%.

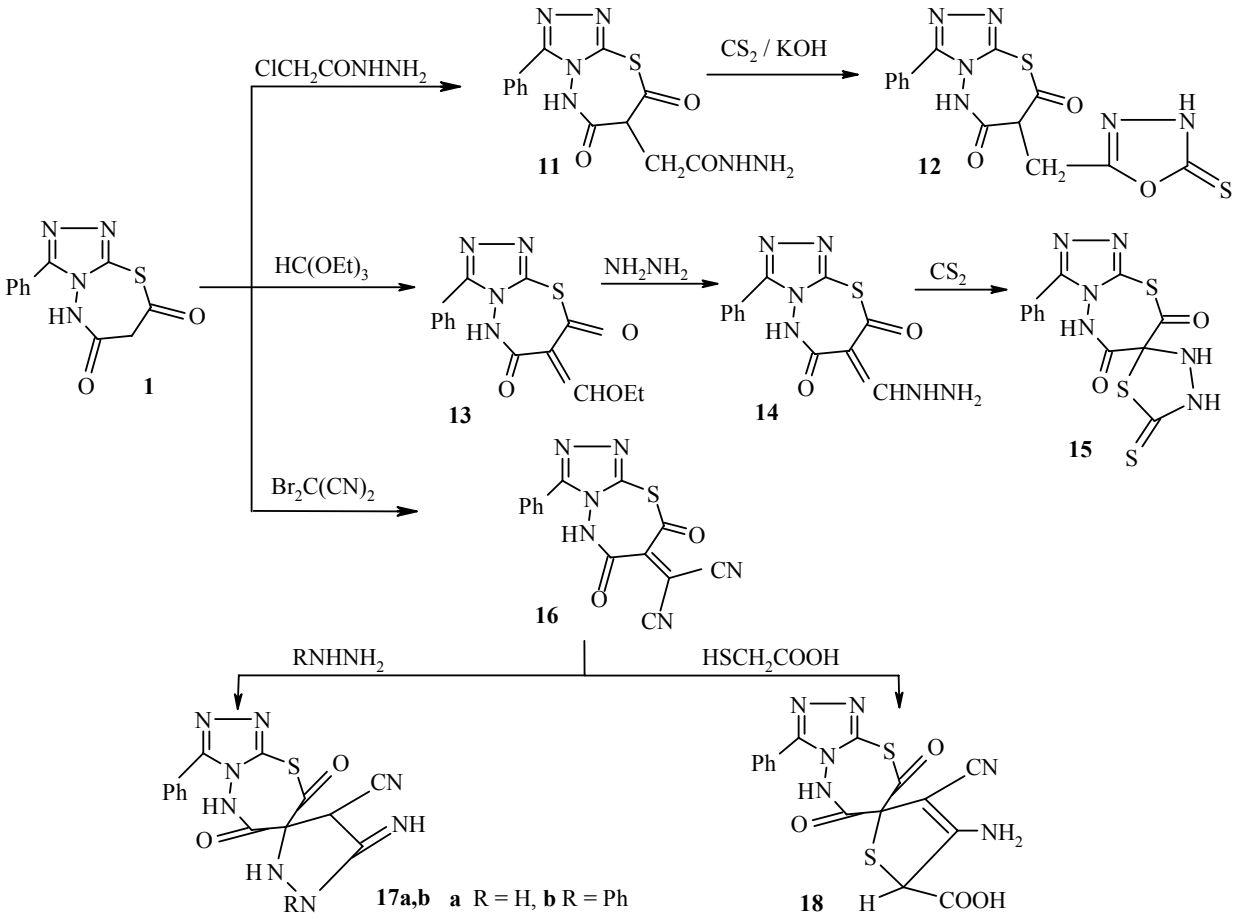
*[3] Measured on a Nicolet 710 FT-IR spectrophotometer.

*[4] Measured with a Varian EM 360L spectrometer at 60 MHz using TMS as an internal standard.

According to the Gewald reaction in the synthesis of numerous 2-aminothiophenes [4-6] by using one-pot procedure, compound **1** reacted with sulfur and activated nitriles, namely, ethyl cyanoacetate, malononitrile, or cyanoacetamide in DMF and in the presence of Et_3N as a catalyst at room temperature yielding thiophenotriazolothiadiazepine derivatives **9**, **10a**,**b**, respectively. (cf. Scheme 1).

6,8-Dioxo-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-7-acetohydrazide (**11**) was prepared by the reaction of compound **1** with chloroacetohydrazide and catalytic amount of Et_3N in boiling dioxane. Compound **11** was allowed to react with CS_2 and KOH to yield 3-phenyl-7-(5-thioxo-1,3,4-oxadiazol-2-ylmethylene)-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**12**) (cf. Scheme 2).

Scheme 2



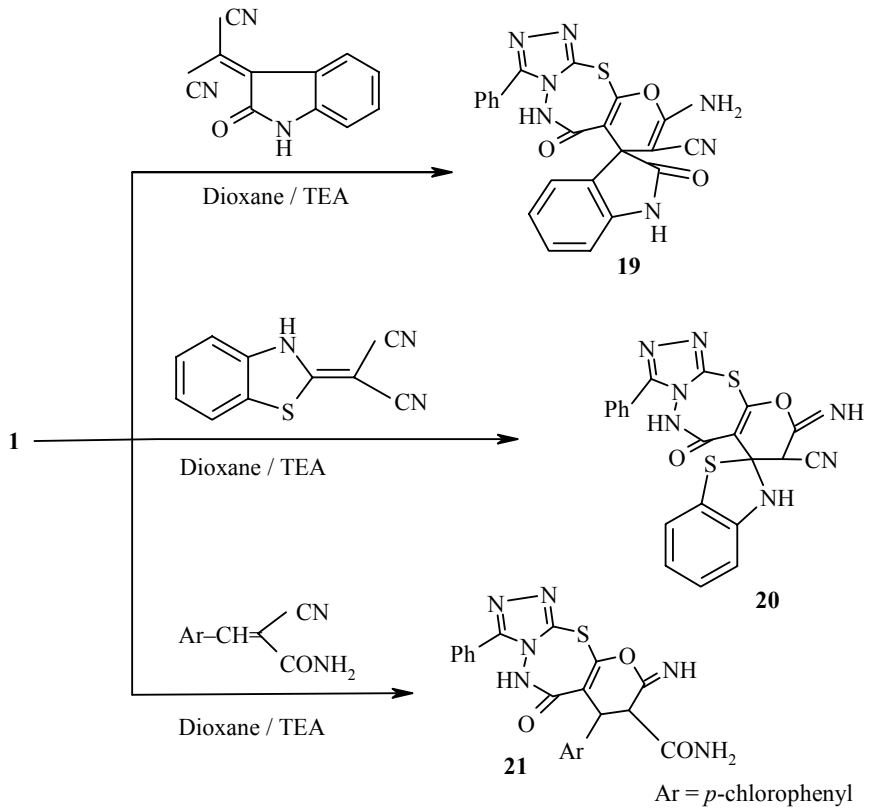
7-[Ethoxymethylene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*]-[1,3,4]-thiadiazepine-6,8-dione (**13**) was prepared in excellent yield through the condensation of compound **1** with ethyl orthoformate *via* the elimination of two EtOH molecules. The corresponding hydrazino derivative **14** was prepared by treating compound **13** with hydrazine hydrate. The product was cyclized with CS_2 through nucleophilic attack of the NH_2 group at CS_2 to form the SH group which in turn underwent a nucleophilic addition at the ethylenic double bond, yielding the spiro polyfused thiadiazolotriazolothiadiazepine derivative **15** in excellent yield.

6,8-Dioxo-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-7-ylidenemalononitrile (**16**) was obtained by treating compound **1** with dibromomalononitrile and double moles of Et_3N. The IR spectrum of this compound showed the presence of the adsorption bands corresponding to 2CN groups at 2197 and 2189 cm^{-1} (Scheme 2).

The spiro polyfused pyrazolotriazolothiadiazepine derivatives **17a**,**b** and thiophenotriazolothiadiazepine **18**, respectively, were prepared *via* the addition reaction of hydrazine hydrate, phenylhydrazine, or mercaptoacetic acid at the activated ethylenic double bond in compound **16** (cf. Scheme 2).

The active methylene group in compound **1** underwent a nucleophilic addition reaction at different activated ethylenic double bonds, namely, 2-oxo-2,3-dihydroindolylidenemalononitrile, benzothiazolidene-nitrile, or *p*-chlorobenzylidenecyanoacetamide in boiling dioxane and catalytic amount of Et_3N to yield a new series of pyranotriazolothiadiazepine derivatives **19-21**, respectively (cf. Scheme 3). The reaction pathway was suggested to proceed *via* the addition of the active CH_2 group of compound **1** to the activated double bond of ylidenenitrile to yield the intermediate Michael adduct which was cyclized through the addition of the OH group at the cyano group. IR spectra of products **19-21** showed characteristic bands corresponding to NH_2 (3320-3450), NH (3500-3425) and CN (2199-2187). ^{1}H NMR spectra of the products are in agreement with the proposed structure.

Scheme 3



EXPERIMENTAL

Synthesis of Compounds 2, 3 (General Procedure). A mixture of compound **1** (0.01 mol), CS_2 (0.01 mol), and NaOH (0.02 mol in 10 ml of water) in DMF (30 ml) was stirred for 4 h, 1,2-bromoethane or chloroacetyl chloride (0.01 mol) was added dropwise, and the mixture was stirred again for 4 h and poured into ice-cold water (300 ml). The resulting solid mass was filtered off, washed with water successively, dried, and recrystallized from the proper solvent.

Synthesis of Compounds 5, 6 (General Procedure). A mixture of compound **2** or **3** (0.01 mol) and mercaptoacetic acid (0.01 mol) in DMF (20 ml) was refluxed for 3 h. The reaction mixture was poured into cold water (200 ml). The separated product was filtered off, dried, and crystallized from the suitable solvent.

Synthesis of Compound 4a,b (General procedure). A mixture of anhydrous potassium carbonate (4 g), compound **1** (0.01 mol), and a catalytic amount of TBAB in DMF (20 ml) was treated with phenyl isothiocyanate or phenyl isocyanate (0.01 mol) and stirred for 1 h at room temperature. 1,2-Dibromoethane (0.01 mol) was added, and the mixture was stirred for an additional 4 h at room temperature. The reaction mixture was filtered, and the filtrate was added to ice-cold water (100 ml). The separated solid was filtered off and crystallized from the proper solvent.

Synthesis of Compound 7. A mixture of compound **1** (0.01 mol) in DMF (20 ml), CS_2 (0.01 mol), and NaOH (0.023 mol in 10 ml water) was stirred for 4 h. CH_3I (0.02 mol) was added, and the reaction mixture was stirred for an additional 4 h and poured into ice-cold water (200 ml). The precipitate was filtered off, dried, and crystallized from DMF–H_2O.

Synthesis of Compound 8. Ethylenediamine (0.002 mol) was added to a solution of compound **7** (0.002 mol) in DMF (20 ml). The reaction mixture was stirred at room temperature until the evolution of MeSH ceased. The reaction mixture was poured into ice-cold water (200 ml), and the separated solid was collected by filtration and crystallized from DMF–H_2O.

Synthesis of Compounds 9, 10a,b (General Procedure). A mixture of compound **1** (0.01 mol), sulfur (0.01 mol), and activated nitriles, namely, ethyl cyanoacetate, malononitrile, or cyanoacetamide (0.01 mol) in dioxane (30 ml) and a few drops of triethylamine was stirred for 6 h. The precipitate was collected by filtration and crystallized from the proper solvent to give compounds **9**, **10a**,**b**.

Synthesis of Hydrazide Derivative 11. Chloroacetohydrazide (0.01 mol) was added to a mixture of compound **1** (0.01 mol) and triethylamine (0.01 mol) in dioxane (20 ml). The reaction mixture was refluxed for 6 h, concentrated, and cooled. The precipitate was filtered off and crystallized from ethanol.

Synthesis of Compound 12. KOH (0.02 mol in 5 ml H_2O) was added to a solution of compound **11** (0.02 mol) in DMF (20 ml), the mixture was cooled, and CS_2 (0.022 mol) was added dropwise. The reaction mixture was refluxed until the evolution of H_2S ceased (~18 h). The mixture was cooled and poured into ice-cold water (200 ml) with several drops of dil. HCl. The resulting solid mass was filtered off, washed with water, dried and crystallized from DMF–H_2O.

Synthesis of Compound 13. A mixture of compound **1** (0.003 mol) and triethyl orthoformate (3 ml) was refluxed for 5 h in acetic anhydride (20 ml). The reaction mixture was concentrated and cooled. The precipitate was filtered off, washed with water, dried, and crystallized from acetic acid–H_2O.

Synthesis of Hydrazino Derivative 14. Hydrazine hydrate (0.02 mol) was added to a solution of compound **13** (0.02 mol) in DMF (20 ml). The reaction mixture was refluxed for 5 h, cooled, and added to ice-cold water (200 ml). The precipitate was filtered off and crystallized from DMF–H_2O.

Synthesis of Compound 15. A mixture of compound **14** (0.03 mol) and CS_2 (0.035 mol) in DMF (30 ml) was refluxed for 6 h. The separated solid was collected by filtration and crystallized from DMF.

Synthesis of Compound 16. A mixture of compound **1** (0.03 mol), dibromomalononitrile (0.03 mol), and Et_3N (0.06 mol) in dioxane (30 ml) was refluxed for 3 h. The reaction mixture was concentrated and filtered off while hot. The precipitate was dried, washed with water, and crystallized from DMF–H_2O.

Synthesis of Compounds 17a,b, 18 (General Procedure). Hydrazine hydrate, phenylhydrazine, or mercaptoacetic acid (0.01 mol) were added to a solution of compound **16** (0.01 mol) in DMF (20 ml). The reaction mixture was refluxed for 3 h. After cooling, the mixture was poured into ice-cold water (100 ml). The separated solid was filtered off, washed with water, dried, and crystallized from the proper solvent.

Synthesis of Compounds 19-21 (General Procedure). Equimolar amounts (0.01 mol) of compound **1** and the proper ylidenemalononitrile or *p*-chlorobenzylidenecyanoacetamide were dissolved in dioxane (30 ml), treated with two drops of Et_3N, and refluxed for 4 h. The reaction mixture was concentrated, the separated solid was filtered off, dried, and crystallized from the suitable solvent.

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