Synthesis of Novel 5-Chlorinated 2-Aminothiophenes Using 2,5-Dimethylpyrrole as an Amine Protecting Group

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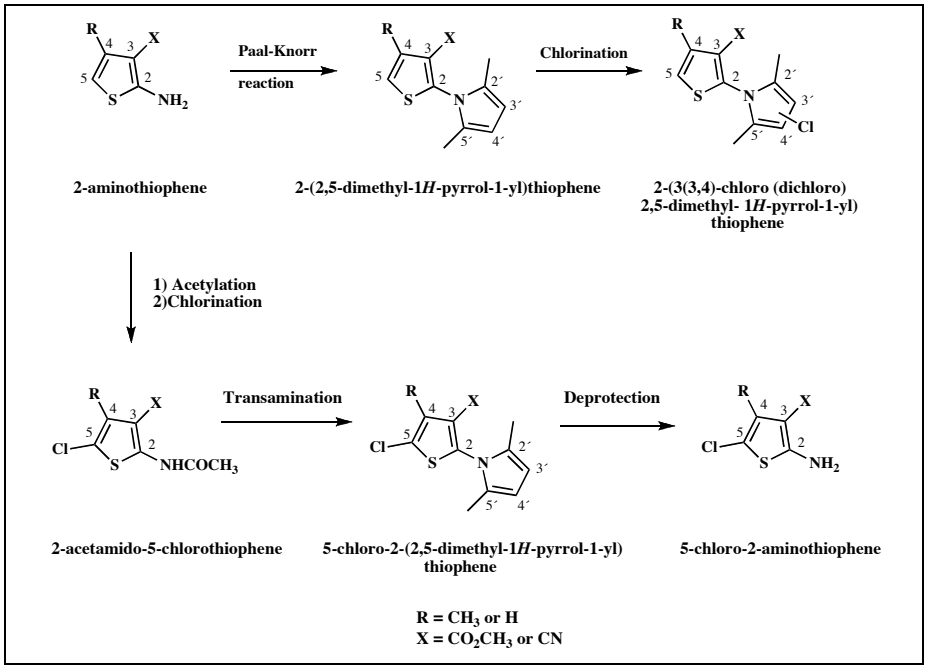

A new synthetic methodology towards substituted 2-amino-5-chlorothiophenes is described. Compounds of this type are important as building blocks for oligomers used in polymer research. Easily available 2-aminothiophenes underwent Paal-Knorr reaction to protect the free amino group before electrophilic substitution. Although the chlorination was predicted to proceed at the thiophene ring, only free positions of 2,5-dimethylpyrrole were substituted. To direct chlorination to the thiophene ring acetamido derivative was prepared first and then chlorinated. Transamination with hexane-2,5-dione created a 2,5-dimethyl pyrrole ring from the acetamido group. In the final step, after treatment with hydroxylamine dihydrochloride, the pyrrole ring is removed and a free amino group is regenerated.

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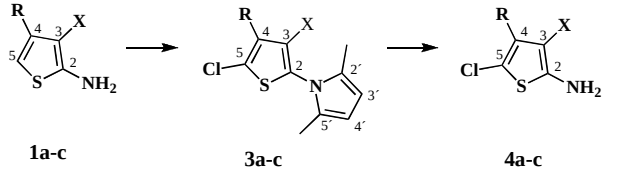
INTRODUCTION

2-Aminothiophenes are widely used in syntheses of pharmaceuticals [1], dyes [2] and agrochemicals [3]. Our interest is aimed at creating good and easily available building blocks for the preparation of designer oligothiophene derivatives. Design of such compounds is important as they form components in molecular devices for polymer research, electronic semiconducting materials, non-linear optical materials and highly ordered molecular assemblies [4,5]. The key criteria among such design process are the yield achievable in each synthetic step and the nature of the terminal groups. Towards this goal, we have prepared a series of substituted 2-amino-5-chloro thiophenes. Such monomers can be used in homocoupling reactions to create thiophene dimers and polyazomethines. In heterocoupling reactions 2-amino-5-chlorothiophenes can produce thiophene trimers and oligomers with potential to vary the existing hydrophilic and hydrophobic substituents.



see Tables 1 and 3 for R, X

Figure 1. Synthetic approach towards 2-amino-5-chlorothiophenes.

Since Gewald and coworkers [6] presented in 1965 a simple synthesis towards 2-aminothiophenes many new methods were published to widen the *compound library* of such compounds with various substituents [7].

However, recently there has been a revival of interest in the synthesis of 2-aminothiophenes [8,9], and none of published methods has pointed to synthesis of 5-halogenated-2-aminothiophenes. Our focus was centred on the use of 2,5-dimethylpyrrole as an amine protecting group in route to 5-chloro-2-aminothiophenes (**4a-c**) (Figure 1). Intermediates **2a-c** and **3a-c** are isosteric analogues of *N*-aryl and *N*-heteroarylpyrroles, which display a manifold of pharmacologically interesting properties [10].

RESULTS AND DISCUSSION

Three types of 2-aminothiophenes (**1a-c**) used in our study were prepared by the Gewald reaction according to the published procedures [2,11,12].

Paal-Knorr Reaction. Paal-Knorr reaction [13] remains one of the most attractive methods for preparation of **2a-c** and similar *N*-aryl and *N*-heteroarylpyrroles. The reaction involves mixing of amino-derivative with hexane-2,5-dione (Figure 2). There are three different reaction conditions published for converting primary amines into *N*-substituted 2,5-dimethylpyrroles. The classical method uses toluene as solvent and *p*-toluenesulphonic acid as catalyst (Method A) [14]. Recently, two new alternatives were published by Banik and coworkers [15,16]. Method B involves the bismuth nitrate-catalyzed procedure of the pyrrole formation [15] and method C makes use of iodine as catalyst [16].

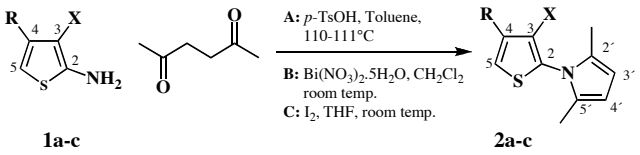


Figure 2. Paal-Knorr reaction of substituted 2-aminothiophenes.

All three methods mentioned above were tested for the conversion of primary amino group of the starting 2-aminothiophenes (**1a-c**) into 2,5-dimethylpyrrole derivatives (**2a-c**). The reason why we have tried all possible methods was based on our observation that the conversion of starting compound into protected derivatives never proceeded to completion. The yields of products were only about 50% and unreacted starting material was isolated from the reaction. The modifications using bismuth nitrate or iodine-catalyzed reaction also failed our expectations to increase the yield of *N*-substituted pyrroles (Table 1). Hexane-2,5-dione was used in 1.2 equiv excess in all cases.

Table 1

Application of the Paal-Knorr reaction on 2-aminothiophenes.

			Pyrrole yield %		
Amine	R	X	Method A	Method B	Method C
1a	CH_3	CO_2CH_3	**2a**, 38	**2a**, 42	**2a**, 40
1b	H	CO_2CH_3	**2b**, 45	**2b**, 47	**2b**, 43
1c	H	CN	**2c**, 53	**2c**, 50	**2c**, 50

Method A: toluene, *p*-TsOH, temperature: 110-111°C, *Method B*: $Bi(NO_3)_2.5H_2O$, dichloromethane, room temperature, *Method C*: I_2, THF, room temperature.

Based upon our theoretical knowledge on synthesis of *N*-aryl and *N*-heteroaryl-pyrroles the yields were higher than 70% in almost all cases [17-20]. Only in one study it is pointed out that the difference between the reactivity of six-membered amino derivatives versus five-membered amines in the Paal-Knorr reaction. Bruekelman [21,22] in his paper showed that when the protection with hexane-2,5-dione is performed for substituted pyridyl amines, the yield of the corresponding *N*-pyridyl-2,5-dimethylpyrroles was more than 90%, whilst when the amino group in substituted 1,3-thiazoles is converted to 2,5-dimethyl-pyrrole the yield is only about 60%. This experimental founding was not disclosed. In our opinion, the lower yield of the pyrrole synthesis for 5-membered rings is caused by twisting of the pyrrole ring from the plane of existing thiophene, during its formation. This causes the decreasing effect on the yield of final *N*-thiophenyl pyrroles.

Chlorination. Electrophilic substitution at the free α-position in substituted 2-aminothiophenes (**1a-c**) is possible only when the amino group is protected. Because of the suitable behaviour, we have chosen 2,5-dimethyl-pyrrole as the protecting group. 2,5-Dimethylpyrroles are stable to strong bases, to reducting agents, show weakly nucleophilic properties – in terms of low reactivity to acid chlorides and the 3-and 4-positions can be left unsubstituted [19,22]. The last mentioned characteristics with the fact-that the pyrrole group is easily removable and after treatment with hydroxylamine hydrochlorides under basic conditions while amino group is being re-created, 2,5-dimethylpyrrole seemed to fit our purpose. Although chlorination was assumed to proceed to the free 5-position on the thiophene in **2a-c**, only pyrrole ring underwent monosubstitution or disubstitution (Figure 3). Chlorination of **2a-c** was investigated under two different sets of reaction conditions, using *N*-chlorosuccinimide (NCS) as the source of chloronium species in 1.5 equiv. and 3.0 equivalent excess. Following the procedure published independently by two different research groups [23,24], the chlorination was done in acetonitrile. The second approach involved a two-phase catalytic method in *n*-hexane with 70% $HClO_4$ as catalyst [25] (Figure 3).

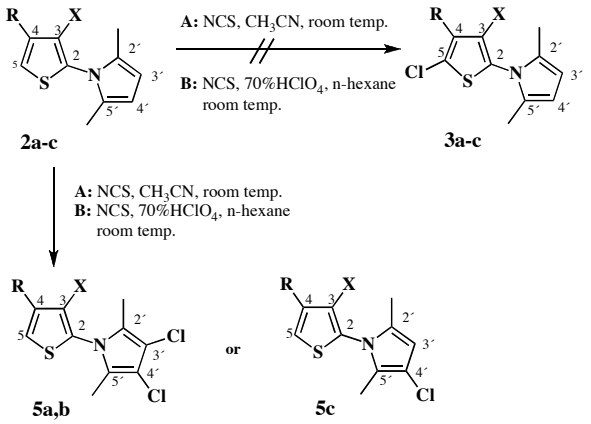


Figure 3. Chlorination of 2-(2,5-dimethyl-1*H*-pyrrol-1- yl)thiophenes

Final products **5a-c** were isolated from the dark slurry after purification by column chromatography in yields not exceeding 30% (Table 2) by both techniques used. The heterolysis of a N-Cl bond releases positive chloronium ions which besides the electrophilic substitution at the pyrrole ring also causes a decrease in pH resulting in an acidic reaction mixture. Under these conditions, pyrroles undergoe uncontrollable polymerization without any chance to identify the by products after halogenation.

Table 2

Chlorination of **2a-c** by use of *N*-chlorosuccinimide.

			Yield % / equiv. of NCS	
Entry	R	X	Method A	Method B
2a	CH_3	CO_2CH_3	**5a**, 21%, 1.5 equiv	**5a**, 28%, 1.5 equiv
2a	CH_3	CO_2CH_3	**5a**, 20%, 3.0 equiv	**5a**, 25%, 3.0 equiv
2b	H	CO_2CH_3	**5b**, 23%, 1.5 equiv	**5b**, 27%, 1.5 equiv
2b	H	CO_2CH_3	**5b**, 20%, 3.0 equiv	**5b**, 22%, 3.0 equiv
2c	H	CN	**5c**, 18%, 1.5 equiv	**5c**, 20%, 1.5 equiv
2c	H	CN	**5c**, 14%, 3.0 equiv	**5c**, 16%, 3.0 equiv

Method A: 1.5 or 3.0 equiv of NCS, CH_3CN, room temperature, *Method B*: 1.5 or 3.0 equiv of NCS, *n*-hexane, 70% $HClO_4$ (0.5 mol %), room temperature.

Substitution of the pyrrole hydrogens at positions 3 and 4 by chlorine have not been described in the literature. We have found similar product only in one case, when the chlorination was directed to free positions of 2-acetyl-pyrrole by using sulphuryl chloride [26].

General Synthesis of 5-Chlorinated 2-Amino-thiophenes. The five-step procedure was employed in the context of synthesis of 5-chlorinated 2-aminothiophenes **3a-c**. As discussed above, our primary plan of synthesis involved using 2,5-dimethylpyrrole as an amine masking group in the key step. This strategy failed to produce the desired compounds. In the second approach, the starting 2-aminothiophenes were first protected with acetyl group (**6a-c**), then chlorinated (**7a-c**) in high yields. To remove the acetyl group we have tried deprotection under basic as well as under acidic conditions. In both cases we failed to get the 2-amino-5-chlorothiophenes **4a-c**. Other types of deprotection of the amino group are rather limited [28]. We have explored a new method where 2,5-dimethyl-pyrrole was re-used in the transamination reaction. The treatment of the 2,5-dimethylpyrrole group in **3a-c** with hydroxylamine hydrochloride in alcohols (*i*-propanol, *n*-butanol) under basic conditions caused deprotection of the amino group (**4a-c**) [27]. Acetylation of amino group was performed using acetic anhydride as both reagent and solvent. Reaction catalysed by $Mg(ClO_4)_2.2H_2O$ led to acetylated derivatives **6a-c** in almost quantitative yields. There are many reports delineating the ability of *N*-chlorosuccinimide to chlorinate reactive anilines in benzene and tetrachloromethane [29]. Unfortunately, the reaction of *N*-acetyl-2-aminothiophenes in these solvents gives products in low yields. This problem is easily obviated using *N*-chlorosuccinimide in a dipolar-aprotic solvent such as acetonitrile [23] or *i*-propanol at reflux [24]. We report herein the use of acetic acid to chlorinate the *N*-acetylated derivatives with *N*-chlorosuccinimide. The mixture of starting compounds **6a-c** with NCS in acetic acid was heated to reflux for one hour. The reaction is clean and generally uncomplicated. Products **7a-c** are easily isolated in high yields. We have applied the Paal-Knorr reaction for the deprotection of acetamido group to free amino group. Whereas such type of deacetylation have never been used, we tried two approaches. First, by the standard technique only 1.2 equiv. of hexane-2,5-dione was mixed with the starting compound in boiling toluene (1 mol % amount of *p*-toluenesulphonic acid, Dean-Stark apparatus). No conversion of the starting material was observed even if the amount of hexane-2,5-dione was increased to 3.0 equiv. and reaction left to run 8-12 hours. We assumed that the reaction in toluene will not proceed because the reaction temperature (110-111°C) is too low.

Thus, by the use of xylenes as solvent, which boil at 138-144°C, we found that the reaction with 1.2 equiv of hexane-2,5-dione utillizing Dean-Stark trap for removal of water and acetic acid was completed after 6-8 hours (with additional of 1 mol% *p*-TsOH and 1 mol% HCl to catalyse the reaction). During the reaction with acetamides **7a-c** not only water eliminates but also acetic acid from the *N*-acetyl group. Once activation energy is achieved, acetic acid leaves the molecule and catalyses the reaction in equimolar quantities. That means that not only sufficiently high reaction temperature is required for reaction to proceed successfully, but autocatalysis by acetic acid as well. The yields of *N*-(5-chlorothiophene-2-yl)-2,5-dimethylpyrroles (**3a-c**) were only about 40%. The

bulky *ortho*-substituents in our substrates inhibit the formation of 2,5-dimethylpyrrole ring at the same site as the substituent and causes the skewed position of the forming pyrrole ring. This decreases the yields in transamination reaction in **3a-c** derivatives, as was the case in the Paal-Knorr reaction in **2a-c**.

methods: 2-amino-4-methylthiophene-3-carboxylic acid methyl ester (**1a**) according to [11], 2-aminothiophene-3-carboxylic acid methyl ester (**1b**) and 2-aminothiophene-3-carbonitrile (**1c**) according to [2, 12].

Thin Layer Chromatography. Thin Layer Chromatography (TLC) was performed on F_{365}, 20x20 cm, silica gel sheets (Merck). Plates were spotted with substrates and were eluted

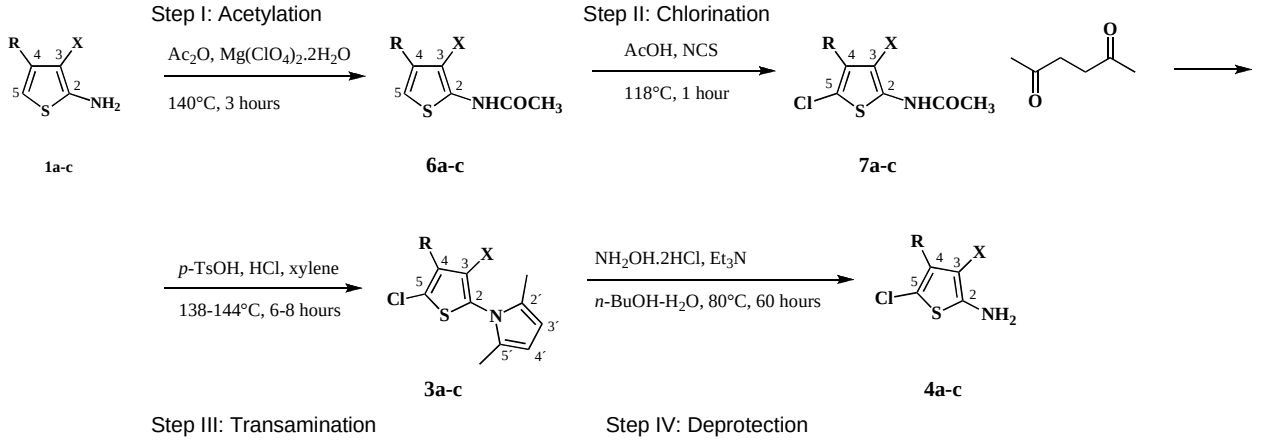


Figure 4. General synthesis of 5-chlorinated 2-aminothiophenes.

The removal of the 2,5-dimethylpyrrole masking group with hydroxylamine dihydrochloride (3.0 equiv) and triethylamine (2.0 equiv) in the mixture *n*-butanol: water (6:1) proceeded smoothly with all substrates. Table 3 summarizes the results from synthesis of substituted 5-chloro 2-aminothiophene derivatives (**4a-c**) shown on Figure 4.

Table 3.

Synthesis of Substituted-5-chloro-2-aminothiophenes.

Starting material	R	X	R.Temp./ °C	R.Time/ hours	Yield / %
1a	CH_3	CO_2CH_3	140	3	**6a**, 95
1b	H	CO_2CH_3	140	3	**6b**, 91
1c	H	CN	140	3	**6c**, 93
6a	CH_3	CO_2CH_3	118	1	**7a**, 72
6b	H	CO_2CH_3	118	1	**7b**, 69
6c	H	CN	118	1	**7c,** 74
7a	CH_3	CO_2CH_3	138-144	6	**3a**, 51
7b	H	CO_2CH_3	138-144	8	**3b**, 48
7c	H	CN	138-144	8	**3c**, 46
3a	CH_3	CO_2CH_3	80	60	**4a**, 30
3b	H	CO_2CH_3	80	60	**4b,** 34
3c	H	CN	80	60	**4c**, 28

EXPERIMENTAL

Chemicals and reagents. The chemicals and reagents were purchased from Sigma-Aldrich, Merck or ACROS. All solvents were of analytical or laboratory grade; for their purification standard methods were used. Starting 2-aminothiophenes were prepared according to published

with appropriate solvent system. The developed plates were analyzed under UV 365 nm or stained with iodine.

Column Chromatography. Column chromatography was performed using silica gel Kiesegel 60 with particle size 40-63 μm (230-400 mesh, Merck) by preparing the slurry with the eluent mixture and packing it into the chromatography column. The collected fraction samples were analyzed by TLC.

Nuclear Magnetic Resonance Spectroscopy (NMR). ^{1}H and ^{13}C spectra were acquired with the Varian VXR 300 spectrometer at 293 K, at 300 MHz for ^{1}H and 75 MHz for ^{13}C. The samples were prepared in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as internal standard. Chemical shifts (δ scale) are quoted in parts per million (ppm) and the following abbreviations are used: s (singlet), d (doublet), br s (broad singlet) some combinations of these were made by DEPT editing of the spectra. Coupling constants (*J*) were measured in Hertz (Hz).

Melting Point Determination. Melting points (mp) were determined with the Kofler hot stage and are uncorrected.

Elemental analyses were performed on CarloErba CHNS-OEA 1108-Elementar Analyser.

Compounds are numbered according to Figure 1-4.

Step I. Paal-Knorr reaction.

Method A. Hexane-2,5-dione (1.2 mmol) was added to a mixture of starting 2-aminothiophene **1a-c** (1 mmol) and *p*-TsOH (0.5-1 mol%) in toluene (30 mL/mmol of amine **1**). Reaction was stirred in refluxing toluene for 2 hours utilizing Dean-Stark trap for removal of water. After cooling down to room temperature, the mixture was washed with saturated aqueous solution of $NaHCO_3$ (2x20mL), water (2x20mL) and aqueous NaCl. The toluene phase was dried over Na_2SO_4. The products **2** were purified by column chromatography, eluent *hexane-ethyl acetate (9:1)*.

Method B. To a solution of amine 1 (1 mmol) and hexane-2,5-dione (1.2 mmol) in dichloromethane (2 mL) at room temperature, bismuth nitrate pentahydrate (0.5–1 mmol) was added. The mixture was allowed to stir at this temperature for 24 hours. The resulting mixture was washed with saturated $NaHCO_3$ solution (2 mL) and brine (2 mL). The organic layer was collected and dried with sodium sulfate and concentrated. The residue was purified through a column on silica gel using *hexane-ethyl acetate (9:1)*.

Method C. To a solution of amine 1 (1 mmol) and hexane-2,5-dione (1.1 mmol) in THF (5 mL) at room temperature, iodine was added (0.1 mmol). The mixture was stirred at this temperature for 24 hours. Dichloromethane (20 mL) was added to this mixture. The resulting mixture was washed successively with 5% $Na_2S_2O_3$ solution (2 mL), saturated $NaHCO_3$ solution (2 mL)and brine (2 mL). The organic layer was dried with sodium sulfate and concentrated. The slurry was purified using column chromatography on silica gel, eluent *hexane-ethyl acetate (9:1*).

Methyl 4-methyl-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylate (2a). Reaction run using methyl 2-amino-4-methylthiophene-3-carboxylate (170 mg, 1 mmol) and hexane-2,5-dione (137 mg, 0.14 mL, 1.2 mmol) in all three methods. Reactions provided **2a** as a pale yellow crystalline product in yields given in Table 1 (95 mg by method A, 104 mg by method B, 100 mg by method C), mp = 81-84°C. ^{1}H NMR ($CDCl_3$,):δ 6.88 (s, 1H, 5-H), 5.86 (s, 2H, 3´-H, 4´-H), 3.64 (s, 3H, CO_2CH_3), 2.43 (s, 3H, CH_3), 2.01 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$): δ 160.0 (CO), 145.0 (C-2), 139.0 (C-4), 137.2 (C-3), 127.6 (C-2´, C-5´), 123.0 (C-5), 107.0 (C-3´), 106.9 (C-4´), 52.0 (CO_2CH_3), 11.7 (CH_3), 11.5 (CH_3), 11.1 (CH_3). *Anal*. Calcd. for $C_{13}H_{15}NO_2S$ (249.3): C, 62.62; H, 6.06; N, 5.62. Found: C, 62.99; H, 5.93; N, 6.08.

Methyl 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylate (2b). Reaction run using methyl-2-aminothiophene-3-carboxylate (157 mg, 1 mmol) and hexane-2,5-dione (137 mg, 0.14 mL, 1.2 mmol) in all three methods. Reactions provided **2b** as yellowish crystalline product in yields given in Table 1 (106 mg by method A, 113 mg by method B, 101 mg by method C), mp = 101-103 °C. ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 1H, *J* = 5.6 Hz, 4-H), 7.22 (d, 1H, *J* = 5.6 Hz, 5-H), 5.91 (s, 2H, 3´-H, 4´-H), 3.72 (s, 3H, CO_2CH_3), 2.01 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$,): δ 161.0 (CO), 144.0 (C-2), 135.2 (C-3), 128.1 (C-2´), 127.3 (C-5´), 126.5 (C-5), 123.0 (C-4), 107.2 (C-3´, C-4´), 51.3 (CO_2CH_3), 11.7 (CH_3), 11.3 (CH_3). *Anal*. Calcd. For $C_{12}H_{13}NO_2S$ (235.3): C, 61.25; H, 5.57; N, 5.95. Found: C, 61.44; H, 5.85; N, 5.88.

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carbonitrile (2c). Reaction run using 2-aminothiophene-3-carbonitril (124 mg, 1 mmol) and hexane-2,5-dione (137 mg, 0.14 mL, 1.2 mmol) in all three methods. Reactions provided **2c** as a light brown oily product in yields given in Table 1 (107 mg by method A, 101 mg by method B, 101 mg by method C), mp = 90-92°C. ^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H, *J* = 5.7 Hz, 3-H), 7.22 (d, 1H, *J* = 5.7 Hz, 4-H), 5.95 (s, 2H, 3´-H, 4´-H), 2.11 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$): δ137.0 (C-2), 130.4 (C-5), 129.5 (C-4), 127.3 (C-2´, C-5´), 115.3 (CN), 111.8 (C-3), 106.5 (C-3´, C-4´), 12.8 (CH_3), 11.9 (CH_3). *Anal*. calcd. For $C_{11}H_{10}NO_2S$ (202.3): C, 65.32; H, 4.98; N, 13.85. Found: C, 65.74; H, 4.85; N, 14.08.

Step II. Chlorination.

Method A. To a mixture of starting 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene derivtive **2a-c** (2 mmol) in dry acetonitrile (10 mL) at room temperature *N*-chlorosuccinimide was added in small portions (1.5 equiv and 3.0 equiv, see Table 2) to avoid harsh exothermic reaction. The mixture was stirred at room temperature for 3 hours. When the reaction was complete (the colour of reaction mixture changes from light to dark during reaction) formed *N*-succinimide was filtered off and the residue was concentrated to get the crude products **5a-c**. Black slurry was purified by column chromatography on silica gel using *hexane-ethyl acetate (9:1*).

Method B. To a suspension of NCS (1.5 equiv. and 3 equiv.) in hexane (5 mL) were added 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene derivtive **2a-c** (2 mmol) and 70% $HClO_4$ (1 mol %) and the reaction mixture was stirred overnight at room temperature. Potassium carbonate (*ca*. 10 mg) was added and the solids were filtered off. The solvent was evaporated to get crude **5a-c**. Purification on column using silica gel, eluent *hexane-ethyl acetate (9:1).*

Methyl 2-(3,4-dichloro-2,5-dimethyl-1*H*-pyrrol-1-yl)-4-methylthiophene-3-carboxylate (5a). Reaction run using **2a** (500 mg, 2 mmol) and *N*-chlorosuccinimide (400 mg, 3 mmol and 800 mg, 6 mmol) to provide **5a** as yellow solid in yields listed in Table 2 (133 mg and 180 mg by method A, 127 mg and 160 mg by method B), mp = 74-76°C. ^{1}H NMR ($CDCl_3$): δ 6.95 (s, 1H, 5-H), 3.58 (s, 3H, CO_2CH_3), 2.21 (s, 3H, CH_3), 2.15 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$,): δ 158.0 (CO), 145.2 (C-2), 138.6 (C-4), 136.6 (C-3), 129.8 (C-2´, C-5´), 123.2 (C-5), 108.9 (C-3´, C-4´), 51.2 (CO_2CH_3), 11.7 (CH_3), 11.9 (2xCH_3). *Anal*. calcd. For $C_{13}H_{13}Cl_2NO_2S$ (318.2): C, 49.07; H, 4.12; N, 4.40. Found: C, 49.22; H, 4.15; N, 4.45.

Methyl 2-(3,4-dichloro-2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylate (5b). Reaction run using **2b** (470 mg, 2 mmol) and *N*-chlorosuccinimide (400 mg, 3 mmol and 800 mg, 6 mmol) to provide **5b** as light yellow solid in yields given in Table 2 (140 mg and 164 mg by method A, 122 mg and 134 mg by method B), mp = 80-83°C. ^{1}H NMR ($CDCl_3$,): δ 7.48 (d, 1H, *J* = 5.6 Hz, H-4), 7.28 (d, 1H, *J* = 5.6 Hz, H-3), 3.72 (s, 3H, CO_2CH_3), 1.96 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$,): δ 159.7 (CO), 144.5 (C-2), 132.6 (C-3), 129.7 (C-2´, C-5´), 126.8 (C-5), 124.1 (C-4), 108.1 (C-3´, C-4´), 50.9 (CO_2CH_3), 11.7 (CH_3), 11.5 (CH_3). *Anal*. Calcd. For $C_{12}H_{11}Cl_2NO_2S$ (304.19): C, 47.38; H, 3.64; N, 4.60. Found: C, 47.45; H, 3.75; N, 4.75.

2-(3-Chloro-2,5-dimethyl-1*H*-pyrrol-1-yl)-3-carbonitrile (5c). Reaction run using **2c** (405 mg, 2 mmol) and *N*-chlorosuccinimide (400 mg, 3 mmol and 800 mg, 6 mmol) to provide **5c** as yellowish solid in yields given in Table 2 (85 mg and 95 mg by method A, 66 mg and 76 mg by method B), mp = 68-70°C, ^{1}H NMR ($CDCl_3$,): δ 7.38 (d, 1H, *J* = 5.7 Hz, 3-H), 7.27 (d, 1H, *J* = 5.7 Hz, 4-H), 5.98 (s, 1H, 4´-H), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). ^{13}C ($CDCl_3$): δ 136.7 (C-2), 129.6 (C-2´), 129.3 (C-5), 129.2 (C-4), 127.0 (C-5´), 116.1 (CN), 111.6 (C-3), 108.7 (C-3), 108 (C-4), 12.3 (CH_3), 10.1 (CH_3). *Anal*. Calcd. For $C_{11}H_9ClNO_2S$ (236.7): C, 55.81; H, 3.83; N, 11.83. Found: C, 56.01; H, 3.95; N, 11.60.

Step III. Acetylation

Procedure. Acetic anhydride (180 mg, 0.185 mL, 2 mmol), starting aminothiophene **1a-c** (2 mmol) and 1 mol% of $Mg(ClO_4)_2.2H_2O$ were heated at reflux for 3 hours. After cooling down to room temperature the precipitated crude product was collected by filtration and washed with water. After recrystallization from aqueous methanol (1:1) acetylated derivatives **6a-c** were obtained.

Methyl-2-acetamido-4-methylthiophene-3-carboxylate (6a). Reaction run using methyl-2-aminothiophene-3-carboxylate (**1a)** (340 mg, 2 mmol) and provided 405 mg of acetylated derivative **6a** (95%). $C_9H_{11}NO_3S$ (213.25), mp = 100-101°C, ^{1}H NMR ($CDCl_3$): δ 11.26 (br s, 1H, NH), 6.38 (s,1H, 5-H), 3.87 (s, 3H, CO_2CH_3), 2.34 (s, 3H, $COCH_3$), 2.26 (s, 3H, CH_3). ^{13}C ($CDCl_3$,): δ 180.1 (C-2), 168.0 ($COCH_3$), 161.0 (CO_2CH_3), 139.1 (C-4), 111.8 (C-5), 98.6 (C-3), 52.4 (CO_2CH_3), 22.6 ($COCH_3$), 11.4 (CH_3).

Methyl-2-acetamidothiophene-3-carboxylate (6b). Reaction run using methyl-2-aminothiophene-3-carboxylate (**1b**) (314 mg, 2 mmol) and provided 362 mg of acetylated derivative **6b** (91%). $C_8H_9NO_3S$ (199.23), mp = 196-201°C, ^{1}H NMR ($CDCl_3$): δ 10.97 (br s, 1H, NH), 7.24 (d, 1H, $J_{4,5}$ = 5.6 Hz, 4-H), 6.73 (d, 1H, $J_{4,5}$ = 5.6 Hz, 5-H), 3.87 (s, 3H, CO_2CH_3), 2.26 (s, 3H, $COCH_3$). ^{13}C ($CDCl_3$,): δ 178.3 (C-2), 168.8 ($COCH_3$), 161.0 (CO_2CH_3), 122.4 (C-4), 118.6 (C-3), 114.5 (C-5), 50.7 (CO_2CH_3), 23.8 ($COCH_3$).

***N*-(3-Cyanothiophen-2-yl)acetamide (6c)**. Reaction run using 2-aminothiophene-3-carbonitril (**1c**) (248 mg, 2 mmol) and provided 309 mg of acetylated derivative **6c** (93%). $C_7H_6N_20S$ (166.2), mp = 167-170°C, ^{1}H NMR ($CDCl_3$,): δ11.2 (br s, 1H, NH), 7.06 (d, 1H, *J* = 6.0 Hz, 4-H), 6.87 (d, 1H, *J* = 6.0 Hz, 5-H), 2.32 (s, 3H, CH_3). ^{13}C ($CDCl_3$,): δ 167.2 ($COCH_3$), 151.0 (C-2), 128.2 (C-4), 117.1 (C-5), 114.9 (CN), 97.3 (C-3), 22.9 (CH_3).

Step IV. Chlorination of acetylated derivatives.

Procedure. To a solution of 2-acetylaminothiophene derivative **6a-c** (1.5 mmol) in 5 mL of glacial acetic acid *N*-chlorosuccinimide (214 mg, 1.6 mmol) was added. Mixture was refluxed for 2 hours and after cooling down to room temperature the solution was poured into water (15 mL) and after standing 2-4 hours the crystals formed were collected by filtration and crystallized from methanol.

Methyl 2-acetamido-5-chloro-4-methylthiophene-3-carboxylate (7a). Reaction run using **6a** (320 mg) and yielded 268 mg (72%) of **7a** as brownish powder, mp = 142-145 °C. ^{1}H NMR ($CDCl_3$, δ): δ 11.5 (br s, 1H, NH), 3.90 (s, 3H, CO_2CH_3), 2.34 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$). ^{13}C ($CDCl_3$) δ 180.0 (C-2), 168.7 ($COCH_3$), 158.9 (CO_2CH_3), 135.6 (C-4), 114.2 (C-5), 96.8 (C-3), 49.7 (CO_2CH_3), 21.6 (CH_3). *Anal*. Calcd. For $C_9H_{10}ClNO_3S$ (247.7): C, 40.88; H, 3.92; N, 6.81. Found: C, 49.01; H, 3.97; N, 6.60.

Methyl 2-acetamido-5-chloro-3-carboxylate (7b). Reaction run using **6b** (299 mg) and yielded 242 mg (69%) of **7b** as pale brown powder, mp = 109-111°C. ^{1}H NMR ($CDCl_3$): δ 10.92 (br s, 1H, NH), 7.15 (s, 1H, 4-H), 3.88 (s, 3H, CO_2CH_3), 2.29 (s, 3H, $COCH_3$). ^{13}C ($CDCl_3$,): δ 177.6 (C-2), 167.9 ($COCH_3$), 158.7 (CO_2CH_3), 130.1 (C-4), 117.4 (C-3), 116.8 (C-5), 50.0 (CO_2CH_3), 22.8 ($COCH_3$). *Anal*. Calcd. For $C_8H_8ClNO_3S$ (233.67): C, 37.60; H, 3.16; N, 7.31. Found: C, 37.36; H, 3.27; N, 7.45.

***N*-(5-Chloro-3-cyanothiophen-2-yl)acetamide (7c)**. Reaction run using **6c** (249 mg) and yielded 222 mg (74%) of **7c** as ash-grey powder., mp = 121-125°C, ^{1}H NMR ($CDCl_3$,): δ 10.95 (br s, 1H, NH), 7.02 (s, 1H, 4-H), 2.22 (s, 3H, $COCH_3$). ^{13}C ($CDCl_3$): δ 168.5 ($COCH_3$), 150.0 (C-2), 124.4 (C-4), 120.0 (C-5), 115.5 (CN), 95.4 (C-3), 21.9 ($COCH_3$). *Anal*. Calcd. For $C_7H_3ClN_2OS$ (200.65): C, 37.86; H, 1.91; N, 17.66. Found: C, 37.51; H, 1.85; N, 17.42.

Step V. Transamination.

Procedure. Hexane-2,5-dione (1.2 mmol) was added to a mixture of 2-acetamido-5-chloro-thiophene derivative **7a-c** (1 mmol) and *p*-TsOH (1 mol%) and conc. HCl (1 mol%) in xylene (30 mL/mmol of acetamide **7**). Reaction was stirred in refluxing xylene for 8 hours utilizing Dean-Stark trap for removal of forming acetic acid and water. After cooling down to room temperature the mixture was washed with saturated solution of $NaHCO_3$ (2x20mL), water (2x20mL) and aqueous NaCl. The toluene phase was dried over Na_2SO_4. The products **3a-c** were purified by column chromatography, eluent *hexane-ethyl acetate (9:1)*.

Methyl 5-chloro-4-methyl-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-thiophene-3-carboxylate (3a). Reaction run using 248 mg of **7a** to give 145 mg (51%) of light yellow crystalline product **3a**, mp = 70-72°C. ^{1}H NMR ($CDCl_3$): δ 5.90 (s, 2H, 3´-H, 4´-H), 3.91 (s, 3H, CO_2CH_3), 2.80 (s, 6H, 2xCH_3), 2.32 (s, 3H, CH_3). ^{13}C ($CDCl_3$): δ 160.0 (CO_2CH_3), 146.5 (C-2), 136.5 (C-4), 135.2 (C-3), 128.0 (C-2´, C-5´), 124.6 (C-5), 107.1 (C-3´, C-4´), 48.9 (CO_2CH_3), 11.2 (CH_3) 12.6 (2xCH_3). *Anal*. Calcd. For $C_{13}H_{14}ClNO_2S$ (283.77): C, 55.02; H, 4.97; N, 4.94. Found: C, 55.40; H, 4.63; N, 4.39.

Methyl 5-chloro-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylate (3b). Reaction run using 234 mg of **7b** to give 130 mg (48%) of pale yellow crystalline product **3b**., mp = 82-84°C. ^{1}H NMR ($CDCl_3$,): δ 7.27 (s, 1H, 4-H), 5.90 (s, 2H, 3´-H, 4´-H), 3.70 (s, 3H, CO_2CH_3), 2.04 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$,): δ 162.0 (CO_2CH_3), 146.2 (C-2), 133.2 (C-4), 131.3 (C-3), 129.0 (C-5), 127.1 (C-3´, C-5´), 106.4 (C-3´, C-4´), 49.8 (CO_2CH_3), 12.2 (2xCH_3). *Anal*. Calcd. For $C_{12}H_{12}ClNO_2S$ (269.75): C, 53.43; H, 4.48; N, 5.19. Found: C, 53.30; H, 4.32; N, 4.54.

5-Chloro-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)thiophene-3-carbonitrile (3c). Reaction run using 201 mg of **7c** to give 109 mg (46%) of light brown crystalline product **3c**, mp = 79-81°C. ^{1}H NMR ($CDCl_3$,): δ 6.87 (s, 1H, 4-H), 5.78 (s, 2H, 3´-H, 4´-H), 2.12 (s, 6H, 2xCH_3). ^{13}C ($CDCl_3$,): δ 138.3 (C-2), 131.2 (C-5), 127.5 (C-2´, C-5´), 124.6 (C-4), 115.7 (CN), 110.8 (C-3), 106.7 (C-3´, C-4´), 12.0 (2xCH_3). *Anal*. Calcd. For $C_{11}H_9ClN_2S$ (236.72): C, 55.81; H, 3.83; N, 11.83. Found: C, 55.70; H, 3.64; N, 11.96.

Step VI. Deprotection.

A round-bottomed flask was charged with 5-chloro-2-(2,5-dimethyl-*1H*-pyrrol-1-yl)thiophene derivative **4a-c** (0.5 mmol), hydroxylamine dihydrochloride (1.5 g, 30 equiv.,15 mmol) and triethylamine (4.0 mL, 20 equiv., 10 mmol), *n*-butanol (6 mL) and water (1 mL), then warmed to 80°C and stirred at this temperature for 60 hours. After cooling down to room temperature saturated solution of $NaHCO_3$ was added slowly to a mixture to increase the pH to basic (10-12) - *caution, during the addition of $NaHCO_3$ the mixture foams heavily*. The mixture was stirred for another 30 minutes. The formed solid was filtered off, washed with dichloromethane. The aqueous phase was then separated from organic phase and extracted with dichloromethane (2x10 mL). Combined organic extracts were concentrated to provide an oily solid. Crude mixture of the product and acetonylacetone related *by*-products of the deprotection were separated using column chromatography, eluent: *dichloromethane*.

Methyl 5-chloro-2-amino-4-methylthiophene-2-carboxylate (2a). Reaction run using 142 mg of **3a** to yield 31 mg (30%) of **2a** as an orange solid, mp = 59-63°C. ^{1}H NMR ($CDCl_3$,): δ

8.75 (br s, 2H, NH_2), 3.70 (s, 3H, CO_2CH_3), 2.75 (s, 3H, CH_3). ^{13}C ($CDCl_3$,): δ 163.7 (C-2), 158.2 (CO_2CH_3), 135.9 (C-4), 124.6 (C-5), 112.0 (C-), 54.3 (CO_2CH_3), 2.7 (CH_3). *Anal.* Calcd. For $C_7H_8ClNO_2S$ (205.66): C, 40.88; H, 3.92; N, 6.81. Found: C, 40.70; H, 3.75; N, 6.88.

Methyl 2-amino-5-chlorothiophene-2-carboxylate (2b). Reaction run using 117 mg of **3a** to yield 29 mg (34%) of **2b** as an yellow solid, mp = 65-67°C. ^1H NMR ($CDCl_3$,): δ 8.50 (br s, 2H, NH_2), 7.36 (s, 1H, 4-H), 3.43 (s, 3H, CO_2CH_3). ^{13}C ($CDCl_3$,): δ 160.9 (C-2), 158.9 (CO_2CH_3), 134.1 (C-3), 131.0 (C-4), 128.3 (C-5), 50.3 ($COCH_3$). *Anal.* Calcd. For $C_6H_6ClNO_2S$ (191.64): C, 37.60; H, 3.16; N, 7.31. Found: C, 37.72; H, 3.20; N, 7.40.

2-Amino-5-chlorothiophene-3-carbonitrile (3c). Reaction run using 118 mg of **3c** to yield 22 mg (28 %) of **2c** as a light brown solid, mp = 75-77°C. ^1H NMR ($CDCl_3$,): δ 8.20 (br s, 2H, NH_2), 6.83 (s, 1H) ppm. ^{13}C ($CDCl_3$,): δ 138.6 (C-2), 131.1 (C-5), 126.0 (C-4), 115.7 (CN), 108.2 (C-3). *Anal.* Calcd. For $C_5H_3ClN_2S$ (158.61): C, 37.60; H, 3.16; N, 7.31. Found: C, 37.72; H, 3.20; N, 7.40.

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