Synthesis of novel water soluble onium salts and thieno[3,4-*c*]thiolactones – precursors of conductive materials derived from substituted 2-aminothiophenes

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Dedicated to Professor Rosa Lederkremer on her 70th anniversary

Abstract

The synthetic utility in the area of synthesis of "smart" conductive materials of the easily accessible 2-aminothiophenes is described. Simple protection of amino group and subsequent radical bromination leads to brominated intermediates. The novel 4-bromomethylthiophene derivatives easily enter into reaction with tertiary amines and thiourea to give ammonium and thiouronium salts – novel water-soluble thiophenes. Thiouronium salts are predisposed to deliver substituted thieno[3,4-*c*]thiolactone derivatives, which are attractive from the point of view of their further utilization in the synthesis of thieno[3,4-*c*]thiophenes. Each of the mentioned compounds showed bioactivity as well as propensity to be polymerized to conductive oligomers and polymers.

Keywords: 2-Aminothiophenes, thieno[3,4-*c*]thiolactones, thieno[3,4-*c*]thiophenes ammonium salts, water soluble conductive materials

Introduction

Functionalized polyheterocycles belong to a class of novel polyconjugated materials possessing unconventional electrical, optical and magnetic properties.[1] Substituted polythiophenes are important members of this family, especially the poly-3- and 3,4-substituted ones.[2,3] Thiophene derivatives are the most promising materials for a variety of applications in electronics and optoelectronics. They are unique for their relative stability, suitable optical nonlinearity and spectral characteristics.[4] In addition to being environmentally stable; they possess good workability and satisfactory solubility in both organic and aqueous media. Their broad range of

properties makes them suitable for a new generation of useful tools in the areas of diagnostics, therapeutics, drug screening.

The aim of our study was to synthesize new ammonium salts (Scheme 1) from the corresponding bromothiophene derivatives by their reaction with tertiary amines in a simple manner. Ammonium salts are water soluble compounds with predictable biological activity.

We were also interested in the synthesis of thieno[3,4-*c*]thiolactone derivates (Scheme 2). Thieno[3,4-*c*]thiolactones seem to be useful intermediates in the synthesis of thieno[3,4-*c*]thiophenes. Such derivatives represents a 10-π electron heteropentalene system containing nonclassical tetracovalent sulphur nucleus and are have been investigated from the synthetic and theoretical point of view;[5-7] they also represents important building blocks in the synthesis of polymeric conductive materials.

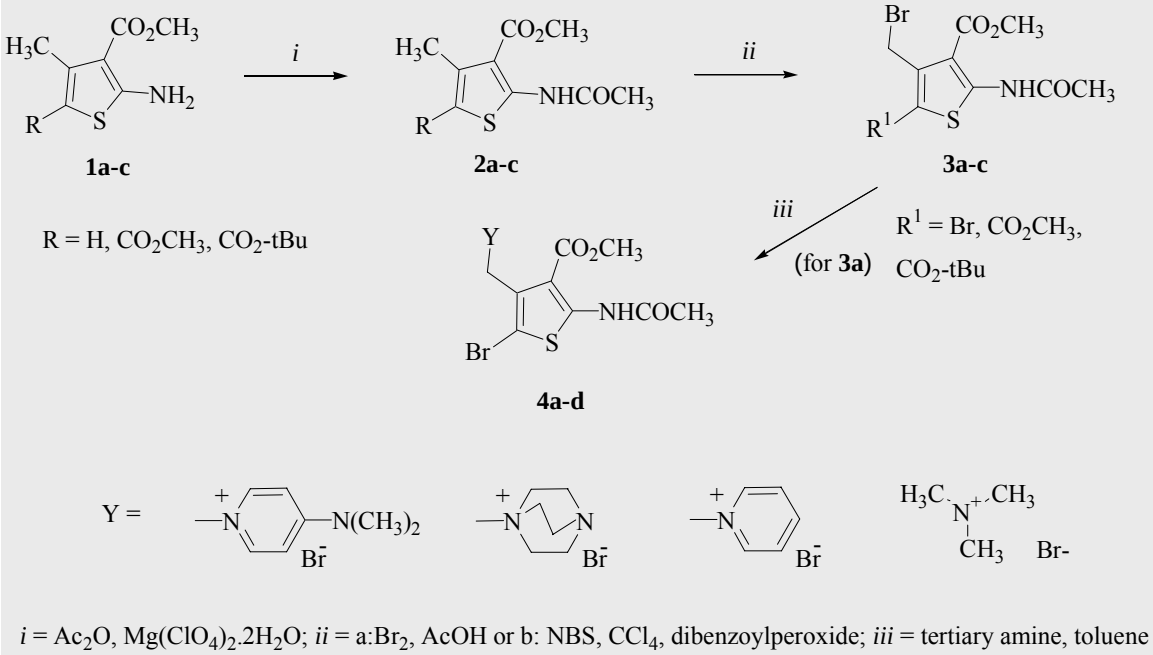
Results and Discussion

The substituted 2-aminothiophenes (**1a-c**) represent an easily available starting material for the synthesis of target thieno[3,4-*c*]thiolactone derivatives (**7a-c**). Preparation of 2-aminothiophenes is a very simple, one-step reaction originally published by Gewald.[8] We have now synthesized three types of 2-aminothiophenes by two of procedures. In the first one we prepared 5-unsubstituted 2-aminothiophene derivative **1a** by the procedure published in our earlier paper.[9] Persubstituted 2-aminothiophenes **1b,c** were prepared afforded the appropriate 2-aminothiophenes in good yields and purity. Simple protection of amino group, necessary for next step bromination, and performed by acetic anhydride with catalytic use of $(MgClO_4)_2.2H_2O$ led to *N*-acetylaminothiophene derivatives (**2a-c**).

The methyl group of *N*-acetylaminothiophenes **2a-c** could be successfully brominated. For bromination of methyl 2-acetylamino-4-methyl-3-thiophene carboxylate (**2a**) two approaches were tried, one by bromine in acetic acid, the other by *N*-bromosuccinimide in carbon tetrachloride (Scheme 1). In the first method two equivalents of bromine were used, and bromination took place at the methyl group in position C-4 as well to at position C-5 to give the 5-bromo-4-bromomethyl derivative **3a** in 90 % yield. In the second approach, the use of *N*-bromosuccinimide in carbon tetrachloride, a typical radical bromination of side chains with use of dibenzoyl peroxide as an initiator, failed to produce bromomethylated derivative without bromine at the C-5 position of thiophene. In this case the thiophene position 5 was the first to be brominated, giving a monobrominated product, followed by bromination of the methyl group and the target bromomethylene thiophene derivate **3a,** isolated from the reaction mixture with monobrominated derivate. Only the use of 2 equiv. of *N*-bromosuccinimide, 4-5 refluxing in carbon tetrachloride pushed the yield of **3a** to the maximum of 69%. However, the use of *N*-bromosuccinimide in CCl_4 (with dibenzoylperoxide) means a simple and successful method for brominating the methyl group in a case of 5-acetylamino-3-methylthiophene–2,4-dicarboxylic acid dimethylester (**2b**) and its 2-*tert*-butoxycarbonyl analogue (**2c**) (Scheme 2) to give

bromoderivates **3b,c** in approximately yield 70%. Bromomethylated derivatives of 2-aminothiophnenes (**3a-c**) are key intermediates in the synthesis of quaternary ammonium salts **4a-d** (Scheme 1) and the thiouronium salts **5a-c** (Scheme 2).

Quaternary ammonium salts **5a-c** were prepared by the treatment of methyl 2-acetylamino-4-bromomethyl-5-bromothiophene-3-carboxylate (**3a**) with tertiary amines in toluene (Scheme 1) at laboratory temperature. The target compounds were prepared in yields 40-90% and were characterized by UV, IR and ^{1}H NMR spectra (for all compounds listed in experimental section). The UV spectra of each quaternary ammonium salts showed characteristic absorption maximum at 220 and 300nm. The characteristic signal of methylene group in ^{1}H NMR spectra was at 4-6 ppm. Quaternary ammonium salts **5a-c** are predisposed to be biological active compounds.

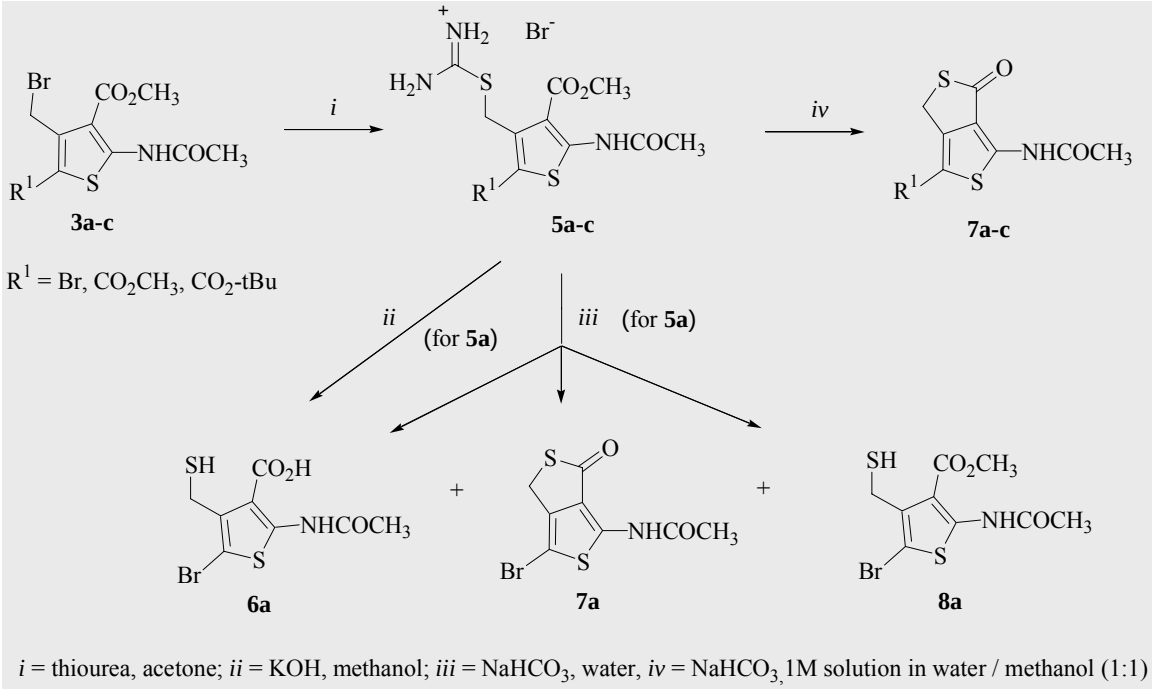


Scheme 1

The thiouronium salts **5a-c** were prepared in a high yields (91-95%) by the reaction of the corresponding bromomethylated aminothiophenes **3a-c** with thiourea in dry acetone under inert argon atmosphere (Scheme 2). Final salts are stable compounds soluble in aqueous media, which in the next step were decomposed by aqueous $NaHCO_3$ to give the target thieno[3,4-*c*]thiolactone derivatives **7a-c**. The hydrolytic decomposition was performed in two manners (Scheme 2). When thiouronium salt **5a** was refluxed in saturated aqueous solution of $NaHCO_3$, a mixture of three compounds was isolated from the reaction mixture – the desired thieno[3,4-*c*]tiolactone derivative **7a** with 5-bromo-4-sulfanylmethylthiophene-3-carboxylic acid **6a** and its methylester **8a**. To simplify the characterisation of the mixture of mentioned three compounds the sulfanylmetylderivate **6a** was also prepared by hydrolysis in methanolic KOH[11] to help identify it

in the mixture of **6a**, **7a** and **8a**. Products were separated by flash column chromatography and characterised by IR and ^{1}H NMR spectra.

In the second approach to hydrolytic decomposition of thiouronium salts to get thieno[3,4-*c*]thiolactone derivatives we used the method developed by Pal and coworkers. For the cyclisation of thiouronium salt **5a-c** we modified Pal´s[12] reaction conditions and 1M methanolic solution of $NaHCO_3$ (50% methanol in water) was used and the mixture heated at 70-80°C under inert atmosphere of argon. However, the yields were low (only 40-50%), only the desired thieno[3,4-*c*]thiolactone derivates **7a-c** were isolated after reaction. In our opinion unreacted thiouronium salts and supplementary products remain completely dissolved in water, while the corresponding thiolactones, being water insoluble compounds, can be easily separated and isolated from the crude mixture.



Scheme 2

The IR, ^{1}H NMR and ^{13}C NMR spectral data are collated in the Experimental section. The ^{1}H NMR spectra display singlets for methylene group in the 4.50—4.90 ppm region for thiouronium salts **5a-c** and in the area 4.30—.50 ppm region for thieno[3,4-*c*]thiophenes **7a-c**. In the ^{13}C NMR spectra the chemical shift for carbonyl of methylene group is in the area 30—5 ppm. The signal for C=O group of new designed thiolactones **7a-c** is in the area 180—90 ppm. It is a significant shift for cyclic lactone derivatives. ^{13}C chemical shifts, given in the experimental section, assignments were straightforward using gs-HSQC (gradient selected Heteonuclear Quantum Coherence) and gs- HMBC (gradient selected Heteronuclear Multiple Bond correlation) spectroscopy.

Experimental Section

General Procedures. All solvents were distilled before use. Melting points were determined with the Kofler hot stage and are uncorrected. Flash column liquid chromatography was performed on silica gel Kiesegel 60 (40-63 μm, 230-400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminium pre-coated with 0.2 mm silica gel (DC-Alufolien, Merck). The compounds were visualised by UV lamp at 254 nm wavelength or by dipping the plates in iodine solution. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian VXR 300 instrument at 293°K in $CDCl_3$. DMSO-d_6. Spectra were internally referenced to TMS. Chemical shifts (δ-scale) are quoted in parts per million (ppm) and the following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (brs) some combinations of these were made by DEPT editing of the spectra. Infrared spectra in the region 400-4000 cm^{-1} were taken with Philips Analytical PU9800 FTIR spectrophotometer as KBr disks (0,3 mg in 300 mg of KBr). Elemental analyses[13] were measured on an Carlo Erba, Milan type instrument. Compounds are numbered according to Schemes 1,2.

Materials. All solvents were distilled before use. Commercial reagents were used without further purification. 2-Amino-4-methylthiophene-3-carboxylic acid methyl ester **(1a)** and 2-Acetylamino-3-methylthiophene-carboxylic acid methyl ester (**2a**) were prepared in the same manner as is published in our previous paper.[9]

5-Amino-3-methylthiophene-2,4-dicarboxylic acid dimethyl ester (1b) according to the procedure described by Gudriniece,[10] a mixture of sulphur (14g) and morpholine (60 mL) was vigorously stirred in a three necked flask at 110°C for 3 hours. After cooling down to laboratory temperature, the mixture of methyl acetoacetate (4.64 g, 40 mmol) and methylcyanoacetate (3.96 g, 40 mmol) in methanol (100 mL) was added dropwise to morpholinepolysulfide prepared *in situ*. The reaction solution was mixed for further 24 hours at laboratory temperature. Resulting yellow powdered product (5.5g, 60%) was filtered of in satisfactory purity for use in consecutive reaction. M.p. = 147-149°C. ^{1}H- NMR (DMSO-d_6, 300MHz) δ 2.66 (s, 3H, CH_3), 3.79 (s, 3H, CO_2CH_3), 3.84 (s, 3H, CO_2CH_3), 6.58 (brs, 2H, NH_2); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 15.39 (CH_3), 50.53, 51.03 (2xCO_2CH_3), 108.09, 110.02, 147.51, 150.2 (C-2, C-3, C-4, C-5), 164.82, 166.54 (2xCO_2CH_3).

5-Amino-3-methylthiophene-2,4-dicarboxylic acid 2-*tert*butylester-4-methylester (1c) was prepared according to the same procedure as **1b**.Yield 84% (9.1g white powdered product) M.p. = 134-137°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.39 (s, 9H, $CO_2C(CH_3)_3$), 2.56 (s, 3H, CH_3), 3.73 (s, 3H, CO_2CH_3), 7.79 (brs, 2H, NH_2); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 15.25 (CH_3), 27.83 ($C(CH_3)_3$), 50.47 (CO_2CH_3), 80.1 ($C(CH_3)_3$), 105.98, 107.84, 146.22, 146.24 (4xC, thiophene), 164.85 (CO_2CH_3), 166.18 ($CO_2(CH_3)_3$).

5-Acetylamino-3-methylthiophene-2,4-dicarboxylic acid dimethyl ester (2b). 2-Aminothiophenecarboxylate (**1b**) (9.6g, 42mmol) in acetic anhydride and 2-3 crystals of $Mg(ClO_4)_2.2H_2O$ were heated on silicon bath for 4 hours. The reaction mixture was then cooled

down and left at laboratory temperature for 12 hours. The white needles of product were filtered on Büchner to get 75% (8.55g white needles) used without cleaning in the next step. M.p. = 177-181°C. ^{1}H-NMR(DMSO-d_6, 300MHz) δ 2.61 (s, 3H, CH_3), 3.26 (s, 3H, $COCH_3$), 3.78 (s, 3H, CO_2CH_3), 3.86 (s, 3H, CO_2CH_3), 11.07 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75MHz) δ 14.61 (CH_3), 23.0 ($COCH_3$), 51.46, 51.74 (2xCO_2CH_3), 110.1, 111.2, 144.3, 145.2 (4xC, thiophene), 165.1, 166.2 (2xCO_2CH_3).

5-Acetylamino-3-methylthiophene-2,4-dicarboxylic acid 2-*tert*butylester-4-methylester (2c) was prepared in the same manner as **2b**. Yield 78% (10.27g light brown crystals). M.p. = 204-207°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.52 (s, 9H, $CO_2(CH_3)_3$), 2.27 (s, 3H, CH_3), 3.21 (s, $COCH_3$), 3.87 (s, 3H, CO_2CH_3), 11.03 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75MHz) δ 14.45 (CH_3), 22.95 ($C(CH_3)_3$), 27.7 ($COCH_3$), 51.62 (CO_2CH_3), 81.06 ($C(CH_3)_3$), 113.99, 117.85, 142.5, 149.99 (4xC, thiophene), 161.32 ($COCH_3$), 164.49 (CO_2CH_3), 168.08 ($CO_2C(CH_3)_3$).

2-Acetylamino-4-bromomethylthiophene-3-carboxylic acid methyl ester (3a)

Method A. Bromine (2.55 mL, 50 mmol) was added dropwise to methyl ester **2a** (10.6 g, 49 mmol) dissolved in 100 mL of acetic acid in an apparatus kept under a slow argon flow. The mixture was gradually warmed up to reflux, the HBr was carried away from the top of the condenser to an absorber. After removing the HBr from reaction mixture (visually identified by loss of dark colour caused by unreacted bromine, after 5 hours), another 8 g portion of bromine (2.55 mL, 50 mmol) was added dropwise and the reaction mixture was heated to reflux for another 5 hours until HBr evolution had finished. The reaction mixture was washed with water solution of $Na_2S_2O_7$, then with water. Acetic acid was then evaporated to get and crude dark product. Crystallisation from ethyl acetate lead to 90 % (17 g dark grey crystals) of **3a**.

Method B. To the vigorously stirred mixture of (8g, 37.6 mmol) of methyl ester **2a**, 1 g (6 mmol) of dibenzoyl peroxide and 300 mL of CCl_4 placed in a three-necked 500 mL flask was gradually added *N*-bromosuccinimide (NBS, 7.9g, 75.2mmol). The reaction mixture was heated to reflux on oil bath. The stirring continued for 4-5 hours at a boiling point of carbon tetrachloride. After cooling down to laboratory temperature the separated succinimide was removed by filtration under vacuum and the solvent was evaporated to dryness and the dark residue was completely dissolved in ethyl acetate. The solution was then refluxed for 30 min and cooled. The dark brown precipitate was isolated by filtration, washed with ethyl acetate to give 91 % (10.9 g) of crude mixture of **3a** and

2-Acetylamino-4-methyl-5-bromothiophene-3-carboxylic acid methyl ester = 2.5 : 1 The separation and purification was carried by flash column liquid chromatography, eluted by chloroform to obtain 62 % (6.8g dark grey crystals) of **3a** and 19 % (2.7g light brown crystals) of monobrominated thiophene derivative (m.p. = 106-109°C).

For **3a** in each procedure M.p. = 156-160°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.25 (s, 3H, $COCH_3$), 3.86 (s, 3H, CO_2CH_3), 4.75 (s, 2H, CH_2), 10.99 (brs, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 14.45 (CH_2), 27.7 ($COCH_3$), 51.62 (CO_2CH_3), 113.99, 117.85, 142.5, 149.99 (4xC, thiophene), 164.58 ($COCH_3$), 168.08 (CO_2CH_3).

5-Acetylamino-3-bromomethyl-thiophene-2,4-dicarboxylic acid dimethyl ester (3b)
To a solution of 3,5-Dimethyl-2-acetamino-4-methylthiophene-3,5-dicarboxylate (**2b**) (1.36g, 5 mmol) in carbon tetrachloride 12.5 mL containing dibenzoylperoxide as initiator (1mg) *N*-bromosuccinimide (0.9g, 5mmol) was added in one portion. The mixture was refluxed for 6 hours, until the starting materials completely disappeared (TLC controlled 40% of EtOAc in *i*-hexane). The mixture was cooled down to room temperature; succinimide was removed by filtration in vacuum. The filtrate was concentrated under reduced pressure and the crude product was crystallised from ethyl acetate to get light brown crystals. Yield 74% (1.3g). M.p. = 203-206°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.57 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 4.49 (s, 2H, CH_2), 11.06 (brs, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 15.67 (CH_2), 26.83 ($COCH_3$), 51.71, 56.43 (2xCO_2CH_3), 111.29, 114.48, 132.58, 147.26 (4xC, thiophene), 163.84 ($COCH_3$), 168.04 (2xCO_2CH_3).
5-Acetylamino-3-bromomethylthiophene-2,4-dicarboxylic acid 2-*tert*butyl-4-methylester (3c) was prepared by the same procedure as **3c**. Yield 67% (1.32g) of light red crystals M.p. = 92-96°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.52 (s, 9H, $C(CH_3)_3$), 2.29 (s, 3H, $COCH_3$), 3.02 (s, 3H, CO_2CH_3), 5.18 (s, 2H, CH_2); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 22.9 (CH_2), 27.58 ($C(CH_3)_3$), 30.1 ($COCH_3$), 51.91 (CO_2CH_3), 82.23 ($C(CH_3)_3$), 128.19, 128.92, 140.43, 150.21 (4xC, thiophene), 160.42 ($COCH_3$), 164.49 (CO_2CH_3), 168.49 ($CO_2C(CH_3)_3$).

Synthesis of quaternary ammonium salts 4a –d. General procedure
Methyl ester **3a** (1g, 3.4 mmol) was dissolved in 50 mL of dry toluene and an equimolar amount of the corresponding tertiary amine (3.4 mmol) was added to a stirred solution. The mixture was left to stir for 24 hours at laboratory temperature. The separated solid was filtrated off and washed with toluene. Gaseous trimethylamine was led directly into the solution of **3a**.
1-(5-Acetylamino-2-bromo-4-methoxycarbonylthiophen-3-ylmethyl)-4–dimethylaminopyridinium bromide(4a). Yield 91% (1.52 g), m.p. = 134-135 °C ^{1}H -NMR (300 MHz, $CDCl_3$): δ: 2.32 (s, 3H, $COCH_3$), 3.29 (s, 6H, $(CH_3)_2N$), 4.00 (s, 3H, CO_2CH_3), 5.66 (s, 2H, CH_2), 7.08 (d, 2H, pyr.), 8.43 (d, 2H, pyr.), 11.25 (s, 1H, NH).
1-[(5-Acetylamino)-2-bromo-4-(methoxycarbonylthiophen-3-yl)methyl]-1,4-diaza[2.2.2]bicyclooctyl bromide (4b). Yield 99 % (1.44g), m.p. = 196-198 °C. ^{1}H-NMR (300MHz, DMSO-d_6): δ: 2.25 (s, 3H, $COCH_3$), 3.03 (s, 9H, $(CH_3)_3N$), 4.87 (s, 3H, $COOCH_3$), 4.66 (s, 2H, CH_2), 11.00 (s, 1H, NH).
1-(5-Acetylamino-2-bromo-4-methoxycarbonyl-3-ylmethyl)-pyridinium bromide (4c). Yield 41 % (0.63 g), m.p. = 201-207 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 2.32 (s, 3H, $COCH_3$), 3.93 (s, 3H, $COOCH_3$), 6.33 (s, 2H, CH_2), 8.27 (t, 2H, H_3, H_4), 8.68 (m, 1H, H_5), 9.45 (d, 2H, H_1), 11.23 (s, 1H, NH).
1-(5-Acetylamino-2-bromo-4-methoxycarbonyl-3-ylmethyl)-trimethylamonium bromide (4d). Yield 69 % (1.13 g), m.p. = subl.<100 °C. ^{1}H-NMR (300MHz, DMSO-d_6): δ: 2.34 (s, 3H, $COCH_3$), 3.24 (t, 6H, $(CH_2)_3$), 3.72 (t, 6H, $(CH_2)_3$), 3.81 (s, 3H, $COOCH_3$), 4.96 (s, 2H, CH_2), 11.24 (s, 1H, NH).

Table 1. UV and IR spectra of quaternary ammonium salts **4a-d**

Compound	Molecular formula / Molecular weight	UV (methanol) λ_{max} / logε	$COCH_3$	IR, CO_2CH_3	(KBr, ν , cm^{-1}) CH_2,CH_3	$C=C_{tioph.}$	NH
4a	$C_{16}H_{19}Br_2N_3O_3S$ 493	292.1 (5.49), 301.7 (4.91)	1576	1691	2949	3150	3422
4b	$C_{12}H_{18}Br_2N_2O_3S$ 430	226.9 (5.18), 301.2 (4.87)	1537	1700	2951	3258	3473
4c	$C_{14}H_{14}Br_2N_2O_3S$ 450	226 (5.31), 302.7 (4.93)	1539	1699	2947	3271	3383
4d	$C_{15}H_{21}Br_2N_3O_3S$ 483	226.4 (5.22), 300.5 (4.92)	1537	1696	2949	3267	3379

Synthesis of thiouronium salts 5a-c. General procedure

Bromomethyl derivates (5 mmol) and thiourea (0.84g, 11 mmol) in 20 mL dry acetone were refluxed under inert atmosphere of argon for 5-10 hrs. The reaction mixture was cooled down do room temperature and left to stay for all night. Precipitated solid was then filtered off, filtrate was concentrated under vacuum, the residue was combined with precipitated and crystallised from methanol to yield thiouronium salts **5a-c**.

1-(5-Acetylamino-2-bromo-4-methoxycarbonyl-3-ylmethyl)-thiouronium bromide (5a). Yield 95% (2g) of white powdered product. M.p. = 194-198°C. ^{1}H-NMR(DMSO-d_6, 300MHz) δ 3.30 (s, 3H, $COCH_3$), 3.88 (s, 3H, CO_2CH_3), 4.57 (s, 2H, CH_2), 9.19 (br s, 4H, 2xNH_2), 10.96 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 22.69 (CH_2), 27.6 ($C(CH_3)_3$), 30.2 ($COCH_3$), 52.14 (CO_2CH_3), 109.96, 109.97, 129.48, 148.16 (4xC, thiophene), 162.71 ($COCH_3$), 168.61 (CO_2CH_3).

1-(5-Acetylamino-2,4-dimethoxycarbonyl-3-ylmethyl)thiouronium bromide (5b). Yield 91% (1.91g) of white powdered product. M.p. = 168-171°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.03 (s, 3H, $COCH_3$), 3.78 (s, 3H, CO_2CH_3), 3.84 (s, 3H, CO_2CH_3), 4.88 (s, 2H, CH_2), 9.03 (brs, 4H, 2xNH_2), 11.02 (brs, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 22.69 (CH_2), 29.41 ($COCH_3$), 51.15 (2xCO_2CH_3), 109.96, 109.97, 129.48, 148.16 (4xC, thiophene), 162.71 ($COCH_3$), 168.61, 169.31 (2xCO_2CH_3) .

1-(5-Acetylamino-2-tertbutoxycarbonyl-4-methoxycarbonyl-3-ylmethyl) thiouronium bromide (5c). Yield 94% (2.14g) of white powdered product. M.p. = 48-51°C. ^{1}H-NMR(DMSO-d_6, 300MHz) δ 1.54 (s, 9H, $C(CH_3)_3$), 2.30 (s, 3H, CH_3), 3.89 (s, 3H, CO_2CH_3), 4.93 (s, 2H, CH_2), 9.07 (brs, 2H, 2xNH_2), 11.02 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75MHz) δ 22.92 (CH_2), 30.10 ($COCH_3$), 52.61 (CO_2CH_3), 81.36 ($C(CH_3)_3$), 106.07, 109.98, 129.48, 148.16 (4xC, thiophene), 162.72 ($COCH_3$), 168.61 (CO_2CH_3), 169.32 ($CO_2C(CH_3)_3$).

Hydrolysis of the thiouronium salt 5a – synthesis of the 2-acetylamino-5-bromo-4-tiomethylthiophene-3-carboxylic acid (6a)

Thiouronium salt **5a** (0.5 g, 1.1 mmol) and methanolic KOH (0.49 g KOH dissolved in 4.4 ml of 1:1 aqueous methanol) was refluxed for 1 h, methanol was distilled off and the flask cooled to 0-

5 °C, acidified by 1M HCl and extracted with ether 3 times. Ether extracts were combined, dried over with sodium sulphate and evaporated to dryness. Yield 61 % (0.21 g) of grey powdered product was obtained, For $C_9H_{10}BrNO_3S_2$
(324) m.p. = 163-167 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.08 (t, 1H, SH), 2.16 (s, 3H, $COCH_3$), 4.11 (d, 2H, CH_2), 9.50 (s, 1H, COOH), 11.27 (s, 1H, NH).

Attempt at cyclization of thiouronium salts – synthesis of *N*-(3-bromo-6-oxo-*4H,6H*-thieno[3,4-*c*]thiophene-1-yl)acetamide (7a)

Thiouronium salt **(5a)** (1g, 2.2 mmol) was hydrolysed by heating 3 hrs. at boiling water bath by aqueous $NaHCO_3$ (0.19 g $NaHCO_3$ in 75 mL of distilled water). After cooling the separated light yellow solid was filtered off to give 51% (0.4g approx.) a mixture of three compounds **6a**, **7a** and **8a** in ratio **22% : 19% : 10%** separated by flash column liquid chromatography (eluent 20% AcOEt in *i*-hexane).

2-Acetylamino-5-bromo-4sulfanylmethylthiophene-3-carboxylic acid (6a). Yield 22 % (0.22 g), m.p. = 163-167 °C. For $C_8H_8BrNO_3S_2$ (M_r = 310.18). ^{1}H-NMR ($CDCl_3$, 300 MHz,) δ 2.08 (t, 1H, SH), 2.16 (s, 3H, $COCH_3$), 4.11 (d, 2H, CH_2), 9.50 (s, 1H, CO_2H), 11.27 (s, 1H, NH).

***N*-(3-Bromo-6-oxo-*4H,6H*-thieno[3,4-*c*]thiophene-1-yl)acetamide (7a).** Yield 19 % (0.095 g), m.p. = 187-190 °C. For $C_8H_6BrNO_2S_2$ (M_r = 292.16).^{1}H-NMR (300 MHz, $CDCl_3$): δ: 2.16 (s, 3H, $COCH_3$), 4.26 (d, 2H, CH_2), 11.27 (s, 1H, NH).

2-*N*-acetylamino-5-bromo-4-mercaptomethyl-3-carbometoxythiophene (6). Yield 9.8 % (0.05g), m.p. = 117-119 °C. For $C_9H_{10}BrNO_3S_2$ (M_r = 324). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ: 2.01 (d, 1H, SH), 2.28 (s, 3H, $COCH_3$), 3.89 (s, 3H, CO_2CH_3), 4.09 (s, 2H, CH_2), 10.11 (s, 1H, NH).

Cyclization of thiouronium salts – synthesis of thieno[3,4-*c*]thiolactones 7a-c, general procedure

Thiouronium salt (**6a-c**) (2.1mmol) was treated with 50mL methanolic solution of $NaHCO_3$ (2.1g of $NaHCO_3$ in 50% aqueous methanol). The reaction mixture was stirred at 70-80°C under inert argon atmosphere for 5 hrs until CO_2 completely removed from the mixture. After cooling down to laboratory temperature the solid was filtered off, washed with diluted HCl, dried up to yield appropriate thieno[3,4-*c*]thiolactone derivate.

***N*-(3-Bromo-6-oxo-*4H,6H*-thieno[3,4-*c*]thiophene-1-yl)acetamide (7a).** Yield 46 % (0.28g) of light grey solid product. M.p. = 187-190°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 3.24 (s, 3H, $COCH_3$), 4.2 (s, 2H, CH_2), 11.05 (brs, 1H, NH); ^{13}C-NMR (DMSO-d_6, 75MHz) δ 22.1 (CH_2), 29.23 ($COCH_3$), 95.15, 122.21, 122.24, 140.92 (4xC, thiophene), 169.13 ($COCH_3$), 187.04 (C=O thiolactone).

3-Acetylamino-4-oxo-*4H,6H*-thieno[3,4-*c*]thiopehene-1-carboxylic acid methyl ester (7b). Yield 48% (0.27g) light yellow product. M.p. = 187-190°C. ^{1}H-NMR (DMSO-d_6, 300MHz) δ 2.03 (s, 3H, $COCH_3$), 3.71 (s, 3H, CO_2CH_3), 4.45 (s, 2H, CH_2), 8.30 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75MHz) δ 22.02 (CH_2), 34.61 ($COCH_3$), 51.16 (CO_2CH_3), 102.23, 116.47, 129.4, 141.5 (4xC, thiophene), 160.87 ($COCH_3$), 163.81 (CO_2CH_3), 186.46 (C=O thiolactone).

3-Acetylamino-4-oxo-*4H,6H*-thieno[3,4-*c*]thiopehene-1-carboxylic acid *tert*-butyl ester (7c). Yield 51% (0.33g) light grey solid product. M.p. = 187-190°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ 1.48 (s, 9H, $C(CH_3)_3$), 4.35 (s, 2H, CH_2), 8.03 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 75MHz) δ 23.01 (CH_2), 27.62 ($C(CH_3)_3$), 52.25 ($COCH_3$), 82.67 ($C(CH_3)_3$), 112.55, 120.63, 137.72, 150.63 (4xC, thiophene), 169.70 ($CO_2C(CH_3)_3$), 183.79 (C=O thiolactone).

Table 2: Molecular formula, molecular weight and IR spectra of compounds **3a-c, 5a-7c**

Comp.	Molecular formula / Molecular weight	CH_2-X	C=C tioph.	IR, $COCH_3$	(KBr, ν cm^{-1}) CO_2CH_3	CO_2tBu	NH	NH_2	C=O tiolact.
3a	$C_9H_9Br_2NO_3S$ 371	569 X=Br	1439 1502 1542	1675	1695	-	3246	-	-
3b	$C_{11}H_{12}BrNO_3S$ 350	579 X = Br	1434 1501 1544	1676	1694 1707	-	3247	-	-
3c	$C_{14}H_{18}BrNO_3S$ 392	572 X =Br	1441 1505 1542	1682	1692	1701	3253	-	-
5a	$C_9H_{13}Br_2N_3O_3S_2$ 435	1410 X = S	1432 1449 1539	1673	1690	-	3250	3169 3370	-
5b	$C_{11}H_{16}BrN_3O_3$ 414	1413 X = S	1436 1502 1549	1675	1695	-	3277	3176 3373	-
5c	$C_{14}H_{22}BrN_3O_3S_2$ 456	1414 X =S	1442 1502 1544	1649	1676	1612	3275	3175 3382	-
7a	$C_8H_6BrNO_2S_2$ 292	1405 X =S	1436 1501 1539	1671	-	-	3278	-	1620
7b	$C_{10}H_9NO_4S_2$ 271	1407 X =S	1431 1477 1528	1637	1695	-	3249	-	1670
7c	$C_{13}H_{15}NO_4S_2$ 313	1408 X =S	1460 1510 1545	1644	-	1682	3274	-	1682

Acknowledgements

We thank to the Slovak Grant Agency, Slovak republic for financial support of this work (Grant N^{o}: 1/1379/04) and the Science and Technology Assistance Agency (contract No. APVT-20-007304). The authors are grateful to Mrs. Silvia Markusová for IR spectra measurements and to Dr. Naďa Prónayová for NMR spectra measurements. ZP appreciates to Prof. Dr. Alžbeta Krutošíková and Ing. Peter Zálupský PhD. for correcting the manuscript.

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