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Facile synthesis of 2-(substituted amino)-4*H*-thieno[3,2-*e*]-1,3-thiazin-4-ones

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Abstract Interaction between 2,5-dichlorothiophene-3-carbonyl isothiocyanate, accessible *via* 2,5-dichlorothiophene-3-carbonyl chloride, and model heterocyclic amines produced the respective 2,5-dichloro-*N*-(substituted aminocarbonothioyl)thiophene-3-carboxamides. Upon heating, the deprotonated form of the latter underwent intramolecular cyclization to deliver the corresponding 2-(substituted amino)-4*H*-thieno[3,2-*e*]-1,3-thiazin-4-ones. The structures of these new bicyclic derivatives and their acyclic precursors are based on microanalytical and spectral (IR, MS, and NMR) data.

Keywords 2,5-Dichlorothiophene-3-carbonyl isothiocyanate; *sec*-Cyclic amines; *N*-(3-thienylcarbonyl)thioureas; Thieno[3,2-*e*]-1,3-thiazin-4-ones; S_NAE reactions.

Introduction

Several 4*H*-1,3-benzothiazin-4-one derivatives (**1**, Fig. 1) have been prepared and showed interesting pharmacological activities, particularly those incorporating heterocyclic or amino appendages at the C-2 locus [1–5]. Examples include **1a**, an inhibitor of apoptosis and cytoprotective agent [1], **1b** useful as heart muscle cell apoptosis inhibitor and remedy for heart diseases [2], **1c** that displays inhibitory effects on xanthine oxidase [3], **1d** patented as agrochemical fungicide [4], and **1e** that acts as bronchodilator, phosphordiesterase inhibitor, and is useful for symptomatic relief in asthma and other respiratory diseases [5].

Few heteroarenes fused to the 1,3-thiazine ring, such as pyrido[3,2-*e*]-1,3-thiazienes (**2**, Fig. 1), are known. The latter **2** are 8-aza analogs of **1** and several derivatives have been synthesized and claimed [6] to possess kainic acid neuronotoxicity inhibitory activity, useful as nervous cell protectors for prevention and treatment of diabetes mellitus, *Parkinson* disease, psychosis, epilepsy, ischemic brain diseases, multiple scleredema, neuroallergy diseases, *Huntington* chorea, *Alzheimer* diseases, drug dependence, and related diseases.

From the point of isosterism, the thiophene ring system is commonly used as replacement of the benzene ring in several pharmaceutical agents. To date the synthesis and chemistry of some thieno[3,2-*d*]-[1,3]thiazin-4-ones, exemplified by **3a** [7], **3b**, and **3c** [8] have been described in literature.

To the best of our knowledge, the isomeric 4*H*-1,3-thieno[3,2-*e*]thiazin-4-one bicyclic system **8**, a bioisostere of 4*H*-1,3-benzothiazin-4-one (**1**), is hitherto undescribed. Accordingly, we thought it would be worthwhile to synthesize a new set of 2-(substituted amino)-4*H*-thieno[3,2-*e*]-1,3-thiazin-4-ones (**8a**–**8d**) utilizing the appropriate acyclic synthons 2,5-dichloro-*N*-(substituted aminocarbonothioyl)thiophene-3-carboxamides (**7a**–**7d**) as illustrated in Scheme 1.

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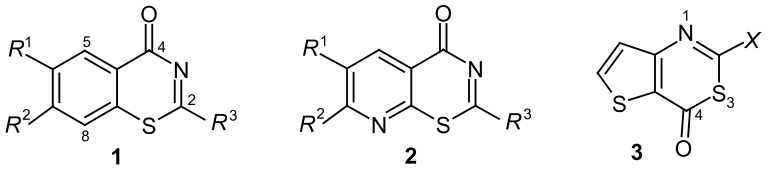
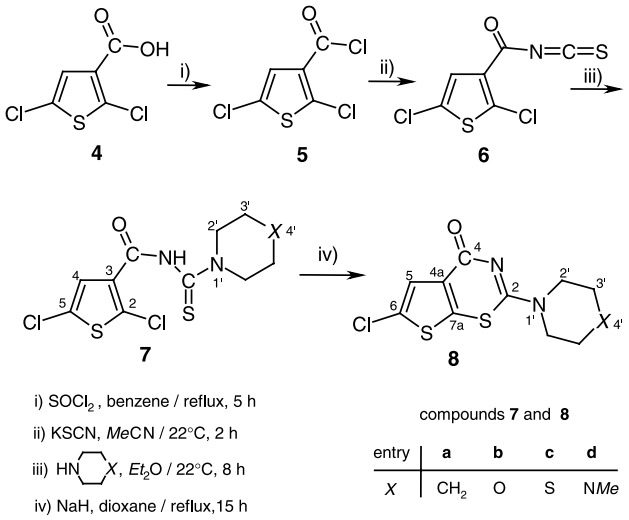


1a (R^1, R^2 = H; R^3 = (6-SO_2Me-2-*Py*))
1b (R^1, R^2 = H; R^3 = 2-*Py*)
1c (R^1, R^2 = H; R^3 = NH_2)
1d (R^1, R^2 = H; R^3 = OC_6H_4-Cl(*p*))
1e (R^1, R^2 = O*Me*; R^3 = NR_2)

3a (X = NH_2)
3b (X = NH-CO*Ph*)
3c (X = NH-CO-tolyl)

Fig. 1



i) $SOCl_2$, benzene / reflux, 5 h
ii) KSCN, *Me*CN / 22°C, 2 h
iii) HN⟨X⟩, Et_2O / 22°C, 8 h
iv) NaH, dioxane / reflux,15 h

compounds **7** and **8**

entry	a	b	c	d
X	CH_2	O	S	N*Me*

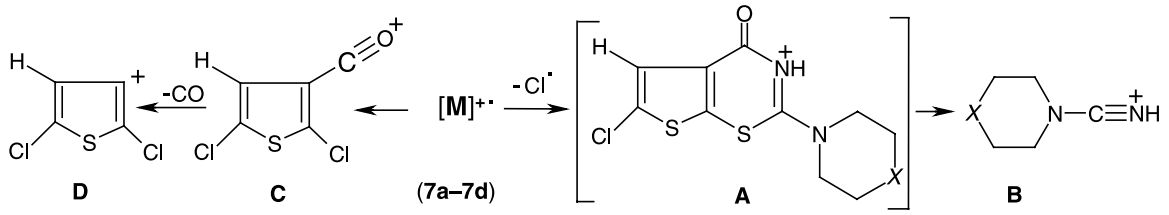
Scheme 1

Results and discussion

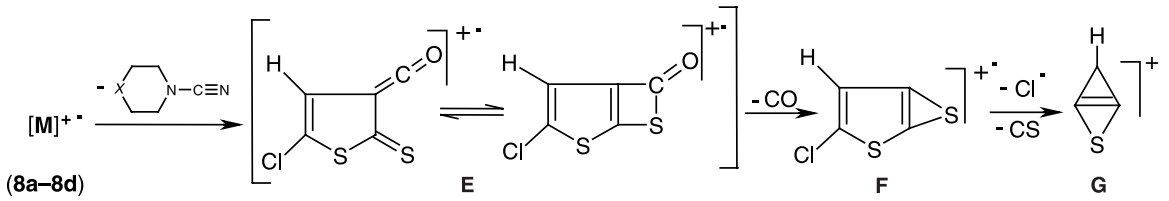
In the present work, a new selected set of 2,5-dichloro-*N*-(substituted amino-carbonothioyl)thiophene-3-carboxamides (**7a**–**7d**) and 2-(substituted amino)-4*H*-thieno[3,2-*e*]-1,3-thiazin-4-ones (**8a**–**8d**) were synthesized, utilizing 2,5-dichlorothiophene-3-carboxylic acid (**4**). The latter acid is prepared according to a reported procedure [10] that involves the reaction of 2,5-dichlorothiophene with acetyl chloride in carbon disulfide in the presence of aluminum trichloride, followed by treatment of the resulting 3-acetyl-2,5-dichlorothiophene with sodium hypochloride solution followed by acidification. The acid **4** was converted into 2,5-dichlorothiophene-3-carbonyl chloride (**5**) upon interaction with thionyl chloride according to Ref. [11].

Treatment of **5** with potassium thiocyanate in acetonitrile yielded 2,5-dichlorothiophene-3-carbonyl isothiocyanate (**6**). The reaction of the latter with cyclic secondary amines (exemplified by piperidine, morphopline, thiomorpholine, and *N*-methylpiperazine) afforded the corresponding 2,5-dichloro-*N*-(substituted aminocarbonothioyl)thiophene-3-carboxamides **7a**–**7d**. Upon heating, deprotonated **7a**–**7d** underwent intramolecular cyclization to produce the desired heterocyclic compounds **8a**–**8g** (Scheme 1).

Elemental analyses and spectral (MS and NMR) data of the new compounds **7** and **8**, 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 formulae. The isotopic cluster for **7** (M, M + 2, and M + 4) with relative intensities 9:6:1 is in accord with the presence of two chlorine atoms. The molecular ion region of the bicyclic compounds **8** displays isotopic cluster (M and M + 2) with relative intensities 3:1, thus confirming the presence of only one chlorine atom. A prominent fragmentation pattern of **7**, under electron impact, involves loss of a chlorine atom to form the cation **A** as the base peak which is equivalent to $[M]^+$-Cl. The latter fragments further to form the corresponding cyanamidium cation **B** (Scheme 2). Another fragmentation mode of the molecular ion involves amide cleavage to produce the corresponding cation **C** ($m/z = 179$), which then extrudes carbon monoxide to give the cation **D** ($m/z = 151$). The EI fragmentation pattern of **8** proceeds *via* elimination of a cyanamide molecule from the molecular ion leading to the formation of the respective ion **E** ($m/z = 176$) as the base peak in **8a**–**8d** (Scheme 3). The latter ion suffers extrusion of CO to deliver ion **F** ($m/z = 148$), which then eliminates a chlorine atom and CS with ultimate production of ion **G** ($m/z = 69$).



Scheme 2



Scheme 3

^{1}H and ^{13}C NMR spectroscopic data of compounds **7a–7d** and **8a–8d** are in agreement with the suggested structures. Signal assignments to the various protons and carbons followed from DEPT and 2D (COSY, HMQC, HMBC) experiments. The thieno H-4 proton resonates as a singlet around $\delta = 7.20$ and 7.49 ppm for compounds **7a–7d** and **8a–8d**, while the exchangeable C(3)-NH proton in **7a–7d** resonates at *ca.* 8.68 ppm. The IR spectra of **7a–7d** showed strong absorption bands, arising from stretching vibrations, around 3180 for N–H, 1670 for C=O, and 1240 cm^{-1} for C=S groups. On the other hand, the IR spectra of **8a–8d** showed also a strong absorption band around 1630 cm^{-1} for the C=O group, but lacked the characteristic peaks for the N–H and C=S groups.

Experimental

2,5-Dichlorothiophene was purchased from Acros. Piperidine, morpholine, thiomoropholine, and 1-methylpiperazine were purchased from Fluka. Melting points were determined by Electrothermal-9002 apparatus. IR Spectra were obtained for 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. Chemical shifts are expressed in ppm with reference to *TMS* as internal standard. Electron impact mass spectra (EIMS) were taken with Finnigan MAT-731 at 70 eV and at ion source temperature of 200°C. For analyses, all new compounds were further purified on preparative TLC silica-gel glass plates using dichloromethane as eluent. Elemental analyses (C, H, N, S) were carried out at Stuttgart University/Germany, and the results were found to be in good agreement (±0.3%) with the calculated values.

3-Acetyl-2,5-dichlorothiophene was prepared *via* reaction of 2,5-dichlorothiophene with acetyl chloride in carbon disulphide in the presence of anhydrous aluminum trichloride, following Ref. [9]. 2,5-Dichlorothiophene-3-carboxylic acid (**4**) was prepared by oxidation of 3-acetyl-2,5-dichlorothiophene using 10% aq. NaOCl solution at 55°C according to Ref. [10]. 2,5-Dichlorothiophene-3-carbonyl chloride (**5**) was prepared by interaction between **4** and thionyl chloride in dry benzene under reflux for 6 h, following Ref. [11].

2,5-Dichlorothiophene-3-carbonyl isothiocyanate (**6**, $C_6H_1Cl_2NOS_2$)

Potassium thiocyanate (3.5 g, 36 mmol) was added portionwise to a stirred solution of 2.8 g 2,5-dichlorothiophene-3-carbonyl chloride (**5**) (13 mmol) in 25 cm^3 acetonitrile at room temp. The reaction mixture was stirred further for 2 h, the precipitated KCl was filtered off, and the organic solvent was evaporated from the filtrate under reduced pressure. The title compound was obtained as a crude orange solid, which was used in the next step without further purification. Yield 2.91 g (94%).

*2,5-Dichloro-N-(substituted aminocarbonothioyl)thiophene-3-carboxamides **7a–7d** (General procedure)*

A solution of 12 mmol of the appropriate secondary amine in 10 cm^3 diethyl ether was added dropwise to a stirred solution of 2.86 g **6** (12 mmol) in 40 cm^3 diethyl ether. The resulting mixture was further stirred at room temp and the reaction was completed within 7–8 h (as evidenced from TLC). The precipitated solid product was collected by suction filtration, washed with water, and purified by recrystallization from dichloromethane/petroleum ether (bp 40–60°C). For analyses, compounds **7a–7d** were further purified on preparative TLC silica-gel glass plates using dichloromethane as eluent.

2,5-Dichloro-N-(piperidin-1-ylcarbonothioyl)thiophene-3-carboxamide (**7a**, $C_{11}H_{12}Cl_2N_2OS_2$)
Yield 82%; mp 120–122°C; IR (KBr): $\bar{\nu} = 3184$ (N–H), 3078, 2887 (C–H), 1772 (C=O), 1534 (C=N), 1242 (C=S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.71$ (br m, H_2-3′ + H_2-4′ + H_2-5′), 3.61, 4.13 (2 br, H_2-2′ + H_2-6′), 7.19 (s, H-4), 8.67 (br s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.1$ (C-4′), 25.2, 26.5 (C-3′, C-5′), 52.4, 52.7 (C-2′, C-6′), 127.3 (C-4), 127.7 (C-3), 130.2 (C-5), 132.3 (C-2), 156.3 (C=S), 176.8 (C=O) ppm; EIMS: m/z (%) = 322 (M^+, 3), 287 (100), 179 (51), 151 (11), 111 (33), 84 (54).

2,5-Dichloro-N-(morpholin-4-ylcarbonothioyl)thiophene-3-carboxamide (**7b**, $C_{10}H_{10}Cl_2N_2O_2S_2$)
Yield 83%; mp 152–153°C; IR (KBr): $\bar{\nu} = 3188$ (N–H), 2966, 2861 (C–H), 1674, C=O), 1516 (C=N), 1240 (C=S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.84$ (br, H_2-3′ + H_2-5′), 3.64, 4.21 (2 br, H_2-2′ + H_2-6′), 7.23 (s, H-4), 8.71 (br s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.5$, 52.6 (C-2′, C-6′), 63.1, 66.9 (C-3′, C-5′), 127.1 (C-4), 127.7 (C-3), 129.8 (C-5), 130.0 (C-2), 156.2 (C=S), 177.9 (C=O) ppm; EIMS: m/z (%) = 324 (M^+, 12), 289 (100), 179 (62), 151 (9), 113 (22), 86 (29).

2,5-Dichloro-N-(thiomorpholin-4-ylcarbonothioyl)thiophene-3-carboxamide (**7c**, $C_{10}H_{10}Cl_2N_2OS_3$)
Yield 84%; mp 154–155°C; IR (KBr): $\bar{\nu} = 3188$ (N–H), 3100, 2910 (C–H), 1662 (C=O), 1520 (C=N),1242 (C=S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.83$ (br, H_2-3′ + H_2-5′), 3.95, 4.43 (2 br, H_2-2′ + H_2-6′), 7.20 (s, H-4), 8.68 (br s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.8$, 28.4 (C-3′, C-5′), 53.6, 54.2 (C-2′, C-6′), 127.2 (C-4), 127.7 (C-3), 129.7 (C-5), 131.0 (C-2), 156.1 (C=S), 178.4 (C=O), ppm; EIMS: m/z (%) = 340 (M^+, 21), 305 (100), 179 (68), 151 (11), 129 (13), 102 (8).

2,5-Dichloro-N-(4-methylpiperazin-1-ylcarbonothioyl)thiophene-3-carboxamide (**7d**, $C_{11}H_{13}Cl_2N_3OS_2$)
Yield 81%; mp 151–152°C; IR (KBr): $\bar{\nu} = 3190$ (N–H), 3097, 2914 (C–H), 1632 (C=O), 1536 (C=N), 1242 (C=S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, NCH_3), 2.55 (br, H_2-3′ + H_2-5′), 3.65, 4.22 (2 br, H_2-2′ + H_2-6′), 7.19 (s, H-4), 8.69 (br s, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.3$ (NCH_3), 51.1, 51.8 (C-2′, C-6′), 54.3, 54.5 (C-3′, C-5′), 127.2 (C-4), 127.5 (C-3), 129.7 (C-5), 131.1 (C-2), 156.2 (C=S), 177.5 (C=O) ppm; EIMS: m/z (%) = 337 (M^+, 15), 302 (100), 179 (75), 151 (18), 126 (23), 99 (25).

2-(Substituted amino)-4H-thieno[3,2-e]-1,3-thiazin-4-ones ***8a–8d*** *(General procedure)*
Sodium hydride (0.48 g, 60% dispersion in mineral oil, 12 mmol) was added portionweise to a stirred solution of 10 mmol of the appropriate **4** in 30 cm^3 dioxane. The reaction mixture was refluxed for 16 h, the solvent was then removed under reduced pressure, the residual solid product was washed with 3×5 cm^3 H_2O, and purified by recrystallization from chloroform/petroleum ether (bp 40–60°C). For analyses, compounds **8a**–**8d** were further purified on preparative TLC silica-gel glass plates using chloroform as eluent.

6-Chloro-2-(piperidin-1-yl)-4H-thieno[3,2-e]-1,3-thiazin-4-one (**8a**, $C_{11}H_{11}ClN_2OS_2$)
Yield 66%; mp 137–138°C; IR (KBr): $\bar{\nu} = 3082$, 2876 (C–H), 1630 (C=O), 1540, 1514 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.72$ (br m, H_2-3′ + H_2-4′ + H_2-5′), 3.79 (br, H_2-2′ + H_2-6′), 7.49 (s, H-5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.4$ (C-4′), 25.5 (C-3′, C-5′) 47.9, (C-2′, C-6′), 125.3 (C-5), 126.0 (C-4a), 128.8 (C-6), 136.1 (C-7a), 160.2 (C-2), 164.3 (C-4) ppm; EIMS: m/z (%) = 286 (M^+, 26), 176 (100), 148 (17), 69 (24).

6-Chloro-2-(morpholin-4-yl)-4H-thieno[3,2-e]-1,3-thiazin-4-one (**8b**, $C_{10}H_9ClN_2O_2S_2$)
Yield 78%; mp 190–191°C; IR (KBr): $\bar{\nu} = 3078$, 2886 (C–H), 1638 (C=O), 1540, 1510 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ (br, H_2-2′ + H_2-6′), 3.83 (br, H_2-3′ + H_2-5′), 7.50 (s, H-5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 46.6$, (C-2′, C-6′), 66.1 (C-3′, C-5′), 125.0 (C-5), 126.0 (C-4a), 129.3 (C-6), 135.7 (C-7a), 161.2 (C-2), 164.0 (C-4) ppm; EIMS: m/z (%) = 288 (M^+, 19), 176 (100), 148 (19), 69 (29).

6-Chloro-2-(thiomorpholin-4-yl)-4H-thieno[3,2-e]-1,3-thiazin-4-one (**8c**, $C_{10}H_9ClN_2OS_3$)
Yield 82%; mp 169–170°C; IR (KBr): $\bar{\nu} = 3086$, 2887 (C–H), 1632 (C=O), 1532, 1512 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.42$ (br, H_2-3′ + H_2-5′), 3.45 (br, H_2-2′ + H_2-6′), 7.48 (s, H-5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.3$ (C-3′, C-5′), 47.1, (C-2′, C-6′), 125.0 (C-5), 126.0 (C-4a), 129.1 (C-6), 135.8 (C-7a), 161.0 (C-2), 164.2 (C-4) ppm; EIMS: m/z (%) = 304 (M^+, 46), 176 (100), 148 (23), 69 (18).

6-Chloro-2-(4-methylpiperazin-1-yl)-4H-thieno[3,2-e]-1,3-thiazin-4-one (**8d**, $C_{11}H_{12}ClN_3OS_2$)
Yield 75%; mp 162–163°C; IR (KBr): $\bar{\nu} = 3085$, 2886 (C–H), 1636 (C=O), 1538, 1515 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (s, NCH_3), 2.44 (br, H_2-3′ + H_2-5′), 3.85 (br, H_2-2′ + H_2-6′), 7.49 (s, H-5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 42.2$ (NCH_3), 46.1 (C-3′, C-5′), 54.4, (C-2′, C-6′), 125.0 (C-5), 126.0 (C-4a), 129.0 (C-6), 136.1 (C-7a), 161.9 (C-2), 163.8 (C-4), ppm; EIMS: m/z (%) = 301 (M^+, 9), 176 (100), 148 (10), 69 (13).

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