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 compounds1 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 1a7a,b and 1b8d that exhibit moderate anticancer activity, compound 1e8b which shows diuretic activity, while 1d8a,c and 1e8a exhibit antihypertensive and diuretic activities, and derivatives of 1f8e 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).
From viewpoint 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 undescribed 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\textsuperscript{12} that involves the reaction of 2,5-dichlorothiophene with chlorosulfonic acid, followed by treatment of the resulting 2,5-dichlorothiophene-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).
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 SO₂, 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).

$^1$H- and $^{13}$C-NMR spectral data of the thieno[2,3-c]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 $\delta$ 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\(_4\)Si as internal
reference. Electron impact mass spectra (EIMS) were taken with Finnigan MAT-731 at 70 eV and at ion
source temperature of 200 °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\(_2\)OH (28 %) at 100 °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 °C for 2 h, by following a literature method.\(^{12}\)

\(\text{N-(Substituted)-6-chlorothieno[2,3-e]-1,4,2-dithiazin-3-amine 1,1-dioxide (9a-g)}\)

A stirred solution of the sulfonamide 6 (3.0 g, 13 mmol) in THF (70 mL) was treated portionwise with
sodium hydride (60 % dispersion 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 °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)**

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\(_3\)): \(\delta\) 2.87 (s, 3H, CH\(_3\)), 7.55 (s, 1H, H-7), 9.59 (br s, 1H, NH); \(^{13}\)C NMR (75
MHz, CDCl\(_3\)): \(\delta\) 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 C₇H₇ClN₂O₂S₃ (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); ¹H NMR (300 MHz, CDCl₃): δ 1.26 (t, J = 7.3 Hz, 3H, CH₃CH₂), 3.56 (q, J = 7.3 Hz, 2H, CH₂Me), 9.55 (br s, 1H, NH), 7.35 (s, 1H, H-7); ¹³C NMR (75 MHz, CDCl₃): δ 13.9 (CH₃CH₂), 40.1 (CH₂Me), 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 C₁₁H₁₃ClN₂O₂S₃ (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); ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₁H₇ClN₂O₂S₃ (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); ¹H NMR (300 MHz, DMSO-d₆): 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); ¹³C NMR (75 MHz, DMSO-d₆): 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 C₁₂H₉ClN₂O₂S₃ (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); ¹H NMR (300 MHz, DMSO-d₆): δ 2.31 (s, 3H, CH₃), 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); ¹³C NMR (75 MHz, DMSO-d₆): δ 20.5 (CH₃), 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 C₁₂H₉ClN₂O₃S₃ (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-$d_{6}$): $\delta$ 3.77 (s, 3H, CH$_{3}$O), 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-$d_{6}$): $\delta$ 55.3 (CH$_{3}$O), 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 °C. Anal. Calcd for C$_{11}$H$_{6}$ClFN$_{2}$O$_{2}$S$_{3}$ (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$_{3}$): $\delta$ 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$_{3}$): $\delta$ 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).

ACKNOWLEDGEMENTS

We are grateful to the Deanship of Graduate Studies of Al al-Bayt University (Mafraq, Jordan) and DFG (Germany) for financial support. The Chemistry Department of Jordan University is acknowledged for providing laboratory facilities enabling us to carry out the experimental part thereat.

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