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SYNTHESIS OF NOVEL *N*-SUBSTITUTED 6-CHLOROTHIENO-[2,3-*e*]-1,4,2-DITHIAZIN-3-AMINE 1,1-DIOXIDES

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Abstract − A series of *N*-(substituted)-6-chlorothieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxides (**9a-g**) were prepared *via* direct interaction of the appropriate isothiocyanate with 2,5-dichloro-3-thiophenesulphonamide **6** in THF in the presence of sodium hydride. The structures of these new bicyclic derivatives are based on microanalytical and spectral (IR, MS, and NMR) data.

INTRODUCTION

Heterocyclic compounds[1] play essential roles in several biological processes and are incorporated in a large number of chemically and pharmacologically important agents.[1,2] The 1,4,2-dithiazine ring system, first synthesized by Hasegawa *et al*.,[3] has recently been reported to have agricultural and industrial uses as fungicides and antibacterials with outstanding ability in the crop protection.[4] In addition, several 1,4,2-benzodithiazine 1,1-dioxide (**1**),[5] imidazo[1,2-b]-1,4,2- benzodithiazine 5,5-dioxide (**2**)[6] and [1,2,4]triazolo[4,3-b]-1,4,2-benzodithiazine 5,5-dioxide derivatives (**3**)[7] (Figure 1) were prepared and showed interesting pharmacological activities.[5-7] Examples include compounds **1a**[7a,b] and **1b**[8d] that exhibit moderate anticancer activity, compound **1c**[8b] which shows diuretic activity, while **1d** [8a,c] and **1e**[8a] exhibit antihypertensive and diuretic activities, and derivatives of **1f** [8e] display antiviral and anti-HIV-1 activities. These compounds were also reported to possess fungicidal and herbicidal activities.[9] Several pyrido[2,3-*e*]-1,4,2-dithiazine 1,1-dioxides (**4**)[10] and pyrazolo[3,4-*e*]-1,4,2-dithiazine 1,1-dioxide (**5**)[11] were also prepared and reported to have biological activities (Figure 1).

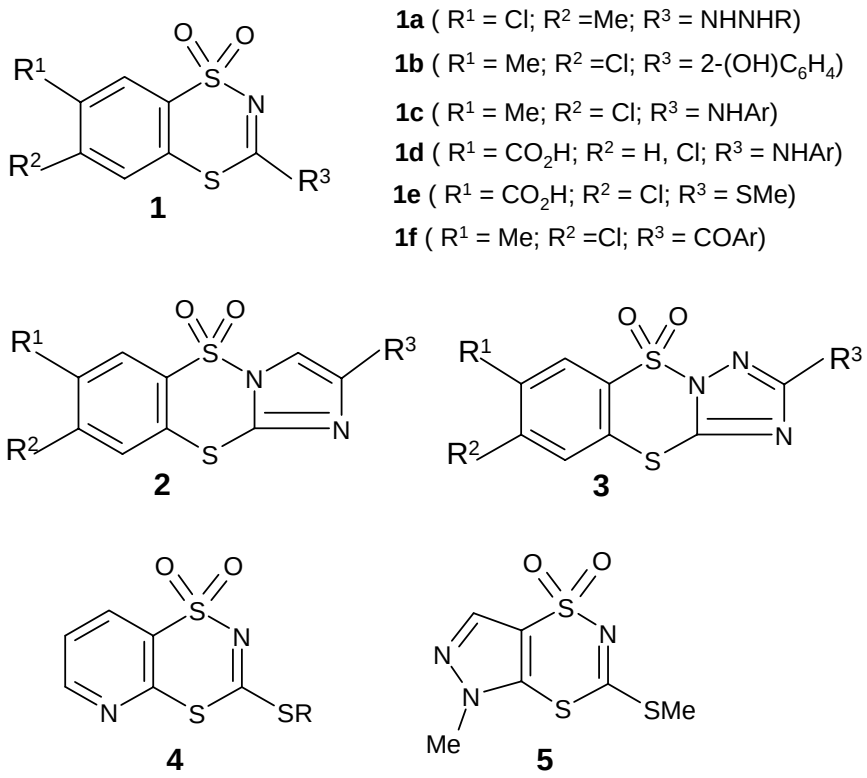
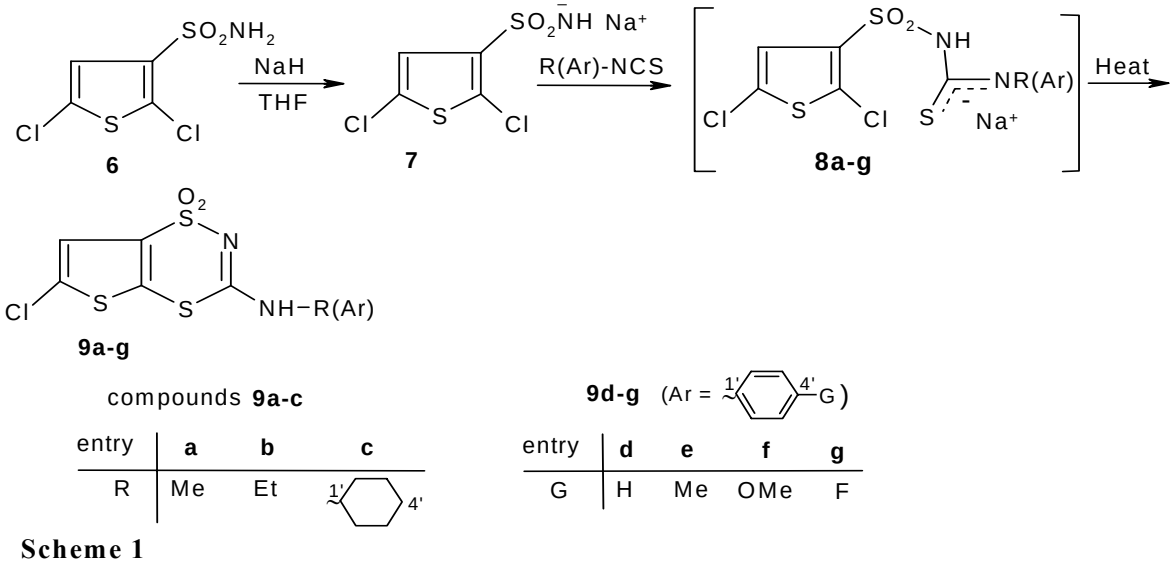


Figure 1

From view-point of isosterism, the thiophene ring system is commonly used in placement of the benzene ring in several pharmaceutical agents. To the best of our knowledge, the thieno[2,3-*e*]-1,4,2-dithiazine 1,1-dioxide bicyclic system (**9**), bioisostere of 1,4,2-benzodithiazine 1,1-dioxide (**1**), is hitherto un-described in the literature. Accordingly, we thought it would be worthwhile to synthesize a new set of *N*-(alkyl / aryl)-6-chlorothieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxides (**9a-g**) as illustrated in Scheme 1.

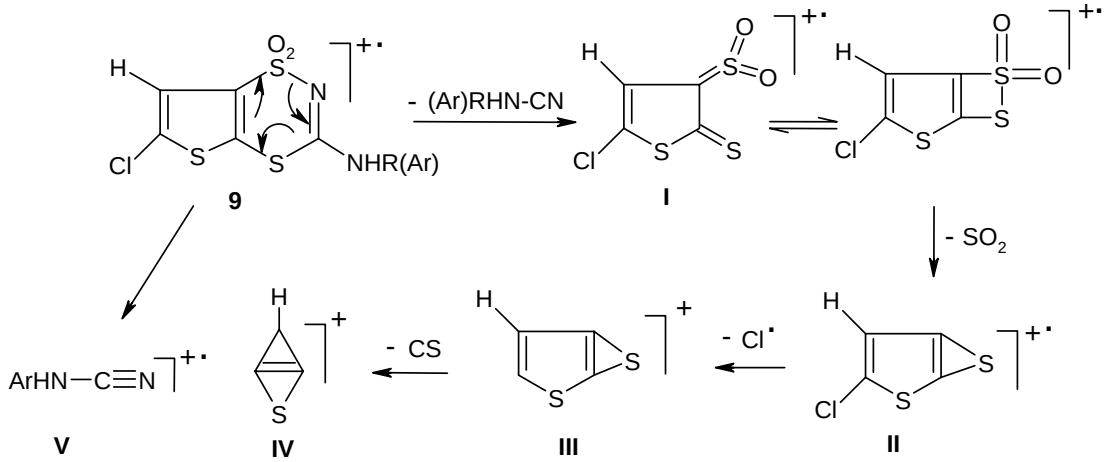
RESULTS AND DISCUSSION

In the present work, a new selected set of *N*-(alkyl- / aryl)-6-chlorothieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxides (**9a-g**) were synthesized, utilizing 2,5-dichloro-3-thiophenesulphonamide (**6**). The latter building block is prepared according to a reported procedure[12] that involves the reaction of 2,5-dichloro-thiophene with chlorosulfonic acid, followed by treatment of the resulting 2,5-dichlrorthiophene-3-sulfonyl chloride with excess 28 % aqueous ammonium hydroxide. Deprotonation of **6** with sodium hydride, produced the nitrogen anion **7** which reacts with the appropriate alkyl / aryl isothiocyanate in THF to deliver the respective intermediates **8a-g**. Upon heating, the latter intermediates underwent intramolecular cyclization to produce the desired heterocyclic compounds **9a-g** (Scheme 1).



Scheme 1

Elemental analyses and spectral (MS and NMR) data of the new compounds **9a-g**, given in the experimental part, are in accordance with the assigned structures. Thus, their MS spectra display the correct molecular ions as suggested by their molecular formulas. The isotopic cluster in the molecular ion region of the prepared compounds **9a-g** (M and M+2), with relative intensities 3:1, is in accordance with the presence of only one chlorine atom. The EI fragmentation pattern of **9a-g** proceeds *via* elimination of cayanamide molecule RHN-CN from the molecular ion leading to the formation of the respective ion **I** (*m/z* = 212). The latter ion suffers consecutive extrusion of SO_2, chlorine atom and CS with ultimate production of ions **II** (*m/z* = 148), **III** (*m/z* = 113) and **IV** (*m/z* = 69), respectively. The fragment ion **V** is also prominent in the MS spectra of **9d-g** (Scheme 2).



Scheme 2

^{1}H- and ^{13}C-NMR spectral data of the thieno[2,3-*e*]dithiazines **9a-g** are in agreement with their suggested structures. Signal assignments to the various protons and carbons followed from DEPT and 2D (COSY, HMQC, HMBC) experiments. The thieno H-7 proton resonates as a singlet around δ 7.3-7.7 ppm, and the

exchangeable C(3)-NH proton resonates in the range 9.50-9.60 ppm for **9a-c**, while in compounds **9d-g** the N-*H* proton resonates in the range 11.25-11.50 ppm. The presence of the N-*H* entity in **9a-g** is also evident from the IR spectra which display medium absorption bands characteristic of the N-*H* stretching vibration in the range 3210-3255 cm^{-1}.

EXPERIMENTAL

2,5-Dichlorothiophene was purchased from Acros. The alkyl- and aryl isothiocyanates, used in this study, were purchased from Fluka. Melting points were determined by Electrothermal-9002 apparatus and are uncorrected. IR Spectra were obtained as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX-300 instrument with Me_4Si as internal reference. Electron impact mass spectra (EIMS) were taken with Finnigan MAT-731 at 70 eV and at ion source temperature of 200 ^{o}C. Elemental analyses were carried out at Göttingen University, Germany.

2,5-Dichloro-3-thiophenesulphonamide (6)[12]

This compound is prepared *via* interaction of 2,5-dichloro-3-thiophenesulphonyl chloride with excess NH_4OH (28 %) at 100 ^{o}C for 30 min. according to a reported procedure.[12] The required 2,5-dichloro-3-thiophenesulphonyl chloride is, in turn, obtained by the reaction of 2,5-dichlorothiophene with excess chlorosulphonic acid at 100-110 ^{o}C for 2 h, by following a literature method.[12]

N-(Substituted)-6-chlorothieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxides (9a-g)

A stirred solution of the sulfonamide **6** (3.0 g, 13 mmol) in THF (70 mL) was treated portionwise with sodium hydride (60 % dispertion in mineral oil, 0.52 g, 13 mmol) at rt. After stirring for 30 min., the appropriate isothiocyanate (13 mmol) was added dropwise and the temperature of the stirred reaction mixture was then raised to 60 ^{o}C and maintained at this temperature for 10 h. The solvent was evaporated, the residual solid product was soaked in water (60 mL) containing glacial AcOH (2 mL), filtered, washed with water, dried and crystallized from chloroform / pet. ether (1:1, v/v). Yields were in the range 32-73 %. For analyses, all new compounds were further purified on preparative TLC silica-gel plates using chloroform as eluent.

6-Chloro-*N*-methylthieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9a)

Yield = 44 %, mp 240-242 ^{o}C. *Anal.* Calcd for $C_6H_5ClN_2O_2S_3$ (268.77): C, 26.81; H, 1.88; N, 10.42. Found: C, 26.88; H, 1.75; N, 10.32; EIMS *m/z* (%): 268 (M^+, 37), 212 (69), 148 (66), 113 (12), 69 (100); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.87 (s, 3H, CH_3), 7.55 (s, 1H, H-7), 9.59 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3 (CH_3), 122.2 (C-7), 129.8 (C-4a), 130.2, 131.5 (C-7a, C-6), 160.2 (C-3).

6-Chloro-*N*-ethylthieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9b)

Yield = 34 %, mp 180-182 °C. *Anal.* Calcd for $C_7H_7ClN_2O_2S_3$ (282.80): C, 29.73; H, 2.49; N, 9.91. Found: C, 29.87; H, 2.44; N, 9.97; EIMS *m/z* (%): 282 (M^+, 38), 212 (80), 148 (75), 113 (12), 69 (100); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.3 Hz, 3H, CH_3 CH_2), 3.56 (q, *J* = 7.3 Hz, 2H, CH_2Me), 9.55 (br s, 1H, NH), 7.35 (s, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3CH_2), 40.1 (CH_2Me), 122.3 (C-7), 129.6 (C-4a), 131.6, 131.7 (C-7a, C-6), 160.1 (C-3).

6-Chloro-*N*-cyclohexylthieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9c)

Yield = 33 %, mp 203-205 °C. *Anal.* Calcd for $C_{11}H_{13}ClN_2O_2S_3$ (336.88): C, 39.22; H, 3.89; N, 8.32. Found: C, 39.24; H, 3.75; N, 8.31; EIMS *m/z* (%): 336 (M^+, 24), 254 (56), 212 (100), 148 (34), 113 (8), 69 (62); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13-1.44 (m, 5H / cyclohexyl), 1.52-1.88 (m, 5H / cyclohexyl), 3.76 (m, 1H, H-1'), 7.55 (s, 1H, H-7), 9.54 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3 (C-3' / C-5'), 24.9 (C-4'), 31.4 (C-2' / C-6'), 53.5 (C-1'), 122.3 (C-7), 129.4 (C-4a), 130.1, 131.6 (C-7a, C-6), 158.9 (C-3).

6-Chloro-*N*-phenylthieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9d)

Yield = 62 %, mp 243-245 °C. *Anal.* Calcd for $C_{11}H_7ClN_2O_2S_3$ (330.84): C, 39.94; H, 2.13; N, 8.47. Found: C, 39.78; H, 2.21; N, 8.49; EIMS *m/z* (%): 330 (M^+, 38), 266 (5), 212 (80), 148 (69), 118 (65), 113 (13), 69 (100); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26 (dd, *J* = 8.2, 1.8 Hz, 1H, H-4'), 7.46 (dd, *J* = 8.1, 1.8 Hz, 2H, H-2' + H-6'), 7.62 (d, *J* = 8.1, 8.2 Hz, 2H, H-3' + H-5'), 7.69 (s, 1H, H-7), 11.44 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.1 (C-2' / C-6'), 119.1 (C-4'), 122.2 (C-7'), 129.4 (C-4a), 129.8 (C-3' / C-5'), 130.1, 130.5 (C-7a, C-6), 148.1 (C-1'), 158.1 (C-3).

6-Chloro-*N*-(4-methylphenyl)thieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9e)

Yield = 48 %, mp 238-240 °C. *Anal.* Calcd for $C_{12}H_9ClN_2O_2S_3$ (344.87): C, 41.79; H, 2.63; N, 8.12. Found: C, 41.90; H, 2.80; N, 7.99; EIMS *m/z* (%): 344 (M^+, 35), 212 (15), 148 (31), 132 (100), 113 (8), 69 (56); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.24 (d, *J* = 7.8 Hz, 2H, H-2' + H-6'), 7.48 (d, *J* = 7.8 Hz, 2H, H-3' + H-5'), 7.64 (s, 1H, H-7), 11.31 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5 (CH_3), 116.0 (C-2' / C-6'), 122.2 (C-7), 128.2 (C-4'), 129.4 (C-3' / C-5'), 129.5 (C-4a), 130.3, 130.7 (C-7a, C-6), 143.8 (C-1'), 158.2 (C-3).

6-Chloro-*N*-(4-methoxyphenyl)thieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9f)

Yield = 73 %, mp 248-250 °C. *Anal.* Calcd for $C_{12}H_9ClN_2O_3S_3$ (360.87): C, 39.94; H, 2.51; N, 7.76. Found: C, 39.79; H, 2.39; N, 7.60; EIMS *m/z* (%): 360 (M^+, 18), 239 (10), 212 (4), 148 (100), 133 (27),

113 (7), 105 (14), 69 (19); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H, CH_3O), 7.00 (d, J = 8.0 Hz, 2H, H-2' + H-6'), 7.49 (d, J = 8.0 Hz, 2H, H-3' + H-5'), 7.63 (s, 1H, H-7), 11.26 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.3 (CH_3O), 114.3 (C-3' / C-5'), 116.1 (C-2' / C-6'), 122.2 (C-7), 130.2 (C-4a), 130.6, 130.9 (C-7a, C-6), 141.1 (C-1'), 154.2 (C-4'), 157.8 (C-3).

6-Chloro-*N*-(4-fluorophenyl)thieno[2,3-*e*]-1,4,2-dithiazin-3-amine 1,1-dioxide (9g)

Yield = 45 %, mp 239-241 ^{o}C. *Anal.* Calcd for $C_{11}H_6ClFN_2O_2S_3$ (348.83): C, 37.88; H, 1.73; N, 8.03. Found: C, 37.78; H, 1.81; N, 7.98; EIMS *m/z* (%): 348 (M^+, 38), 284 (7), 212 (89), 148 (53), 136 (38), 118 (65), 113 (12), 69 (100); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (dd, J_{H-H} = 8.8 Hz, $^4J_{H-F}$ = 4.7 Hz, 2H, H-2' / H-6'), 7.40 (dd, J_{H-H} = 8.8 Hz, $^3J_{H-F}$ = 9.4 Hz, 2H, H-3' / H-5'); 7.63 (s, 1H, H-7), 11.50 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.8 (d, $^2J_{C-F}$ = 20.1 Hz, C-3' / C-5'), 116.0 (d, $^3J_{C-F}$ = 4.8 Hz, C-2' / C-6'), 122.3 (C-7), 130.3 (C-4a), 130.6, 130.9 (C-7a, C-6), 149.0 (d, $^4J_{C-F}$ = 2.3 Hz, C-1'), 156.1 (d, $^1J_{C-F}$ = 235 Hz, C-4'), 160.8 (C-3).

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