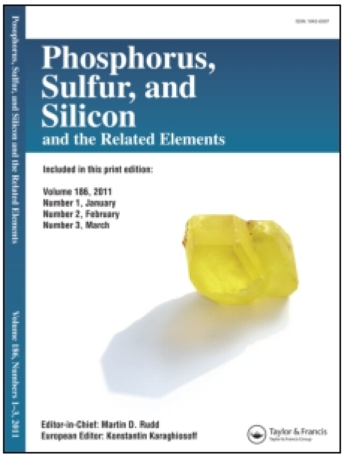

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NOVEL HETEROCYCLIZATION OF N-SUBSTITUTED THIOSEMICARBAZIDES

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NOVEL HETEROCYCLIZATION OF N-SUBSTITUTED THIOSEMICARBAZIDES

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N-Phenyl- and N-benzyl thiosemicarbazide **1a,b** reacted with tetracyanoethylene (TCNE) *via*charge-transfer (CT) complex formation giving thiadiazepine and thiadiazole derivatives **(6. 7** and **16).** On mixing **1a,b** with 2.3 -dichloro-5,6-dicyano-1,4 -benzoquinone (DDQ), oxathiadiazoles and dithiadiazole derivatives **(20** and **24)** were formed. The mechanism of the formation of these products has been elucidated.

Keywords: Thiosemicarbazides; biological activity; tautomerism; NMR spectra

Generally, sulfur and nitrogen containing compounds have widespread applications in the biological field. The thiourea derivatives are considered an interesting class of biologically active compound[1–4]. It has been reported that the tautomerism that exists in such compounds is responsible for the biological activity as observed in their utility as antimalarial[5] drugs. Moreover, thiourea derivatives are useful as fungicides and bactericides as well as insecticides[6].

During the course of our long-standing interest in the chemistry of biologically active sulfur[7–15] and phosphorus[16] compounds, we have investigated the behavior CT of ethyl dithiocarbazate and 3-benzyoyldithiocarbazate with π-acceptors[17]. In the present investigation, we turned our attention to the N-substituted thiosemicarbazides **1a,b** as electron donors, aiming to shed more light on the basicity of system **1a,b** and its behavior towards TCNE and DDQ as π-acceptors.

Thiosemicarbazide and thiosemicarbazones are versatile compounds which have been extensively used in the preparation of heterocyclic ring systems[18–24]. Recently, it has been reported that aromatic aldehyde, thiosemicarbazones, and thiosemicarbazide itself reacted with TCNE *via*

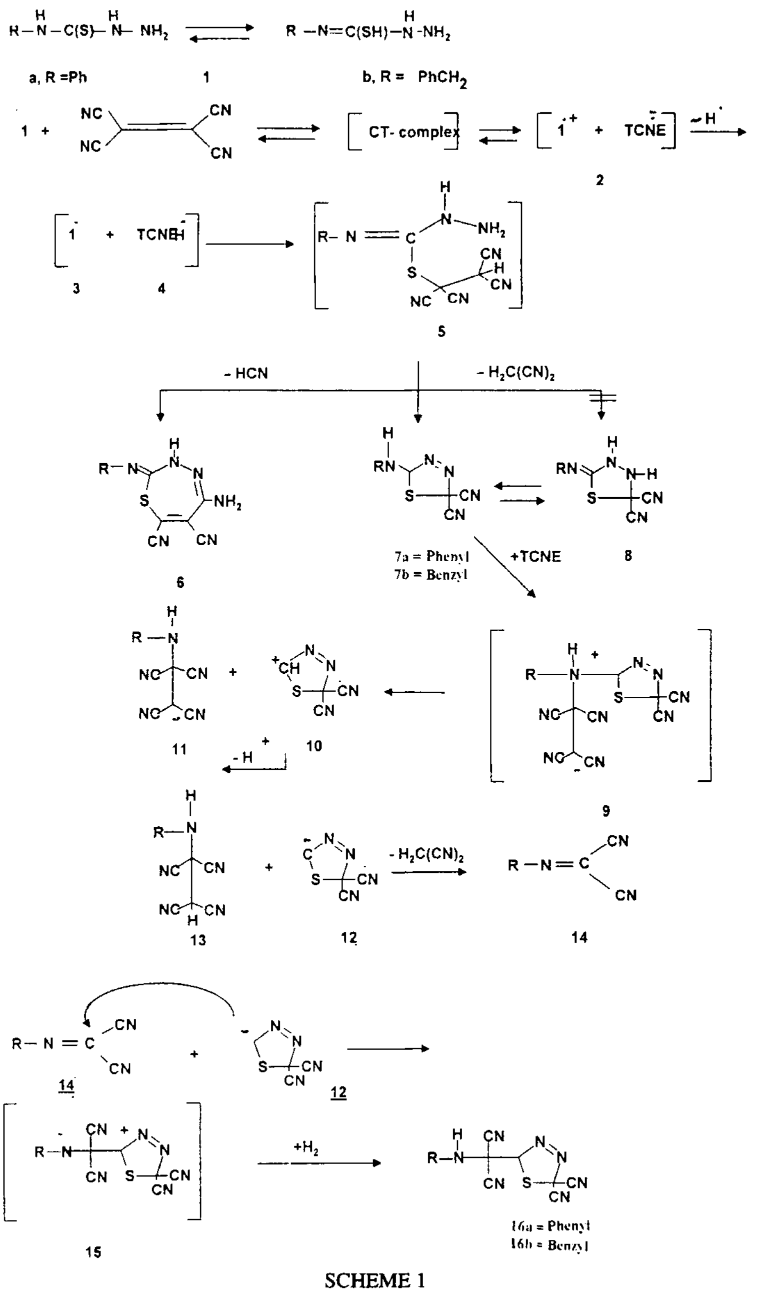
CT-complex formation to give 1,3-thiazine and pyridazine derivatives[25]. Also, thiosemicarbazones reacted with DDQ to yield 3-amino-5-arylthiadiazoles[26]. One of the reason for our continuing interest in the reactivity of N-substituted thiosemicarbazides is that their chemical behavior differs considerably from those of thiosemicarbazone derivatives.

Ethyl acetate solutions of **1a,b** and doubled molar amounts of TCNE were stirred at room temperature. Chromatographic separation of all the residue obtained after concentration gave numerous colored zones, from which products **7** and **16** could be isolated. In addition, compound **6** precipitated (Scheme 1).

Structural assignments of compounds **6, 7** and **16** are based on spectral data and on elemental analysis. For **6a** the formula $C_{12}H_8N_6S$ was confirmed by its mass spectrum which exhibited the molecular ion at m/z 268 (41%). Its IR spectrum showed absorption bands at 3350–3230 and 2210 cm^{-1} NH, NH_2, and cyano group, respectively. The ^{1}H-NMR (DMSO [D_6], 400 MHz) spectrum displayed two broad singlets at $\delta = 7.52$ (2H, NH_2) and at $\delta = 11.10$ (1H, thiadiazepine-NH) in addition to the signals of the aromatic protons. The structure of **6a** has been established by an ^{13}C-NMR (DMSO [D_6], 100.64 MHz) spectrum, which confirmed the presence of the ph-N=$\underline{C}$ group attached to the thiadiazepine ring with a peak at 179.9 ppm and a cyclic carbon ($\underline{C}$-5) attached to the NH_2 group with an absorption at 148.4 ppm in addition to the presence of two cyano groups with peaks at 120.7 and 123.5 ppm.

Two colored compounds were isolated in low yield and from their IR, ^{1}H-, ^{13}C-NMR, mass spectra and elemental analyses were assigned to be compounds **7** and **16**. The mass spectrum of **7a** exhibits a molecular ion at m/z 229 (26%). The ^{1}H-NMR (DMSO [D_6], 400 MHz) spectrum clearly shows the presence of a broad singlet at $\delta = 9.64$ (1H, NH, HN-ph) and another singlet at $\delta = 5.19$ (1H, thiadiazole-CH) in addition to the signals of the aromatic protons. The ^{13}C-NMR of **7a** showed the presence of thiadiazole-CH at 178.5 ppm and thiadiazole $\underline{C}(CN)_2$ at 112.5 ppm.

The structure of **16a** has been assigned on the basis of elemental analysis supporting the expected formula $C_{13}H_7N_7S$. This assignment was conformed by mass spectral evidence agreeing with the expected molecular ion at m/z 293 (36%). The IR-spectrum clearly shows the presence of -NH at 3400–3270 cm^{-1}, and a cyano group at 2220 cm^{-1}. The ^{1}H-NMR (DMSO [D_6], 400 MHz) spectrum indicated the presence of a NH group



SCHEME 1

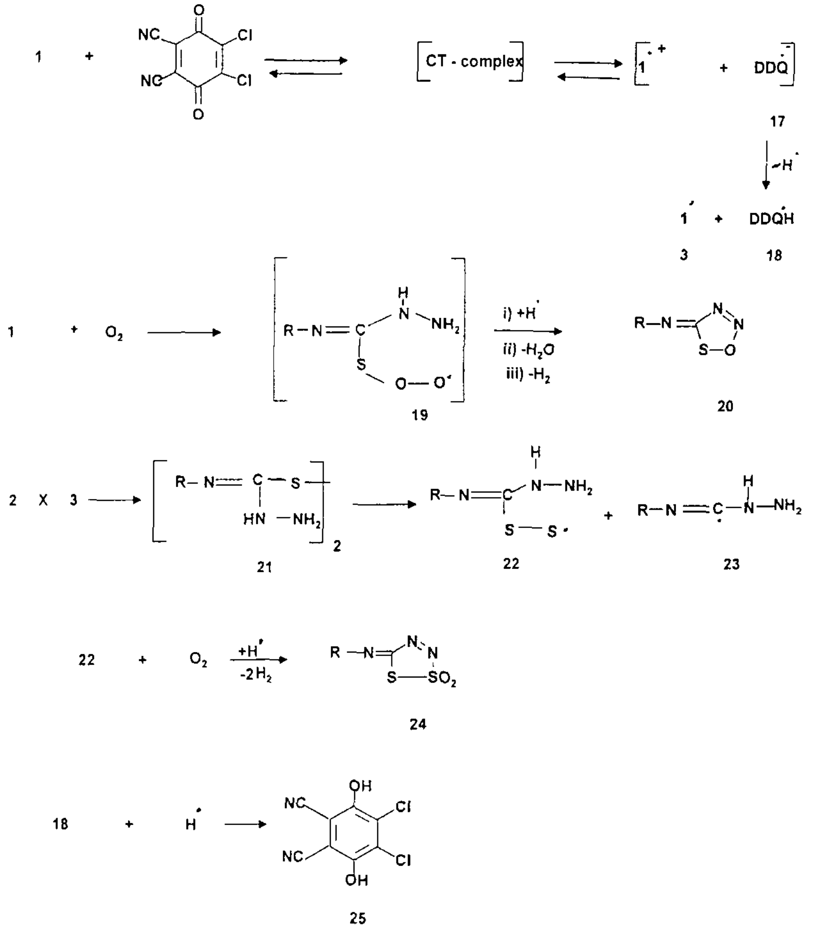
attached to the aromatic ring with an absorption at $\delta = 10.42$ ppm and a thiadiazole-CH peak appearing at $\delta = 5.30$ ppm besides the aromatic protons. The ^{13}C-NMR clearly shows the presence of two types of $\underline{C}(CN)_2$, one for $\underline{C}(CN)_2$ at $\delta = 114.2$ ppm and the side chain $\underline{C}(CN)_2$ at $\delta = 61.6$ ppm.

In Scheme 1 the formation of the reaction products **6, 7** and **16** is illustrated. The thiadiazol **7** may well originate from the adduct **5** *via* elimination a molecule of malonitrile to afford compound **7** rather than the formation of tautomer **8.** This statement is based on ^{1}H-NMR spectrum of compound **7** which clearly shows the presence of a thiadiazole CH-ring at $\delta = 5.19$–5.29 ppm, and an exocyclic NH at $\delta = 9.55$–9.64 ppm. Compound **7** reacted with a second molecule of TCNE to form the adduct **9,** which after cleavage gave **10** and **11**. A proton transfer from **10** to **11** followed by elimination of the malonitrile molecule from **13** resulted in formation of **14** which reacted with **12** to afford the final products **16** *via* abstraction of a molecule of hydrogen.

Mixing DDQ with the donors **1a,b** in benzene gave a green color which changed gradually to brown with the formation of a solid product. This behavior can be explained by the initial formation of unstable CT-complexes followed by chemical reactions. Dichlorodicyanohydroquinone (DDQ-H_2) **25** was first filtered off as a precipitate from the reaction mixture. Chromatographic separation of the concentrated filtrate gave oxathiadiazole **20** and dithiadiazole derivatives **24.** The proposed structures of **20** and **24** were confirmed by their elemental analysis and spectral data (exp. part). The mechanism of formation of the products **20, 24** and **25** is based on the formation of radical **3** and the disulfide **21** as intermediates. The interaction of radical **3** with arial oxygen followed by elimination a molecule of water and deprotonation in the presence of hydrogen radical to give oxathiadiazole **20.** The formation of **24** requires the formation of the disulfide **22** (Scheme 2).

EXPERIMENTAL

Melting points are uncorrected. IR spectra Shimadzu 470 KBr pellets. Mass spectra were obtained on a Finnigan MAT 90. ^{1}H-NMR spectra were taken with a Brucker AM 400 (400 MHz) and ^{13}C-NMR (at 100.64 MHz)



SCHEME 2

spectra were obtained on Brucker AM 400 spectrophotometers in DMSO-$d_6$solution. Chemical shifts for ^1H and ^{13}C are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Elemental analysis were performed at microanalytical unit at Kaiserslautern University, Germany.

Preparation of layer chromatography

Air dried 1.00 mm layer of silica gel, Merck Pf_{254} on plates were employed for preparative TLC and zones were detected by indicator fluoresence quenching exposure to 254 UV light.

Reaction of 1 or 1b with TCNE

A solution of **1a,b** (1 mmol) in 15 ml dry ethyl acetate was added to a solution of TCNE (2 mmol) in 10 ml of dry ethyl acetate. The reaction mixture was stirred for 2 hrs and then left set a side over night at room temperature during which a crystalline product separated. The resulting solid material was filtered and precipitate was washed with ethyl acetate, dried and recrystallized from a suitable solvent to give the thiadiazepine derivatives **6**. The filtrate was concentrated and the residue was chromatographed (PTLC) using toluene/ethyl acetate (2:1) as eluent to give two coloured zones. The first zone contained the thiadiazole derivatives **7** and the second contained compound **16**. Extraction of these zones with acetone and recrystallisation afforded pure compounds **6, 7** and **16.**

5-Amino-6,7-dicyano-3H-1,3,4-thiadiazepine -ylidene -2-phenylamine 6a

Yield 110 mg (41%); m.p. = 249–51 °C, pale yellow crystals (ethanol), IR (KBr): ν = 3350–3230 cm^{-1} (NH, NH_2), 2215 (CN), 1610 (C=C), ^{1}H-NMR (DMSO [D_6])δ = 6.66–6.85 (m, 5H, Aromatic-H), 7.52 (br, 2H, NH_2), 11.10 (br, 1H, NH thiadiazepine ring); ^{13}C-NMR (DMSO [D_6]) δ = 109.8 ($\underline{C}$-6), 118.8 ($\underline{C}$-7), 120.7 (C-6, CN), 123.5 (C-7, CN), 128.2, 129.6, 132.8, 153.8 (Aromatic-*C*), 148.4 ($\underline{C}$-5), 179.9 ($\underline{C}$-2); MS (70 eV) m/z (%), 268 (M, 19), 150 (6), 135 (M, 12), 118 (M, 52), 91 (44), 77 (100), 66 (36); $C_{12}H_8N_6S$ (268.302); found: C, 53.58; H, 2.95; N, 31.28; S, 11.87; requires; C, 53.72; H, 3.01;N, 31.32; S, 11.95.

5-Amino-6, 7-dicyano-3H-1, 3, 4-thiadiazepine-ylidene-2-benzylamine 6b

Yield 104 mg (37%); m.p. = 192–4 °C, pale yellow crystals (ethanol), IR (KBr): ν = 3390–3250 cm^{-1} (NH, NH_2), 2998–2890 (Ali-CH), 2210 (CN), 1620 (C=C), ^{1}H-NMR (DMSO [D_6]) δ = 4.34 (s, 2H, CH_2), 6.95–7.55 (m, 5H, Aromatic-H), 7.58 (br, 2H, NH_2), 11.30 (br. 1H, NH thiadiazepine ring); ^{13}C-NMR (DMSO [D_6]) $\delta = 47.90$ (CH_2), 109.6 (C-6), 118.9 (C-7), 121.7 (C-6, CN), 124.5 (C-7, CN), 128.1–134.7 (Aromatic-C), 151.4 (C-5), 174.2 (C-2); MS (70 eV) m/z (%), 282 (M, 4), 149 (M, 28), 134 (M, 10), 91 (100), 65 (16); $C_{13}H_{10}N_6S$ (282.329); found: C, 55.20; H, 3.49; N, 29.63; S, 11.47; requires; C, 55.31; H, 3.57; N, 29.77; S, 11.36.

5-Dicyano-2-phenylamino-1,3,4-thiadiazole 7a

Yield 53 mg (23%); m.p. = 228–30 °C, colorless crystals (ethanol), IR (KBr): $\nu = 3450–3360\ cm^{-1}$ (NH), 2210 (CN), 1580 (N=N), ^{1}H-NMR (DMSO [D_6]) $\delta = 5.19$ (s, 1H, CH-thiadiazole ring), 6.84–7.18 (m, 5H, Aromatic-H), 9.55 s, 1H, NH); ^{13}C-NMR (DMSO [D_6]) $\delta = 112.5$, (C-5), 125.1, 128.3, 133.1, 153.3 (Aromatic-C), 118.2 (CN), 178.5 (C-2); MS (70 eV) m/z (%), 230 ($M^{\cdot}$, 26), 204 (22), 157 (7), 104 (100), 77 (86); $C_{10}H_7N_5S$ (228.689); found: C, 52.29;H, 2.65; N, 30.48; S, 13.83; requires; C, 52.52; H, 2.83; N, 30.62; S, 14.02.

2-Benzylamino-5-dicyano-1,3,4-thiadiazole 7b

Yield 48 mg (20%); m.p. = 205–7 °C, colorless crystals (acetonitrile), IR (KBr): $\nu = 3490–3310\ cm^{-1}$ (NH), 2995–2895 (Ali-CH), 2210 (CN), 1590 (N=N); ^{1}H-NMR (DMSO [D_6]) $\delta = 4.31$ (s, 2H, CH_2), 5.19 (s, 1H, CH-thiadiazole ring), 7.30–7.92 (m, 5H, Aromatic-H), 9.64 (s, 1H, NH); ^{13}C-NMR (DMSO [D_6]) $\delta = 49.40$ (CH_2), 111.5 (C-5), 118.9 (CN), 128.2–135.4 (Aromatic-C), 174.5 (C-2); MS (70 eV) m/z (%), 242 (M^+, 16), 223 (M, 4), 191 (6), 166 (15), 149 (M, 100), 91 (59), 77 (9); $C_{11}H_8N_5S$ (242.284); found: C, 54.41; H, 3.18; N, 28.80; S, 13.17; requires; C, 54.53; H, 3.33; N, 28.92; S, 13.23.

2-Phenylamino-(5-Dicyano-1,3,4-thiadiazolyl)dicyanomethame 16a

Yield 76 mg (26%); m.p. = 299–301 °C, colorless crystals (acetonitrile), IR (KBr): $\nu = 3400–3270\ cm^{-1}$ (NH), 2220 (CN), 1590 (N=N); ^{1}H-NMR (DMSO [D_6]) $\delta = 5.30$ (s, 1H, CH-thiadiazole ring), 6.90–7.15 (m, 5H, Aromatic-H), 10.42 (s, 1H, NH); ^{13}C-NMR (DMSO [D_6]) $\delta = 61.6$, (HN-C $(CN)_2$), 114.3 (C-5), 118.7 (CN-thiadiazole ring), 124.3, 127.2, 133.0, 153.6 (Aromatic-C), 155.5 ($(CN)_2$) 184.6 (C-2); MS (70 eV) m/z (%), 295 ($M^{\cdot}$, 36), 267 (51), 240 (45), 223 (11), 160 (7), 133 (100), 93

(18), 77 (86); $C_{13}H_7N_7S$ (293.312); found: C, 52.98; H, 2.30; N, 33.29; S, 11.05; requires; C, 53.23 ; H, 2.41; N, 33.43; S, 10.93.

2-Benzylamino -(5-Dicyano-1.3.4-thiadiazolyl)dicyanomethane 16b

Yield 64 mg (21%); m.p. = 338–40 °C, colorless crystals (acetonitrile), IR (KBr): $\nu = 3390–3260\ cm^{-1}$ (NH), 2995–2870 (Ali-CH), 2215 (CN), 1585 (N=N); ^{1}H-NMR (DMSO [D_6]) $\delta = 4.35$ (s, 2H, CH_2), 5.35 (s, 1H, CH-thiadiazole ring), 7.10–7.99 (m, 5H, Aromatic-H), 10.61 (s, 1H, NH), ^{3}C-NMR (DMSO [D_6]) $\delta = 48.5$ (CH_2), 58.5 (HN-$\underline{C}(CN)_2$), 109.8 ($\underline{C}$-5), 117.9 (CN-thiadiazole ring), 127.7–133.9 (Aromatic-$\underline{C}$), 153.5 ($(CN)_2$) 174.2 ($\underline{C}$-2); MS (70 eV) m/z (%), 307 (M, 7), 136 ($M^{\cdot}$, 9), 92 (100); $C_{14}H_9N_7S$ (307.321); found: C, 54.60; H, 2.81; N, 31.79; S, 10.35; requires; C, 54.72; H, 2.95; N, 31.90; S, 10.43.

Reaction of 1 with DDQ

A solution of **1** (1 mmol) in 20 ml dry benzene was added to a solution of the DDQ (1.5 mmol) in 15 ml dry benzene. The reaction mixture was stirred for 72 hrs at room temperature, filtered and the precipitate was washed with benzene giving yellow crystals of DDQ-H_2. The filtrate was concentrated and chromatographed on PTLC using toluene/ethyl acetate (5:1) as eluent to give two zones. The fastest migrating one contained oxathiadiazole derivatives **20** and the second zone contained compound **24.** Extraction of these zones with acetone and recrystallized from a suitable solvent afforded the pure compounds **20** and **24.**

2-Phenylamino-1,2,4,5-oxathiadiazolylidene 20a

Yield 57 mg (32%) m.p. 280–82 °C, colorless crystals (ethanol); IR (KBr): $\nu = 3070\ cm^{-1}$ (Aromatic-CH), 1620 (C=N), 1580 (N=N) ; ^{1}H-NMR (DMSO [D_6]) $\delta = 7.10–7.50$ (m, 5H, Aromatic-H), ^{13}C-NMR (DMSO [D_6]) $\delta = 125.8$, 128.9, 130.5, 155.2 (Aromatic-$\underline{C}$), 189.6 ($\underline{C}$-5); MS (70 eV) m/z (%), 178 (M^+, 100), 150 (87), 135 (47), 91 (27), 77 (88); $C_7H_5N_3SO$ (179.201); found: C, 46.55; H, 2.69; N, 23.36; S, 17.95; requires; C, 46.91; H, 2.81; N, 23.45; S, 17.89.

2-Benylamino-1,2, 4,5-oxathiadiazolylidene 20b

Yield 54 mg (28%) m.p. 271–73 °C, colorless crystals (ethanol); IR (KBr): $\nu = 3090\ cm^{-1}$ (Aromatic-CH),1660 (C=N) 1585 (N=N) ; ^{1}H-NMR

(DMSO [D_6]) $\delta = 4.53$ (s, 2H, CH_2), 7.15–7.53 (m, 5H, Aromatic-H); ^{13}C-NMR (DMSO [D_6])$\delta = 50.3$ ($\underline{C}H_2$), 128.6–135.5 (Aromatic-$\underline{C}$), 184.6 ($\underline{C}$-5); MS (70 eV) m/z (%), 193 (M, 35), 177 (85), 149 (49), 102 (36), 77 (80); $C_8H_7N_3SO$ (193.228); found: C, 49.36; H, 3,32; N, 21,60; S, 16.44; requires; C, 49.73; H, 3.65; N, 21.75; S, 16.59.

2-Phenvlamino-2-oxo –1,2,3,4-dithiadiazole 24a

Yield 61 mg (27%) m.p. 131–33 °C, colorless crystals (ethanol); IR (KBr): $\nu = 3050$ cm^{-1} (Aromatic-CH),1660 (C=N), 1590 (N=N), 1660, 1030–1050 (SO_2); ^{1}H-NMR (DMSO [D_6]) $\delta = 6.89$–7.50 (m, 5H, Aromatic-H); ^{13}C-NMR (DMSO [D_6]) $\delta = 124.7$, 125.5, 129.6, 149.6 (Aromatic-$\underline{C}$), 180,7 ($\underline{C}$-5); MS (70 eV) m/z (%), 228 ($M^{\cdot}$, 28), 135 (70), 92 (100), 77 (64), 65 (18); $C_7H_5N_3S_2O_2$ (227.264); found: C, 36.75; H, 2.11; N, 18.41; S, 28.11; requires; C, 36.99; H, 2.22; N, 18.49; S, 28.22.

2-Benzylamino-2-oxo-1,2,3,4-dithiadiazolesulfonylylidene 24b

Yield 75 mg (31%) m.p. 181-83 °C, colorless crystals (ethanol); IR (KBr) $\nu = 3070$ cm^{-1} (Aromatic-CH), 2995–2890 (Ali-CH), 1625 (C=N), 1585 (N=N), 1035–1055 (SO_2); ^{1}H-NMR (DMSO [D_6]) $\delta = 4.55$ (s, 2H, CH_2), 6.85–7.70 (m, 5H, Aromatic-H); ^{13}C-NMR (DMSO [D_6]) $\delta = 58.5$ ($\underline{C}H_2$), 128.6–135.7 (Aromatic-$\underline{C}$), 179.2 ($\underline{C}$-5); MS (70 eV) m/z (%), 241 (M, 35), 177 (60), 91 (100), 77 (72), 65 (18); $C_8H_7N_3S_2O_2$ (241.291); found: C, 39.65; H, 2.89; N, 17.11; S, 26.31 ; requires; C, 39.82; H, 2.92; N, 17.42; S, 26.58.

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