Pergamon

Tetrahedron Vol. 50, No. 17, pp. 5091-5098, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $6.00+0.00

0040-4020(94)E0171-O

One-Step Synthesis of Novel 2,2'-Bi(4,5-dihydro-1,3,4-thiadiazole) and 2,3-Disubstituted 1,4-Benzothiazine Derivatives

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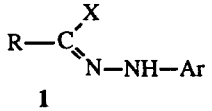
Abstract *: N,N'-Diaryloxalodihydrazonoyl dihalides 2 react with potassium thiocyanate or thiourea and yield the hitherto unknown bi-4,5-dihydrothiadiazol-5-imine derivatives 5. Reaction of 5 with acetic anhydride, benzoyl chloride and nitrous acid yield N-acetyl, N-benzoyl and N-nitroso derivatives 7, 8 and 9, respectively. Thermolysis of 9 afforded the bi-4,5-dihydrothiadiazol-5-ones 10. The dihalides 2 react also with 2-aminothiophenol to afford the 1,4-benzothiazine derivatives 11 which upon oxidation gave 12.*

Hydrazonoyl halides of type **1** have been extensively studied and have proved to be versatile precursors for synthesis of nitrilimines which undergo various 1,3-dipolar cycloaddition reactions leading to heterocyclic products.[1,2] The chemistry of the related dihydrazonoyl dihalides **2** has not received so much attention.[3,4] In connection with our interest to study the synthetic potential of the dihalides **2**,[5,6] we wish to report here the use of such dihalides in the synthesis of the title compounds.



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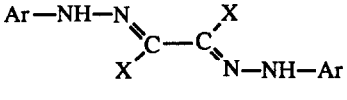
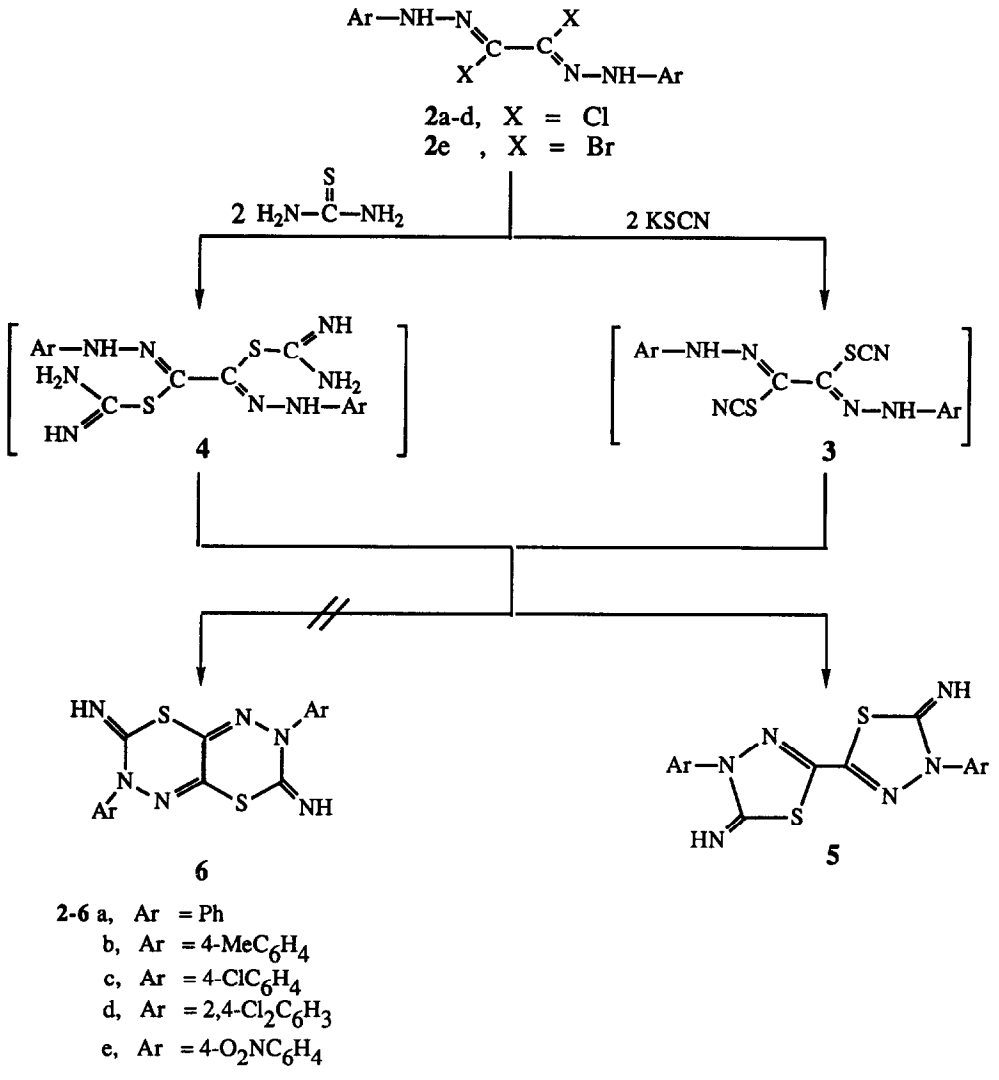


2

Thus, when *N,N'*-diaryloxalodihydrazonoyl dihalides **2** and potassium thiocyanate or thiourea were refluxed in ethanol, they afforded products for which the two possible structures **5** and **6** can be written (Scheme 1). Between these two possible structures, the bi-(1,3,4-thiadiazol-5-imine) structure **5** was assigned to the products isolated on the basis of their mass spectra. These spectra showed, in addition to the molecular ion peak, a fragment ion of m/e = $M/2^+$ (see experimental). This mode of fragmentation excludes the fused bicyclic structure **6.** Mass spectrometry has perviously been applied to the problem of distinguishing pendant from alternative fused-ring systems.[7,8] The formation of **5** is assumed to proceed via a nucleophilic substitution of the thiocyanate anion to afford the non-isolable intermediates **3** which undergo intramolecular cyclization to afford the final isolable products **5**. The bi-thiadiazolimines **5** were also obtained from the reaction

of the dihalides **2** with thiourea through the formation of the non-isolable intermediates **4** which cyclised readily via loss of ammonia (Scheme 1).

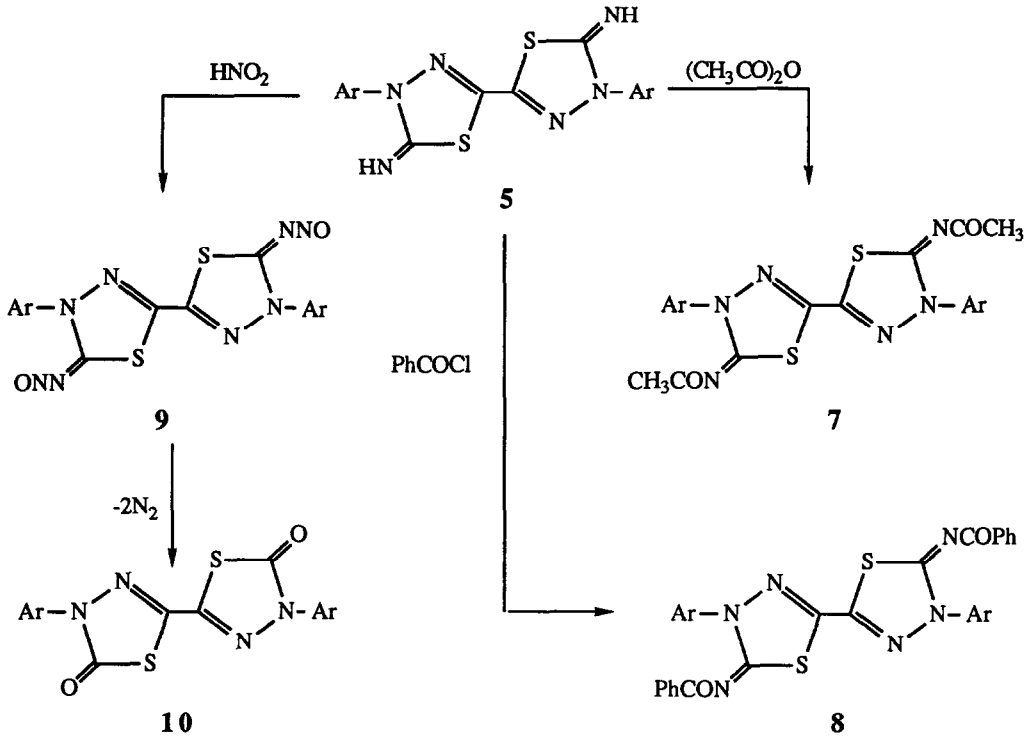


2-6 a, Ar = Ph
b, Ar = 4-MeC_6H_4
c, Ar = 4-ClC_6H_4
d, Ar = 2,4-$Cl_2C_6H_3$
e, Ar = 4-$O_2NC_6H_4$

Scheme 1

Structure **5** was further evidenced by its chemical transformations outlined in Scheme 2. Thus, heating of **5** with acetic anhydride or benzoyl chloride gave the corresponding *N*-acetyl derivatives **7** and *N*-benzoyl derivatives **8**, respectively. Also, compounds **5** underwent nitrosation to afford the *N*-nitroso derivatives **9**. The latter upon thermolysis were converted into the corresponding oxo derivative **10**. Both the microanalyses and

the spectral data of the products **5** and **7-10** are compatible with their assigned structures. For example, the ^1H NMR spectra of **5a** revealed the presence of an imino NH signal at δ 9.3 ppm. Their IR spectra showed an absorption band near 3327 cm^{-1} assignable to NH stretching. On the other hand, the IR spectra of the derivatives **7-10** were free of such bands. The ^1H NMR spectra of **7a** revealed a characteristic singlet signal at δ 2.4 ppm assignable to CH_3CO proton resonance. The IR spectra of the products **7a** , **8a** and **10a** showed carbonyl absorption bands at 1637, 1630 and 1678 cm^{-1}, respectively. The latter band is characteristic of the ring carbonyl absorption of 1,3,4-thiadiazol-5-ones.[9,10]

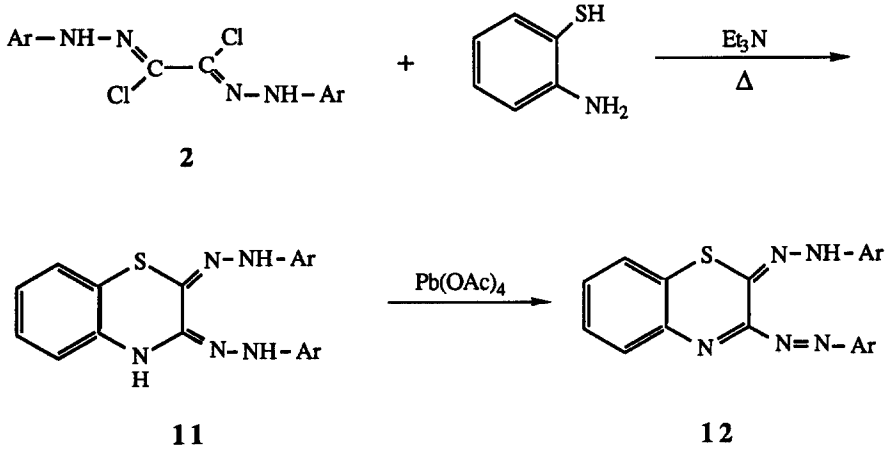


2,7-10 a ; Ar = Ph
b; Ar = 4-MeC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 2,4-$Cl_2C_6H_3$
e; Ar = 4-$NO_2C_6H_4$

Scheme 2

The dihydrazonoyl dichlorides **2** also reacted with 2-aminothiophenol in refluxing ethanol in the presence of triethylamine affording good yields of 2,3-bis(arylhydrazono)-2,3-dihydro-4H-1,4-benzothiazines **11**. Upon

treatment of the product **11** with lead tetracetate in acetic acid at room temperature, the respective oxidation product **12** was produced (Scheme 3). The structure of the isolated compounds **11** and **12** were established from their microanalyses and spectral data. For example, the IR spectra of **11** exhibit in each case three NH stretching bands near 3470, 3365 and 3250 cm^{-1}; the IR spectra of **12** revealed, however, only one NH absorption band at 3215 cm^{-1}.



2,11,12 a; Ar = Ph
c; Ar = 4-ClC_6H_4
d; Ar = 2,4-$Cl_2C_6H_3$

Scheme 3

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded on a Perkin-Elmer 1430 spectrometer. The ^1H NMR spectra were recorded in deuterated chloroform or DMSO-d_6 on a Varian T-60 NMR spectrometer using tetramethylsilane as internal reference. Mass spectra were recorded on GCMS-QP1000 EX spectrometer. Elemental analyses were carried out at the Microanalytical Laboratory, University of Cairo, Giza, Egypt.

***N,N'* - Diaryloxalodihydrazonoyl dichlorides 2a-d** were prepared following the procedure reported in litrerature.[3]

2b: Yield (51%); m.p. 198-200 °C; IR (KBr) ν 3325 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s,6H), 7.4–7.8(m,8H), 8.7(s,2H) ppm; (Calcd. for $C_{16}H_{16}Cl_2N_4$: C, 57.32; H, 4.81; Cl, 21.15, N, 16.72. Found: C, 57.1; H, 4.8; Cl, 21.3; N, 16.5).

2C: Yield (58%); m.p. 223-25 °C; IR (KBr) ν 3314 (NH) cm^{-1}; ^1H NMR (DMSO) δ 8.6 (s, 2H), 7.2-7.9 (m, 8H); (Calcd. for $C_{14}H_{10}Cl_4N_4$: C, 44.71; H, 2.68; Cl, 37.71N, 14.90. Found: C, 45.0; H, 2.8; Cl, 37.6; N, 15.1).

***N,N'* - Di-(4-nitrophenyl)oxalodihydrazonyl dibromide 2e.**

To a stirred suspension of glyoxal bis-(4-nitrophenylhydrazone) (3.5g, 10.5 mmol) in acetic acid (40 ml) was added bromine solution (3.36g, 21 mmol) in acetic acid (10 ml) dropwise over a period of 1/2 h. The reaction mixture was stirred for further 5h and the product was collected, washed with acetic acid and crystallized from DMF. Yield (86%) , m.p. 304-305 °C; IR (KBr) ν 3305 (NH) cm^{-1}; ^1H NMR (DMSO) δ 8.6 (s, 2H), 7.1-7.9 (m, 8H); (Calcd. for $C_{14}H_{10}Br_2N_6O_4$: C, 34.59; H, 2.07 ; Br, 32.87 N, 17.29. Found: C, 34.3 ; H, 2.1; Br, 32.6 ; N, 17.1).

2,2'-Bi(4-aryl-4,5-dihydro-5-imino-1,3,4-thiadiazoles) 5a-e.

Method A . General procedure.

To a suspension of **2** (5 mmol) in ethanol or dimethylformamide (20 ml), was added a solution of potassium thiocyanate (1.4g, 15 mmol) in water (5 ml). The reaction mixture was refluxed for 3h then cooled to room temperature. Water (50 ml) was added to the reaction mixture and the crude product was filtered off and crystallized from dimethylformamide.

The products **5**a-e were obtained in 68-85% yield and their physical constants are given below :

5a : Yield (85%); m.p. 213-14 °C; IR (KBr) ν 3327 (NH), 1601 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 9.3 (s,2H), 7.2 - 8.1 (m, 10 H) ppm; MS, m/e (%) 352 (M^+,75.2), 351 (6.0), 178 (8.9), 177 (0.9), 176 (1.5), 143(6.8), 118(7.4), 91(100), 77(27.3); (Calcd. for $C_{16}H_{12}N_6S_2$: C, 54.52; H, 3.43; N, 23.85; S, 18.19. Found : C, 54.8; H, 3.5; N, 23.5; S, 18.1).

5b : Yield (79%); m.p. 230-32 °C; IR (KBr) ν 3314 (NH), 1617 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 9.2 (s,2H), 7.2-8.2 (m, 8H), 2.22 (s, 6H) ppm; MS, m/e (%) 380 (M^+,25.9), 321 (7.1), 217 (5.1), 190 (2.3), 189 (1.1), 105 (100), 104 (30), 78 (25.6), 77 (12.1); (Calcd. for $C_{18}H_{16}N_6S_2$: C, 56.81; H, 4.24; N, 22.09; S, 16.85. Found : C, 56.5; H, 4.0; N, 22.3; S, 16.6).

5c : Yield (72%); m.p. 265-67 °C; IR (KBr) ν 3295 (NH), 1601 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 9.1 (s,2H), 7.1-8.0 (m, 8H)ppm; MS, m/e (%) 422 (M^++1, 9.7), 421(M^+, 3.3), 420 (13.9), 361 (6.0), 152 (9.9), 127(32.3), 125(100), 111(11.6), 90 (24.5); (Calcd. for $C_{16}H_{10}Cl_2N_6S_2$:C,45.6; H, 2.39; N, 19.95; S, 15.21. Found :C, 45.3; H, 2.4; N, 19.7; S, 14.9).

5d : Yield (68%); m.p. 248-50 °C; IR (KBr) ν 3320 (NH), 1615 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 9.2 (s,2H); 7.3-8.0 (m, 6H)ppm; MS, m/e (%) 490 (M^+, 9.4), 246 (1.3), 245 (1.1); (Calcd. for $C_{16}H_8Cl_4N_6S_2$: C, 39.19; H, 1.64; N, 17.14; S, 13.08 . Found : C, 38.9; H, 1.8; N, 16.9; S, 13.0).

5e : Yield (75%); m.p.> 350 °C; IR (KBr) ν 3313 (NH), 1620 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 9.1 (s, 2H), 7.2 - 8.1 (m, 8H) ppm; MS, m/e (%) 442 (M^+, 100), 383 (19.8), 247 (14.1), 221 (3.3), 220 (1.2); (Calcd. for $C_{16}H_{10}N_8O_4S_2$: C, 43.43; H, 2.28; N, 25.32; S, 14.49. Found : C, 43.2; H, 2.3; N, 25.1; S, 14.3).

Method B. General Procedure.

The appropriate dihalide **2** (5 mmol) was added to a solution of thiourea (15 mmol) in ethanol (30 ml) and the reaction mixture was heated under reflux for 3h and then left to cool. The produced solid was filtered, washed with water, and dried. Recrystallization from dimethylformamide gave products identical in all respects (IR spectra, m.p. and mixed m.p.) with compounds **5**a-e obtained from the reaction of **2** with potassium thiocyanate by method A above.

Acylation of Compounds 5.

Acetylation.

The appropriate bi-thiadiazolimine **5** (0.5 mmol) in excess acetic anhydride (5 ml) was refluxed for 30 minutes. The mixture was cooled and then poured on crushed ice. The solid formed was collected, washed with water and dried. Crystallization from dimethylformamide afforded 85-90% yield of the *N*-acetyl derivatives **7**a-d.

7a : Yield (87%); m.p. 305-7 °C; IR (KBr) ν 1637 (C=O), 1565 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.2-7.9 (m,10H), 2.36 (S, 6H) ppm; (Calcd. for $C_{20}H_{16}N_6O_2S_2$: C, 55.02; H, 3.69; N, 19.25; S, 14.68. Found : C, 55.3; H, 3.7; N, 18.9; S, 14.8).

7b : Yield (85%); m.p. 295-97 °C; IR (KBr) ν 1640 (C=O); 1562 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.1-7.8 (m, 8H), 2.36 (s, 6H)ppm; (Calcd. for $C_{22}H_{20}N_6O_2S_2$:C, 56.87; H, 4.33; N, 18.09; S, 13.80. Found : C, 56.7; H, 4.1; N, 17.9; S, 13.6).

7c : Yield (93%); m.p. 310-12 °C; IR (KBr) ν 1638 (C=O), 1587 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.3-7.9 (m, 8H), 2.21 (s, 6H) ppm. (Calcd. for $C_{20}H_{14}Cl_2N_6O_2S_2$: C, 47.79; H, 2.79; N, 16.63. S, 12.68. Found : C, 47.6; H, 3.0; N, 16.7; S, 12.5).

7d : Yield (86%); m.p. 319-21 °C; IR (KBr) ν 1638 (C=O), 1590 (C=N) cm^{-1}; ^1H NMR (DMSO) δ 7.3-7.9 (m, 8H), 2.33 (s, 6H) ppm. (Calcd. for $C_{20}H_{12}Cl_4N_6O_2S_2$:C, 41.82; H, 2.10; N, 14.63; S, 11.16. Found : C, 41.5; H, 2.2; N, 14.7; S, 11.2).

7e : Yield (90%); m.p. > 350 °C; IR (KBr) ν 1640 (C=O), 1585 (C=N) cm^{-1}; ^1H NMR (insoluble in the usual NMR solvents). (Calcd. for $C_{20}H_{14}N_8O_6S_2$: C, 45.63; H, 2.68; N, 21.28; S, 12.18. Found : C, 45.4; H, 2.9; N, 21.0; S, 12.1).

Benzoylation .

A solution of the appropriate bi-thiadiazolimine **5** (0.5 mmol) and benzoyl chloride (0.3 ml) in pyridine (10 ml) was refluxed for 30 minutes then cooled. The reaction mixture was poured onto crushed ice containing hydrochloric acid (10 ml). The precipitated product was filtered off, washed with water and dried. Crystallization from DMF gave 77-90 % yield of the N-benzoyl derivatives **8**. ^1H NMR spectra were not obtained, owing to the insolubility in the usual NMR solvents.

8a : Yield (87%); m.p. > 350 °C; IR (KBr) ν 1630 (C=O), 1579 (C=N) cm^{-1}; (Calcd. for : $C_{30}H_{20}N_6O_2S_2$ C, 64.26; H, 3.59; N, 14.99; S, 11.43. Found : C, 63.9; H, 3.7; N, 14.8; S, 11.3).

8b : Yield (75%) ; m.p. > 350 °C; IR (KBr) ν 1636 (C=O), 1580 (C=N) cm^{-1}; (Calcd. for : $C_{32}H_{24}N_6O_2S_2$: C, 65.28; H, 4.11; N, 14.27; S, 10.89. Found : C, 65.4; H, 4.0; N, 14.1; S, 10.7).

8c : Yield (90%) ; m.p. > 350 °C; IR (KBr) ν 1638 (C=O), 1585 (C=N) cm^{-1}; (Calcd. for : $C_{30}H_{18}Cl_2N_6O_2S_2$: C, 57.23; H, 2.88; N, 13.35;S, 10.18. Found : C, 57.1; H, 3.0; N, 13.2; S, 10.1).
8d : Yield (77%) ; m.p. > 350 °C;IR (KBr) ν 1637 (C=O), 1577 (C=N) cm^{-1}; (Calcd.for $C_{30}H_{16}Cl_4N_6O_2S_2$: C, 51.58; H, 2.30; N, 12.03; S, 9.18. Found: C, 51.3; H, 2.3; N, 12.2; S, 9.0).
8e: Yield (70%) ; m.p. > 350 °C; IR (KBr) ν 1636 (C=O), 1577 (C=N) cm^{-1};(Calcd. for $C_{30}H_{18}N_8O_6S_2$: C, 55.33; H,2. 78; N, 17.21; S, 9.85. Found : C, 55.1; H , 2.8; N, 17.2; S, 9.7).

Nitrosation of 5.

To a cold solution of the appropriate bi-thiadiazolimine **5** (1 mmol) in acetic acid (10 ml), was added a saturated solution of sodium nitrite (2 g) in water (5 ml) portionwise. The red precipitate that separated was filtered off, washed with water, dried and finally crystallized rapidly from dioxane to give **9** in 75-90% yield.
9a: Yield (75%); m.p; 165 °C (decomp.) ; (Calcd. for $C_{16}H_{10}N_8O_2S_2$: C, 46.81; H,2.45; N, 27.30; S,15.62. Found: C, 47.0; H, 2.3; N, 27.5; S, 15.5).
9b: Yield (75%); m.p. 151 °C (decomp.); (Calcd. for $C_{18}H_{14}N_8O_2S_2$: C, 45.30; H, 3.22; N ,25.56; S, 14.62. Found : C, 45.5; H, 3.1; N, 25.5; S, 14.7).
9c: Yield (90%); m.p. 176 °C (decomp.); (Calcd. for $C_{16}H_8Cl_2N_8O_2S_2$: C, 40.0; H, 1.66; N, 23.36; S,13.37. Found: C, 40.2; H, 1.8; N, 23.2; S, 13.3).

Thermolysis of 9

The appropriate N-nitroso derivative **9** (1 mmol) in ethylene glycol (10 ml) was refluxed untill the red colour disappeared and then cooled. The mixture was diluted with water (20 ml) and the crude product was filtered off. It was dried and crystallized from acetic acid or DMF to afford the bi-thiadiazolone derivatives **10** in an almost quantitative yield.
10a: Yield (98%); m.p. 183-85 °C , IR (KBr) ν 1678 (C=O), 1594 (C=N) cm^{-1};^{1}H NMR (DMSO) δ 7.2-7.8 (m); MS, m/e (%), 354 (M^+, 32.3), 294 (13.0), 177 (3.3); Calcd. for $C_{16}H_{10}N_4O_2S_2$: C, 54.22; H, 2.84; N, 15.81; S, 18.09. Found: C, 53.9; H, 2.9; N,16.0; S, 17.9).
10b: Yield (96%); m.p. 238-40 °C; IR(KBr) ν 1675 (C=O), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO) δ 7.3- 8.0. (m, 8H), 2.2 (s, 6H) ppm; MS, m/e (%), 382 (M^+, 27.6), 191 (1.9); (Calcd. for $C_{18}H_{14}N_4O_2S_2$:C, 56.52; H, 3.79; N, 14.65; S, 16.76. Found: C, 56.7; H, 3.9; N, 14.4; S, 16.8).
10c : Yield (98%); m.p. 208-10 °C ; IR (KBr) ν 1678 (C=O), 1599 (C=N) cm^{-1}; ^{1}H NMR (DMSO) δ7.3-7.8 (m); MS, m/e (%), 424 (M^++1, 2.8), 423 (M^+, 0.7), 422 (3.1), 211 (0.6); (Calcd. for $C_{16}H_8Cl_2N_4O_2S_2$: C, 45.39; H, 1.90; N, 13.23; S, 15.14. Found : C, 45.1; H, 2.0; N, 13.2; 5, 14.9).

2,3-Bis(arylhydrazono)-2,3-dihydro-4H-1,4-benzothiazine 11.

To a suspension of **2** (3 mmol) in ethanol (25 ml) was added 2-aminothiophenol (0.44g; 3.5 mmol). The mixture was refluxed for 6h, during which triethylamine (0.6 ml, 6 mmol) was added dropwise. The mixture was cooled and the precipitate was filtered, washed with water, dried and finally crystallized from benzene or DMF/water to afford the 1,4-benzothiazine derivatives **11** as yellow crystals in 55-68% yield.

11a : Yield (55%) ; m.p. 198 °C (benzene); IR (KBr) ν 3430, 3347, 3175 (3NH), 1605 (C=N) cm^{-1}; MS, m/e (%), 360(M^++1, 8.1), 359(M^+, 12.9); (Calcd. for $C_{20}H_{17}N_5S$: C, 66.82; H, 4.76; N, 19.48; S, 8.92. Found: C, 66.1; H, 4.8; N, 19.2; S, 9.1).

11c: Yield (65%); m.p. 200 °C (DMF); IR (KBr) ν 3470, 3365, 3250 (3NH); 1613 (C=N) cm^{-1}; MS,m/e (%) 428(M^+, 7.5); (Calcd. for $C_{20}H_{15}Cl_2N_5S$: C, 56.07; H, 3.53; N, 16.35; S, 7.48; Cl, 16.55. Found: C, 55.9; H, 3.5; N, 16.2; S, 7.3; Cl, 16.4).

11d: Yield (68%); m.p. 212 °C (DMF); IR (KBr) ν 3471, 3379, 3260 (3NH); 1590 (C=N) cm^{-1}; MS, m/e (%) 497 (M^+, 10.8); (Calcd. for $C_{20}H_{13}Cl_4N_5S$: C, 48.30; H, 2.60; N, 14.08; S, 6.44; Cl, 28.52. Found: C, 48.4; H, 2.8; N, 14.2; S, 6.3; Cl, 28.4).

Oxidation of 11c.

To a stirred suspension of **11c** (0.43g; 1 mmol) in glacial a acetic acid (20 ml), was added lead tetraacetate (0.52g, 1.2 mmol) portionwise. The reaction mixture was stirred at room temperature for 4h, then diluted with water. The solid that precipitated was collected, washed with water and dried. Crystallization from DMF afforded 2-(4-chlorophenylhydrazono)-3-(4-chlorophenylazo)-2H-1,4-benzothiazine **12c** as orange yellow crystals :

Yield (85%); m.p. 221-23 °C; IR (KBr)ν 3215 (NH), 1638 (C=N), 1601 (C=N) cm^{-1}; (Calcd. for $C_{20}H_{13}Cl_2N_5S$: C, 56.33; H, 3.05; N, 16.43. Found: C, 56.0; H, 3.2; N, 16.2).

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(*Received in UK* 24 *November* 1993; *revised* 8 *February* 1994; *accepted* 18 *February* 1994)