Tetrahedron 64 (2008) 11262–11269

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of π-conjugated thiophenes starting from substituted 3-oxopropanenitriles via Gewald reaction

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ARTICLE INFO

Article history:
Received 17 June 2008
Received in revised form 25 August 2008
Accepted 11 September 2008
Available online 20 September 2008

ABSTRACT

This paper describes the synthesis of β-aryl and β-heteroaryl substituted 2-aminothiophenes as a novel class of building blocks in oligo- and polythiophenes. The synthesis was carried out in two steps, involving synthesis of substituted 3-oxopropanenitrile intermediates, followed by the Gewald reaction.

1. Introduction

Substituted 3-oxopropanenitriles represent a category of versatile synthetic intermediates. They provide miscellaneneous building blocks in the synthesis of several types of heterocyclic ring systems. The synthesis of 4-cyano pyrroles, 1,4-dithiafulvenes, 4-aryl-5-cyano-2-amino pyrimidines, asymmetric reduction of β-ketonitriles followed by enzymatic transformation to optically pure β-hydroxy carboxylic acids, one-step fusion of 1,3-thiazine and pyrimidine cycles, regio- and stereoselective synthesis 4-cyano-2,3-dihydrofuran-3-carboxamides or biotransformation of nitriles to amides using nitrile hydratase starting from substituted 3-oxopropanenitriles were investigated recently.[1] The unique reactivity of oxonitriles arises from the closeness of two strongly electron-withdrawing groups. In general, the reactions of saturated oxonitriles reflect the high acidity of protons adjacent to carbonyl and nitrile group. Moreover, the keto and cyano functions are suitably situated to facilitate reactions with common bidentate reagents.[2]

Here we present our approach to synthesis of some 3-aryl and 3-heteroaryl 3-oxopropanenitriles as reactants for the conjugated structures.

Several new oligo- and polythiophene-forming methods were employed to construct novel types of semiconducting polymers, which has become one of the most challenging scientific research areas. Since the initial discovery of organic compounds showing metallic conductivity, for which 2000 Nobel prize in chemistry was awarded,[3,4] oligo- and polythiophenes have attracted much attention as advanced molecules with a practical use in electronic devices.[5] The main interest has concentrated on sophisticated syntheses leading to well defined thiophene structures, allowing variation of substituents and chain extension by a number of functionalized thiophene units.[6] It is well-established that the substitution and chain length critically influence the electronic properties of oligothiophenes.[5b,6b,7]

We have explored the synthesis of model derivatives of β-aryl or β-heteroaryl substituted 2-aminothiophenes utilizing the Gewald reaction.[8] The free amino group allows chain elongation and the growth of π-conjugated systems upon its modification via deamination reactions,[9] followed by the Gewald reaction. The Gewald reaction represents a simple technique where in one step—by choosing suitable substrates—the functionalization of the final oligomer is precisely predicted.

2. Results

The group of four 3-oxopropanenitriles Ar–CO–CH_2–CN **4a–d** (where Ar=phenyl, thiophen-2-yl, 1-methyl-1*H*-pyrrol-2-yl and ((9*H*-fluorenylidene)methyl)-1-methyl-1*H*-pyrrol-2-yl) selected for this study were prepared in three different ways. Aromatic 3-oxopropanenitriles can be accessed via the Claisen reaction of carboxylic acid esters with carboxylic acid nitriles in the presence of strong bases (*Method A*).[10] By this procedure derivatives **4a** and **4b** were obtained starting from the appropriate methyl esters **1a**,**b** in a reaction with acetonitrile in dry THF in the presence of sodium hydride (Scheme 1).[11] In a parallel experiment, the same 3-oxopropanenitriles **4a** and **4b** were prepared by the Guareshi/Thorpe type condensation starting from carbonitriles—benzonitrile (**2a**) and thiophen-2-carbonitrile (**2b**) (*Method B*). In the presence of bulky base *tert*-butanol and strong base sodium hydride, the reaction with acetonitrile in diethylether proceeded to form 3-oxo-3-phenylpropanenitrile **4a** and 3-oxo-3-(thiophen-2-yl)propanenitrile **4b** (Scheme 1) in higher yields than by the first method (Table 1). It was noted earlier that there is a danger of self-condensation of the starting methyl esters producing 3-oxopropanenitriles by the

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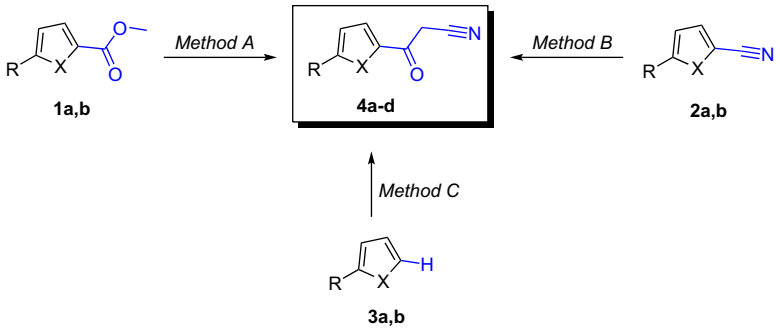
doi:10.1016/j.tet.2008.09.032



Scheme 1. Synthesis of substituted 3-oxopropanenitriles.

Table 1
Substituted 3-oxopropanenitriles produced via Scheme 1

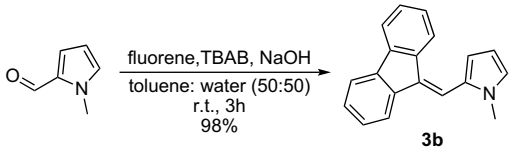
Substrate	Method	Conditions	Product	R	X	Yield (%)
1a	*Method A*	CH_3CN (1.0 equiv), NaH (2.0 equiv), THF, 67 °C, 2.5 h	**4a**	H	CH=CH	35
1b	*Method A*	CH_3CN (1.0 equiv), NaH (2.0 equiv), THF, 67 °C, 2.5 h	**4b**	H	S	60
2a	*Method B*	CH_3CN (1.0 equiv), *tert*-BuOH (0.1 equiv) NaH (2.0 equiv), Et_2O, rt, 7 h	**4a**	H	CH=CH	70
2b	*Method B*	CH_3CN (1.0 equiv), *tert*-BuOH (0.1 equiv) NaH (2.0 equiv), Et_2O, rt, 7 h	**4b**	H	S	66
3a	*Method C*	$CNCH_2CO_2H$ (4.0 equiv), $Mg(ClO_4)_2\cdot 2H_2O$ (0.01 equiv), Ac_2O, 80 °C, 4 h	**4c**	H	N–CH_3	87
3b	*Method C*	$CNCH_2CO_2H$ (4.0 equiv), $Mg(ClO_4)_2\cdot 2H_2O$ (0.01 equiv), Ac_2O, 80 °C, 4 h	**4d**	9-Ethylidene-9*H*-fluorene	N–CH_3	65

Claisen type condensation.[10,12] In agreement with this knowledge, the requisite products **4a** and **4b** were obtained in only 35–50% yields using *Method A* and in 66–70% yields by *Method B* (Table 1).

Direct electrophilic acylation performed with mixed carboxylic acid anhydrides in the presence of acetic anhydride acting as both catalyst and a solvent, first published in 2004[13] seems to be the most straightforward route of producing substituted 3-oxopropanenitriles. Until then, only acylations of nitriles with acylchlorides in the presence of suitable catalyst have been known to afford the 3-oxopropanenitriles.[14] The reaction takes place only with substituted or unsubsituted indoles and pyrroles, proceeding in almost quantitative yields, but completely fails to produce aromatic 3-oxopropanenitriles. In our case, as discussed earlier, the only way to 3-oxo-3-phenylpropanenitrile **4a** and 3-oxo-3-(thiophen-2-yl)propanenitrile **4b** seems to be the base catalyzed condensation. 1-Methyl-1*H*-pyrrole (**3a**) and 2-((9*H*-fluoren-9-ylidene)methyl)-1-methyl-1*H*-pyrrole (**3b**) were chosen as suitable reagents for direct acylation. The reaction with cyanoacetic acid in acetic anhydride with magnesium perchlorate—$Mg(ClO_4)_2\cdot 2H_2O$ as a catalyst (Scheme 1) afforded the 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile **4c** and the 3-[5-((9*H*-fluoren-2-ylidene)methyl)-1*H*-pyrrol-2-yl]-3-oxopropanenitrile **4d** smoothly in high yields (Table 1).

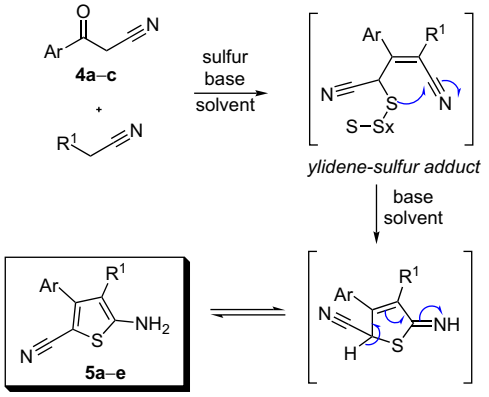
One of the substrates used for the synthesis of substituted 3-oxopropanenitriles, derivative **3b**— 2-((9*H*-fluoren-ylidene)methyl)-1-methyl-1*H*-pyrrole belongs to the class of (9*H*-fluoren-9-ylidene)methyl terminated chromophores. Thiophene and oligothio phene analogues of **3b** show interesting optical properties, and it was clearly demonstrated that the fluorene moiety present in the molecule effectively influences optical, photoluminescence and electrochemical properties.[15] The synthesis of the compound was carried out according to the scheme published for the synthesis of fluorene–thiophene type of structure.[16] A condensation between 1-methyl-1*H*-pyrrole-2-carbaldehyde and fluorene in a heterogeneous water/toluene mixture using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst afforded product **3b** in 98% yield (Scheme 2).

Substituted 3-oxopropanenitriles **4a–c** are promising *CH*-active substrates for the synthesis of new types of 2-aminothiophenes



Scheme 2. Synthesis of fluorene–pyrrole type structure **3b**.

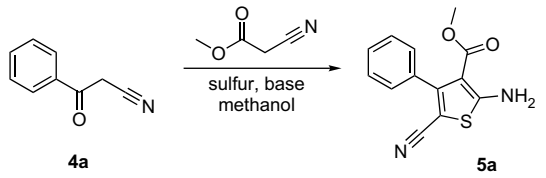
with aryl or heteroaryl substituents at the β-position of **5a–e**. The $-COCH_2-$ alignment in 3-oxopropanenitriles is suitable for the Gewald reaction, which encompasses a Knoevenagel condensation and cyclization reaction sequence.[8] By condensation between the oxo group of starting 3-oxopropanenitriles **4a–c** with the active methylene group of an activated nitrile (derivative of cyanoacetic acid), an ylidene (α,β-unsaturated nitrile) is created. The addition of sulfur to the CH_2 group of the formed ylidene is followed by subsequent intramolecular cyclization resulting in the final 2-aminotiophenes **5a–e** (Scheme 3).



Ar = phenyl, thiophene–2yl, 1-methyl-1*H*-lpyrrol-2-yl, (9*H*-fluoren-ylidene)methyl)-1-methyl-1*H*-pyrrol-2-yl, $\mathbf{R^1}$= CO_2CH_3, CN

Scheme 3. Reaction sequence in a synthesis of 2-aminothiophene.

Classical conditions for the Gewald thiophene synthesis involve the reaction of two starting substrates with sulfur and a base, the latter being required in each reaction step as shown in Scheme 3. To find the best reaction conditions, a base screen in methanol as solvent was performed for the reaction starting from 3-oxo-3-phenylpropanenitrile **4a** leading to methyl 2-amino-5-cyano-4-phenylthiophene-3-carboxylate **5a** (Scheme 4). The reaction was



Scheme 4. Synthesis of 2-aminothiophene **5a** from 3-oxo-3-phenylpropanenitrile **4a** by variation of the Gewald reaction conditions.

Table 2
Base and reaction screen for the Gewald reaction outlined in Scheme 4

Reaction conditions: amount of used base and sulfur, reaction temperature (°C), reaction time (h)	Yield of **5a** (%)
Et_3N (2.0 equiv),[a] S_8 (1.2 equiv),[a] 60 °C, 72 h	30
Morpholine (2.2 equiv),[b] S_8 (1.0 equiv),[b] 45 °C, 5 h	50
Morpholine (3.0 equiv),[c] S_8 (2.0 equiv),[c] (20–45) °C, 24 h	72

[a] Base was added to sulfur, compound **4a** and methylcyanoacetate suspended in methanol in one portion.
[b] Base was added to sulfur, compound **4a** and methylcyanoacetate suspended in methanol dropwise.
[c] Morpholine-polysulfide (**MPS**) prepared at 150 °C first and then methanolic solution of starting substrates was added dropwise.

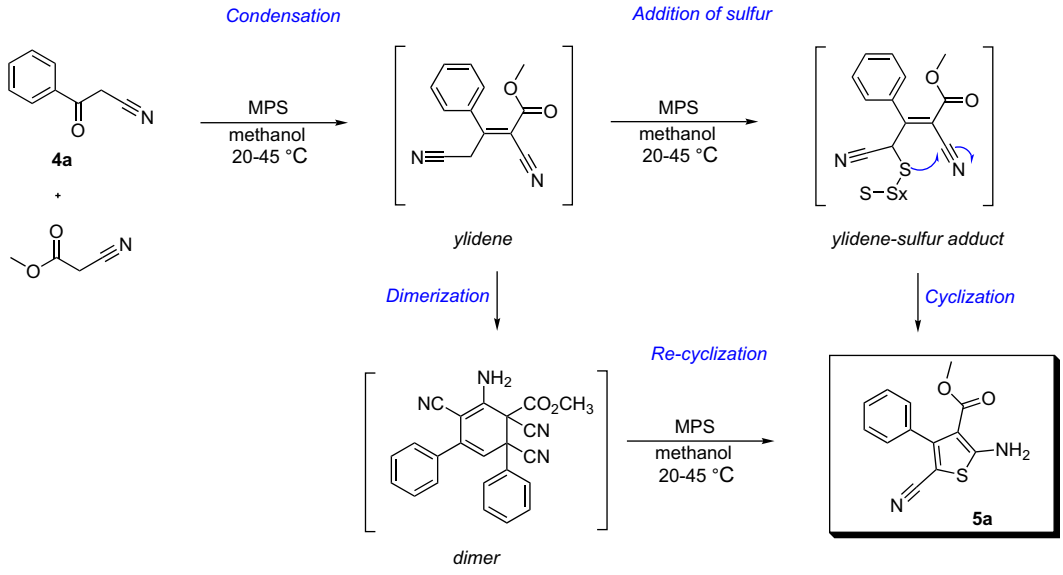
carried out in the presence of triethylamine (2.0 equiv),[17] and formed the corresponding product in only 30% after 3 days (Table 2). Using morpholine (2.2 equiv)[18] as a base caused an increase in the yield of **5a** to 50% after 5 h reaction time (Table 2). Even if the yield and the time of the reaction were in that case satisfactory, we turned to a procedure published by Gudriniece and co-workers in 1983.[19] Morpholine-polysulfide (**MPS**) is formed first in situ by mixing the sulfur (2.0 equiv) with morpholine (3.0 equiv) at 150 °C and adding the starting substrates (compound **4a** and methylcyanoacetate (1.0 equiv amount each) in methanol) at temperature not exceeding 45 °C. The increase of the yield is significant—the product **5a** was obtained in 72% yield after 24 h (Table 2).

The structure of **MPS** and the mechanism of its activity have not yet been clarified. Authors[19] in their study had only described the formation by recyclization of substituted 2-acetylaminothiophene in low yield from the appropriate substituted hexa-1,3-diene, as was later summarized in a Russian review.[20] Another study[21] contains an account of the discovery that morpholine-polysulfide, in combination with a substituted triazine, provides excellent vulcanization of rubbers. Herein the composition of **MPS** is presumed to contain from two to five sulfur atoms within two morpholine molecules.

In our opinion, the morpholine shows the best solubility of sulfur from all the organic bases used in the Gewald reaction (i.e., diethylamine, piperidine, pyridine). **MPS** acts then in two ways—as a base needed in each reaction step, and also as a sulfurization agent in the addition step of the reaction (Scheme 3). Indeed, while applying the **MPS**, the reaction is not only directed towards substituted 2-aminothiophenes, but at the same time the recyclization of dimerized six-membered hexa-1,3-diene to the appropriate thiophene ring **5a** is favoured. During the stepwise Gewald reaction process, dimerization of the ylidene occurs spontaneously as a side reaction (Scheme 5). The yields of dimer are highly dependent on the reaction conditions.

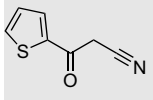
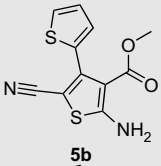
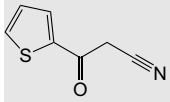
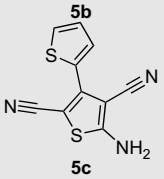
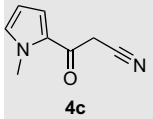
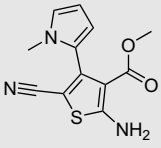
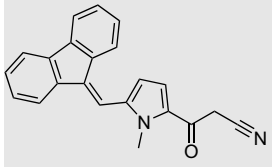
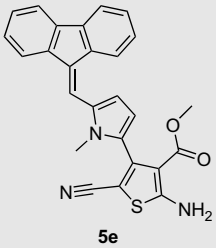
In our case, its concentration was not significant enough for further identification. Our declarations on the formation of dimer as a product of the parallel side reaction are based on the latest study[22] in which the structure of an analogous dimer was claimed. However, it is clear that by the one-pot and one-step technique utilizing **MPS**, the reaction is directed towards the target 2-amino thiophenes. Employing the same reaction conditions as in our previous work[23] we have used **MPS** in a synthesis of β-heteroaryl substituted 2-aminothiophenes **5b–e** from the appropriate 3-oxo-propanenitriles **4b–d** in yields ranging from 50 to 62% (Table 3).

Structures **5a–e** represent such novel types of π-conjugated thiophenes where the elongation of the conjugated system is well-established with the heteroaromatic substituent in the β-position. Their synthesis by the Gewald reaction using **MPS** represents a convenient and easy route to substituted oligothiophenes, and



Scheme 5. The study of the Gewald reaction mechanism involving the dimerization and recyclization step using **MPS**.

Table 3
Products of the Gewald reaction **5b–e** starting from 3-oxopropanenitriles **4b–d**

Substituted 3-oxopropanenitrile	Reaction time (h)	Product	Yield (%)
 **4b**	24	 **5b**	62[a]
 **4b**	18	 **5c**	58[b]
 **4c**	18	 **5d**	52[a]
 **4d**	20	 **5e**	50[a]

[a] With methylcyanoacetate using **MPS**.
[b] With malonodinitrile using **MPS**.

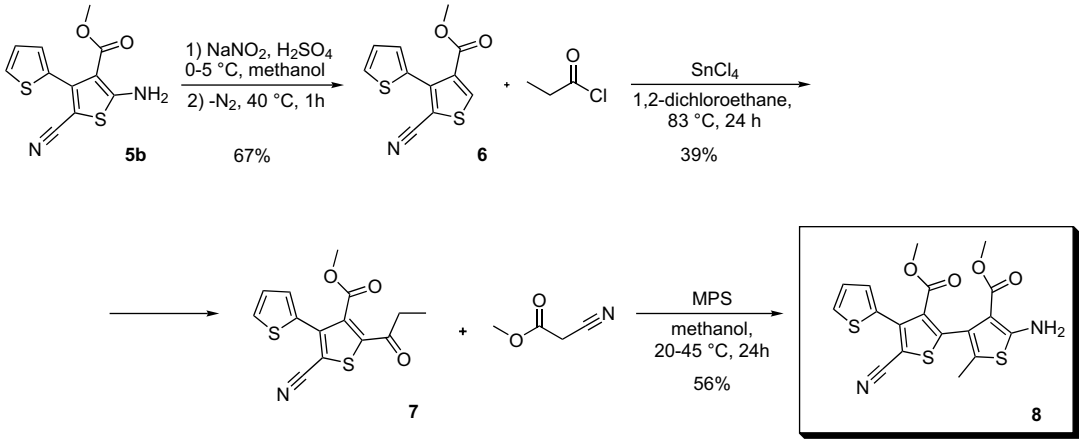
other oligomers in which the basic properties of different components are fused together (i.e., stability of thiophene—derivatives **5b**,**c**, optical and electrochemical properties of thiophene and pyrrole—**5d**, fluorescent properties of fluorene—**5e**) providing good candidates for applications.

The creation of longer systems containing more than two thiophene units is exemplified by the derivative **5b**. The first step—deamination—was performed under classical conditions with sodium nitrite and sulfuric acid.[9a] After the evolution of nitrogen from the intermediate diazonium salt, the deaminated product **6** was obtained in 67% yield. The free α-position underwent substitution by Friedel–Crafts acylation. The acylated product **7** was formed only in 39% yield. In general, it is a fact that substituted thiophenes are rather unreactive towards acylchlorides. The reaction succeeded only when propionylchloride (1.5 equiv) was used as acylating agent and tin tetrachloride (3.0 equiv) as a Lewis agent[24] in boiling 1,2-dichlorethane (Scheme 6). The propan-1-one side chain allows formation of the 2-aminothiophene ring in the final step. Performing the Gewald type cyclization of compound **7** with cyanoacetic acid in the presence of **MPS** under the same conditions as in case of compounds **5a–e** resulted to final structure **8** in which three thiophene rings are combined. The product was achieved in an acceptable 56% yield (Scheme 6).

The target derivatives **5a–e**, **6–8** are highly stable, soluble in common solvents such as methanol, ethanol, dichloromethane, ethylacetate, and particularly in chloroform, hexane, toluene. Our proposal of their preparation by the Gewald reaction represents a comfortable route with the possibility of the connection of another thiophene ring by repeating the three-step process as shown on Scheme 6. By this procedure, the conjugated system can be easily prolonged to oligothiophene type structure (in general the oligothiophene is a structure with six thiophene rings fused together). The free amino group allows its change to halogen— bromine or iodine. Such halogenated derivatives undergo coupling reactions. With the right choice of starting substrates the functionalization of final structures can be achieved (i.e., aryl or heteroaryl substitution, prediction of hydrophilic or hydrophobic character of final structures)—Figure 1.

3. Conclusion

In summary, we have disclosed the convenient synthesis of β-aryl and β-heteroaryl substituted 2-aminothiophenes as useful tools in development of thiophene oligomers and polymers for molecular devices in optoelectronics (i.e., organic switchers, Langmuir/Blodgett films, light emitting diodes, photovoltaic cells, etc.). Our main interest was concerned with the utilization and development of the Gewald reaction and its synthetic potential in material chemistry and synthesis. The mechanism of the Gewald type cyclization involving a parallel side reaction is discussed. Starting from substituted 3-oxopropanenitriles, novel variously substituted 2-aminothiophenes have been prepared showing interesting optical and electrochemical properties. Work to that end is in progress.



Scheme 6. Elongation of conjugated thiophene system in a three-step procedure: deamination reaction/Friedel–Crafts acylation/Gewald reaction.

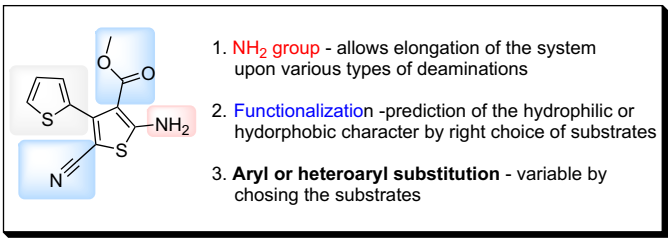


Figure 1. Possible variations on **5a–e** type structures prepared by the Gewald reaction.

4. Experimental

4.1. General

All chemicals were purchased from Sigma–Aldrich or Merck and used without further purification. All solvents were of HPLC grade and used as supplied. The melting points were measured on a Griffin Melting Point apparatus. Elemental analyses were determined using a Carlo Erba 1108-Elemental Analyser. The IR spectra of compounds **3b**, **4c** and **4d** were recorded on a Perkin–Elmer System 1600 FTIR instrument using KBr pellets. IR spectra of the compounds **5a–e**, **6–8** were measured using diamond smart orbit ATR on Nicolet 5700 FTIR instrument. All mass spectra were recorded on a Buker Esquire LC-00050 electrospray ionisation mass spectrometer using CH_3CN or CH_3OH as a matrix. Routine ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a VARIAN VXR 300 instrument at 25 °C. The measurements were done using protiated solvents—$CDCl_3$ and DMSO-d_6, with TMS as an internal standard reference. Two dimensional spectra gs-H,H-COSY, 1D-gs-NOESY, gs-HSQC and gs-HMBC were measured using standard software programs provided by VARIAN. Coupling constans (J) are quoted to the nearest 0.1 Hz and chemical shifts (δ-scale) are quoted in parts per million (ppm) and following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. 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 into chromatography column. The collected fraction samples were analyzed by TLC. Compounds are numbered according to Schemes 1–6.

4.2. General procedure for the synthesis of fluorene–pyrrole type structure

*4.2.1. 2-((9H-Fluoren-9-ylidene)methyl)-1-methyl-1H-pyrrole (**3b**)*

Fluorene (6.0 mmol, 1.0 g) and 1-methyl-1*H*-pyrrole-2-carbaldehyde (6.0 mmol, 0.66 g) were dissolved in toluene (8.5 mL). Then, TBAB (1.0 mmol, 0.35 g) in 10.0 mL of NaOH solution (6.0 g of NaOH in water) was added. The mixture was stirred vigorously at room temperature for 3 h. After the reaction was complete, the water and toluene layers were separated. The organic phase was washed with diluted HCl (1:1, 5.0 mL), water (5.0 mL) and saturated brine (5.0 mL), then dried with Na_2SO_4. After evaporation of the solvent, the crude product was dried and crystallized from *n*-heptane. Yield: 98% (3.0 g) of yellowish crystals; mp 80–82 °C. IR (KBr) ν 3137 (N–CH_3), 3059 (=C–$H_{ethylidene}$), 3024, 3001, 2942, 1650 (C=$C_{ethylidene}$), 1611, 1592, 1586, 1510, 1479, 1405, 1376, 830, 770, 688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 6.32–6.30 (m, 1H), 6.79–6.83 (m, 2H), 7.18–7.24 (m, 1H), 7.30–7.39 (m, 4H), 7.73–7.79 (m, 3H), 8.23 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.4, 108.4, 112.8, 115.7, 119.5, 119.6, 119.8, 123.7, 123.8, 124.4, 126.7, 127.6, 128.2, 129.0, 134.4, 136.6, 138.6, 139.7, 140.6. Anal. Calcd for $C_{19}H_{15}N$ (257.33): C, 88.68; H, 5.88; N, 5.44. Found: C, 88.80; H, 6.11; N, 5.37. Mass (ESI) m/z (%) 258.12 (M+H), 280.12 (M+Na).

4.3. General procedures for the synthesis of substituted 3-oxopropanenitriles

Method A. The appropriate methyl ester (methyl benzoate **1a**: 7.0 mmol, 0.95 g; methyl thiophene-2-carboxylate **1b**: 7.0 mmol, 1.0 g) and NaH (14.0 mmol, 0.35 g) in boiling tetrahydrofuran (5.0 mL) were treated with solution of acetonitrile (7.0 mmol, 0.29 g, 0.4 mL) in tetrahydrofuran (1.0 mL) dropwise. The mixture was heated to reflux for 2.5 h and after cooling down to room temperature, it was diluted with diethylether (15.0 mL) and left to stand at room temperature for 48 h. The precipitated sodium salt was filtered and washed with diethylether. The dry compound was dissolved in water (5.0 mL) and acidified with HCl (1:1) to pH 2. The product was extracted with a 3:1 mixture of diethylether/benzene (3×10 mL). The collected extracts were washed with a saturated solution of $NaHCO_3$, dried with Na_2SO_4 and evaporated. The product was crystallized from toluene.

Method B. To a stirred suspension of NaH (20.0 mmol, 0.5 g) in diethylether (10.0 mL) at reflux a solution of *tert*-butanol (1.0 mmol, 80 mg, 0.1 mL) in diethylether (0.5 mL) was added first, then the appropriate nitrile (benzonitrile **2a**: 10.0 mmol, 1.0 g; thiophene-2-carbonitrile **2b**: 10.0 mmol, 1.1 g) and finally acetonitrile (10.0 mmol, 0.4 g, 0.5 mL). Reflux was continued for 7 h. After cooling down to room temperature it was allowed to stand at 4 °C overnight. The precipitated sodium salt was filtered off and washed with diethylether. The dry sodium salt was dissolved in ethanol (10.0 mL) and treated with hydrochloric acid (3.2 mL) and kept at room temperature for 30 min while stirring. After diluting with water (5.0 mL), the solution was extracted with diethylether (3×10 mL). Extracts were dried with Na_2SO_4 and evaporated. The crude product was crystallized from diethylether.

*4.3.1. 3-Oxo-3-phenylpropanenitrile (**4a**)*

Yield: 35% (355 mg)—*Method A*, 70% (711 mg)—*Method B*, white crystals; mp 80–81 °C. Analytical data corresponds to those published for 3-oxo-3-phenylpropanenitrile, C_9H_7NO (145.16), see Refs. 10 and 11.

*4.3.2. 3-Oxo-3-(thiophen-2-yl)propanenitrile (**4b**)*

Yield: 60% (635 mg)—*Method A*, 66% (700 mg)—*Method B*, yellowish crystals; mp 112–115 °C. Analytical data corresponds to those published for 3-oxo-3-(thiophen-2-yl)propanenitrile, C_7H_5NOS (151.19), see Ref. 25.

Method C. To a solution of cyanoacetic acid (16.0 mmol, 1.4 g, 1.3 mL) in acetic anhydride (3.0 mL), the appropriate pyrrole was added (1-methyl-1*H*-pyrrole **3a**: 4.0 mmol, 0.32 g; 2-((9*H*-fluoren-9-ylidene)methyl)-1-methyl-1*H*-pyrrole **3b**: 4.0 mmol, 1.0 g) at 80 °C under an inert argon atmosphere. The solution was heated at 80 °C for a further 4 h. After cooling down to room temperature, the reaction mixture was poured onto ice water (5.0 mL) and extracted into dichloromethane (3×10 mL). The collected extracts were dried with Na_2SO_4 and evaporated to dryness. Crude products were crystallized from dichloromethane.

*4.3.3. 3-(1-Methyl-1H-pyrrol-2-yl)-3-oxopropanenitrile (**4c**)*

Yield: 87% (516 mg)—*Method C*, white solid; mp 109–110 °C. IR (KBr) ν 3141 (N–CH_3), 2259 (CN), 1639 (C=O), 1530, 1467, 1438, 1410, 1396, 1384, 1294, 1250, 1212, 1105, 1074, 923, 907, 880, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.42 (s, 2H), 6.16–6.17 (m, 1H), 7.12–7.13 (m, 1H), 7.24–7.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 37.0, 108.5, 116.1, 121.3, 128.0, 133.3, 178.2. Anal. Calcd for $C_8H_8N_2O$ (148.16): C, 64.85; H, 5.44; N, 18.91. Found: C, 65.10; H, 5.70; N, 19.03. Mass (ESI) m/z (%) 149.0 (M+H), 171.0 (M+Na).

*4.3.4. 2-((9H-Fluoren-9-ylidene)methyl)-1-methyl-1H-pyrrole (**4d**)*

Yield: 65% (843 mg)—*Method C*, yellow solid; mp 133–135 °C. IR (KBr) ν 3119 (N–CH_3), 3061 (=C–$H_{ethylidene}$), 3040, 3012, 2246 (CN), 1688 (C=O), 1654 (C=$C_{ethylidene}$), 1605, 1560, 1512, 1455, 1400, 1372, 810, 714. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.52 (s, 2H), 6.58 (d, J=4.4 Hz, 1H), 7.07 (d, J=4.4 Hz, 1H), 7.12 (t, J=7.7 Hz, 1H), 7.19 (s, 1H), 7.29–7.42 (m, 4H), 7.56 (d, J=7.8 Hz, 1H), 7.68 (d, J=7.2 Hz, 1H), 7.74 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 34.4, 112.2, 112.7, 114.5, 119.8, 120.0, 120.5, 120.6, 124.2, 127.2, 127.3, 128.7, 129.3, 129.6, 135.8, 138.4, 139.5, 139.6, 141.1, 141.5, 176.1. Anal. Calcd for $C_{22}H_{16}N_2O$ (324.38): C, 81.46; H, 4.97; N, 8.64. Found: C, 81.70; H, 5.02; N, 8.43. Mass (ESI) m/z (%) 325.13 (M+H), 347.13 (M+Na).

4.4. Gewald reaction: synthesis of β-aryl and β-heteroaryl substituted 2-aminothiophenes

General procedure A. To a mixture of 3-oxo-3-phenylpropanenitrile **4a** (4.0 mmol, 581 mg), sulfur (4.8 mmol, 154 mg) and methylcyanoacetate (4.0 mmol, 396 mg, 350 mL) in methanol (15.0 mL), triethylamine (14.0 mmol, 1.42 g, 2.0 mL) was added. After stirring at 60 °C for 3 days, the reaction mixture was evaporated and water was added (10 mL). The formed crystals were filtered off and filtrate extracted with dichloromethane (2×20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evaporated. The residue combined with the filtered crystal product was purified by column chromatography on silica gel (absorbed with 1% triethylamine) eluting with a mixture of dichloromethane/methanol (98:2) followed by crystallization from a mixture of methanol/1,4-dioxane (50:50).

General procedure B. A mixture of 3-oxo-3-phenylpropanenitrile **4a** (4.0 mmol, 581 mg), sulfur (4.8 mmol, 154 mg) and methylcyanoacetate (4.0 mmol, 396 mg, 350 mL) in methanol (15.0 mL) was treated dropwise with morpholine (8.8 mmol, 766 mg, 0.8 mL) at 45 °C. After being stirred for 5 h at 45 °C, the mixture was diluted with water (20 mL) and extracted with dichloromethane (3×20 mL). Collected extracts were washed with water (20 mL) and with brine (20 mL) and dried with Na_2SO_4. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (absorbed with 1% triethylamine) eluting with a mixture of dichloromethane/methanol (98:2) followed by crystallization from mixture methanol/1,4-dioxane (50:50).

General procedure C. A mixture of morpholine (12.0 mmol, 1.0 g, 1.0 mL) and sulfur (8.0 mmol, 256 mg) was stirred at 110 °C for 3 h under an inert argon atmosphere. The formed morpholine-polysulfide (dark reddish mass) was cooled down to room temperature and solution of starting compounds (4.0 mmol of starting 3-oxopropanenitriles **4a**–**d**, 4.0 mmol of cyanoacetic acid derivative—methylcyanoacetate or malononitrile) in methanol (40 mL) were added dropwise over 30 min at a temperature not exceeding 45 °C. After addition was complete, the reaction mixture was stirred for a further 24 h at room temperature. The reaction mixture was diluted with water (40 mL). The formed crystals were filtered off and the filtrate extracted with dichloromethane (2×20 mL). The combined organic layers were washed with brine and dried with Na_2SO_4 and evaporated. The residue combined with the filtered crystalline product was purified by column chromatography on silica gel (absorbed with 1% triethylamine) eluting with a mixture of dichloromethane/methanol (98:2) followed by crystallization from a mixture of methanol/1,4-dioxane (50:50).

*4.4.1. Methyl 2-amino-5-cyano-4-phenylthiophene-3-carboxylate (**5a**)*

Yield: 30% (310 mg)—*Method A*, 50% (520 mg)—*Method B*, 72% (744 mg)—*Method C*, yellow solid; mp 109–111 °C. IR (diamond smart orbit ATR) ν 3276 (NH_2), 2988, 2860, 2234 (CN), 1676 (C=O_{ester}), 1618, 1526, 1430, 1232 (C–O_{ester}), 1020, 970, 888, 750, 540 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.77 (s, 3H, CO_2CH_3), 5.24 (br s, 2H, NH_2), 7.34 (d, J=7.2 Hz, 1H), 7.43 (t, J=7.8 Hz, 1H), 7.87 (t, J=7.8 Hz, 2H), 7.99 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.4 (CO_2CH_3), 128.5, 129.7, 140.1, 141.8 (C-3), 152.2 (C-4), 159.2 (CO_2CH_3), 168.6 (C-2). Anal. Calcd for $C_{13}H_{10}N_2O_2S$ (258.30): C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.80; H, 4.00; N, 11.03; S, 12.54. Mass (ESI) m/z (%) 259.1 (M+H), 281.0 (M+Na).

*4.4.2. Methyl 2-amino-5-cyano-4-(thiophene-2-yl)thiophene-3-carboxylate (**5b**)*

Yield: 62% (660 mg)—*Method C*, light orange solid; mp 128–132 °C. IR (diamond smart orbit ATR) ν 3270 (NH_2), 2972, 2928, 2264 (CN), 1693 (C=O_{ester}), 1541, 1450, 1429, 1217 (C–O_{ester}), 1105, 1031, 975, 840, 719, 587 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.87 (s, 3H, CO_2CH_3), 4.41 (br s, 2H, NH_2), 7.10 (d, J=5.8 Hz, 1H, H-3′), 7.37 (dd, J=5.8 Hz, 1H, H-4′), 7.64 (d, J=5.8 Hz, 1H, H-5′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.8 (CO_2CH_3), 111.0 (C-5), 114.1 (CN), 126.1 (C-5′), 127.3 (C-3′), 129.1 (C-4′), 136.2 (C-2′), 140.3 (C-3), 151.8 (C-4), 163.4 (CO_2CH_3), 172.3 (C-2). Anal. Calcd for $C_{11}H_8N_2O_2S$ (264.32): C, 49.98; H, 3.05; N, 10.60; S, 24.26. Found: C, 49.70; H, 3.18; N, 10.75; S, 24.42. Mass (ESI) m/z (%) 265.0 (M+H), 287.0 (M+Na).

*4.4.3. 5-Amino-3-(thiophen-2-yl)thiophene-2,4-dicarbonitrile (**5c**)*

Yield: 58% (613 mg)—*Method C*, orange solid; mp 138–142 °C. IR (diamond smart orbit ATR) ν 3319 (NH_2), 2972, 2257 (CN), 2230 (CN), 1520, 1448, 1046, 962, 792, 565 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.21 (br s, 2H, NH_2), 7.08 (d, J=6.2 Hz, 1H, H-5′), 7.44 (dd, 1H, J=6.2 Hz, H-4′), 7.62 (d, 1H, J=6.2 Hz, H-3′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 110.9 (C-2), 111.4 (C-4), 113.6 (CN), 115.1 (CN), 126.1 (C-5′), 127.2 (C-3′), 127.8 (C-4′), 140.9 (C-2′), 157.1 (C-3), 165.3 (C-5). Anal. Calcd for $C_{10}H_5N_3S_2$ (231.30): C, 51.93; H, 2.18; N, 18.17; S, 27.73. Found: C, 52.10; H, 2.24; N, 18.22; S, 27.83. Mass (ESI) m/z (%) 232.0 (M+H), 254.0 (M+Na).

*4.4.4. Methyl 2-amino-5-cyano-4-(1-methyl-1H-pyrrol-2-yl)-thiophene-3-carboxylate (**5d**)*

Yield: 52% (543 mg)—*Method C*, orange solid; mp 138–142 °C. IR (diamond smart orbit ATR) ν 3291 (NH_2), 3122 (N–CH_3), 2952, 2237 (CN), 1651 (C=O_{ester}), 1515, 1435, 1291, 1239 (C–O_{ester}), 1108, 1024, 843, 747, 549 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.10 (s, 3H, N-CH_3), 3.86 (s, 3H, CO_2CH_3), 4.35 (br s, 2H, NH_2), 6.16 (d, J=6.6 Hz, 1H, H-5′), 7.12 (d, J=6.6 Hz, 1H, H-3′), 7.2 (dd, J=6.6 Hz, 1H, H-4′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.4 (CO_2CH_3), 30.1 (N–CH_3), 107.4 (C-5), 113.6 (CN), 115.5 (C-4′), 116.6 (C-3′), 118.9 (C-5′), 130.5 (C-2′), 144.6 (C-3), 158.2 (C-4), 160.0 (CO_2CH_3), 174.4 (C-2). Anal. Calcd for $C_{12}H_{11}N_3O_2S$ (261.30): C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.28; H, 4.36; N, 16.19; S, 12.19. Mass (ESI) m/z (%) 262.1 (M+H), 284.0 (M+Na).

*4.4.5. Methyl 2-amino-5-cyano-4-(5-(9H-fluoren-9-ylidene)-methylpyrrol-2-yl)thiophen-3-carboxylate (**5e**)*

Yield: 52% (875 mg)—*Method C*, red solid; mp 194–198 °C. IR (diamond smart orbit ATR) ν 3332 (NH_2), 3233 (N–CH_3), 2183 (CN), 2960 (=C–$H_{ethylidene}$), 1724 (C=O_{ester}), 1614 (C=$C_{ethylidene}$), 1541, 1427, 1261, 1231 (C–O_{ester}), 1108, 1022, 887, 775, 729, 619 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.11 (s, 3H, N–CH_3), 3.91 (s, 3H, CO_2CH_3), 4.12 (br s, 2H, NH_2), 5.90 (d, J=6.8 Hz, 1H, H-3′), 6.20 (d, J=6.8 Hz, 1H, H-4′), 6.92 (s, 1H), 7.65 (d, J=8.0 Hz, 2H, ArH fluorene), 7.50 (t, J=8.2 Hz, 2H, ArH fluorene), 7.35 (t, J=8.2 Hz, 2H, ArH fluorene), 7.20 (d, J=8.0 Hz, 2H, ArH fluorene); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.6 (CO_2CH_3), 28.4 (N–CH_3), 109.9 (C-5), 111.9, 112.4 (C-4′, C-3′), 114.8 (CN), 116.6 (C-α), 131.4 (C-5′), 141.8 (C-3), 126.3, 127.0, 128.8, 138.0, 140.3, 142.2 (13×C fluorene), 144.6 (C-2′), 156.7 (C-4), 162.4 (CO_2CH_3),172.6 (C-2). Anal. Calcd for $C_{26}H_{19}N_3O_2S$ (437.5): C,

71.38; H, 4.38; N, 9.60; S, 7.33. Found: C, 71.54; H, 4.46; N, 9.47; S, 7.25. Mass (ESI) *m*/*z* (%) 437.2 (M+H), 460.0 (M+Na).

4.5. Synthesis of trithiophene system utilizing a three-step procedure: deamination reaction/Friedel–Crafts acylation/Gewald cyclization

*4.5.1. Deamination reaction: synthesis of methyl 5-cyano-4-(thiophen-2-yl)thiophene-3-carboxylate (**6**)*

To an ice cold solution of methyl 2-amino-5-cyano-4-(thiophene-2-yl)thiophene-3-carboxylate (**4b**, 10.0 mmol, 2.6 g) in methanol (40 mL), concentrated sulfuric acid (2.0 mL) was added with vigorous stirring. The mixture was cooled down to −5 °C and solution of sodium nitrite (12.0 mmol, 1.2 g) in 6 mL of water was added dropwise via a syringe whose tip is kept below of the reaction solution, with vigorous stirring keeping the temperature below −2 °C. The dark red solution was stirred at −2 °C for 30 min, then gently warmed to 40 °C and heated at 40–50 °C 1 h. After the evolution of nitrogen had ceased, the reaction mixture was cooled to room temperature, neutralized with saturated $NaHCO_3$ (*intensively foaming*!) and then extracted with chloroform (3×30 mL). The combined chloroform extracts were washed with 5% aqueous $NaHCO_3$, saturated NaCl, water and dried with Na_2SO_4 and evaporated to yield dark red-brown solid. The crude product was chromatographed over SiGel using mixture of dichloromethane/methanol (97:3) to give deaminated bithiophene as shiny yellow solid. Yield: 67% (1.7 g); mp 128–132 °C. IR (diamond smart orbit ATR) ν 2221 (CN), 1650 (C=O_{ester}), 1525, 1277, 1215 (C–O_{ester}), 1006, 927, 860, 756, 623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H, CO_2CH_3), 6.96 (d, *J*=6.0 Hz, 1H, H-3′), 7.17 (dd, *J*=6.0 Hz, 1H, H-4′), 7.41 (d, *J*=6.0 Hz, 1H, H-5′), 8.2 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8 (CO_2CH_3), 108.2 (C-5), 112.0 (CN), 125.3 (C-5′), 127.6 (C-3′), 128.0 (C-4′), 130.1 (C-3), 139.3 (C-2′), 142.9 (C-2), 153.4 (C-4), 162.1 (CO_2CH_3). Anal. Calcd for $C_{11}H_7NO_2S_2$ (249.3): C, 52.99; H, 2.83; N, 5.62; S, 25.72. Found: C, 53.10; H, 2.92; N, 5.73; S, 25.88. Mass (ESI) *m*/*z* (%) 250.0 (M+H), 270.0 (M+Na).

*4.5.2. Friedel–Crafts acylation: synthesis of methyl-5-cyano-2-propionyl-4-(thiophen-2-yl)thiophen-3-carboxylate (**7**)*

To methyl 5-cyano-4-(thiophen-2-yl)thiophene-3-carboxylate (**6**, 4.5 mmol, 1.1 g) dissolved in dry 1,2-dichloroethane (15 mL), propionylchloride (6.75 mmol, 600 mg, 0.6 mL) was added and the mixture was stirred for 30 min under an inert argon atmosphere. Tin tetrachloride (13.5 mmol, 3.3 g, 1.5 mL) was added dropwise via a syringe with vigorous stirring at room temperature. After addition had completed, the reaction mixture was stirred at 83 °C for 24 h and then cooled down to room temperature. The mixture was carefully poured into water (45 mL) and neutralized with a saturated solution of Na_2CO_3 (*consumption of solution 15–20 mL, intensively foams during neutralization*!). The mixture was stirred at room temperature for 1 h and then extracted into chloroform (3×30 mL), and washed with water. The combined organic layers were dried with Na_2SO_4 and evaporated to yield a yellow powder. Yield: 39% (536 mg); mp 112–114 °C. IR (diamond smart orbit ATR) ν 2260, 1707 (C=O_{ketone}), 1670 (C=O_{ester}), 1518, 1446, 1212 (C–O_{ester}), 974, 922, 796, 740, 632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, $COCH_2CH_3$), 3.82 (s, 3H, CO_2CH_3), 4.11 (q, 2H, $COCH_2CH_3$), 7.06 (d, *J*=6.2 Hz, 1H, H-3′), 7.27 (dd, *J*=6.2 Hz, 1H, H-4′), 7.31 (d, *J*=6.2 Hz, 1H, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 ($COCH_2CH_3$), 38.0 ($COCH_2CH_3$), 48.6 (CO_2CH_3), 112.4 (CN), 115.2 (C-5), 126.6 (C-5′), 127.0 (C-3′), 127.5 (C-4′), 137.1 (C-2′), 138.4 (C-3), 155.8 (C-4), 160.0 (CO_2CH_3), 165.1 (C-2), 179.6 ($COCH_2CH_3$). Anal. Calcd for $C_{14}H_{11}NO_3S_2$ (305.37): C, 55.06; H, 3.63; S, 21.00; N, 4.59. Found: C, 55.15; H, 3.80; N, 4.75; S, 21.16. Mass (ESI) *m*/*z* (%) 306.0 (M+H), 328.0 (M+Na).

*4.5.3. Gewald reaction: synthesis of methyl 2-amino-5-methyl-4-[3′-methoxycarbonyl-5′-cyano-4′-(thiophen-2″-yl)thiophen]-3-carboxylate (**8**)*

Morpholine-polysulfide was prepared in situ by mixing sulfur (4.5 mmol, 150 mg) with morpholine (6.0 mmol, 300 mg, 0.3 mL) at 110 °C for 3 h. A solution of methyl-5-cyano-2-propionyl-4-(thiophen-2-yl)thiophen-3-carboxylate (**7**, 1.5 mmol, 450 mg) and methylcyanoacetate (3.0 mmol, 300 mg, 0.1 mL) in methanol (6.0 mL) was added dropwise to the in situ prepared **MPS** at room temperature with stirring. The reaction mixture was stirred at room temperature for 24 h, and then poured into water (15 mL). The aqueous solution was extracted with ethylacetate (3×15 mL), then the combined organic layers washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography on silica gel (absorbed with 1% triethylamine) eluting with a mixture of dichloromethane/methanol (90:10) followed by crystallization from mixture methanol/1,4-dioxane (50:50) to yield a red powder. Yield: 56% (351 mg)—*Method C*, orange solid; mp 138–142 °C. IR (diamond smart orbit ATR) ν 3312 (NH_2), 2927, 2227 (CN), 1650 (C=O_{ester}), 1502, 1466, 1434, 1271 (C–O_{ester}), 1234 (C–O_{ester}), 1190, 1105, 1065, 1024, 976, 841, 780, 588 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.12 (s, 3H, CH_3), 3.68 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 7.16 (d, *J*=6.0 Hz, 1H, H-3″), 7.69 (dd, *J*=6.0 Hz, 1H, H-4″), 7.76 (d, *J*=6.0 Hz, 1H,H-5″), 7.88 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.9 (CH_3), 44.2 (2×CO_2CH_3), 110.1 (C-5′), 113.6 (CN), 126.1 (C-5″), 127.7 (C-3″), 129.3 (C-4″), 136.2 (C-5), 138.8 (C-2″), 140.6 (C-3′), 142.1 (C-3), 144.1 (C-4), 154.2 (C-4′), 156.7 (C-2′), 162.1 (2×CO_2CH_3), 165.5 (C-2). Anal. Calcd for $C_{18}H_{14}N_2O_4S_3$ (418.51): C, 51.66; H, 3.37; N, 6.69; S, 22.99. Found: C, 51.85; H, 3.64; N, 6.90; S, 23.12. Mass (ESI) *m*/*z* (%) 419.01 (M+H), 441.02 (M+Na).

Acknowledgements

This work was supported by the Ministry of Education of the Slovak Republic—VEGA Grant No. 1/4453/07. Z.P. is indebted to Dr. Peter Zálupský for correcting the language of the manuscript. The authors are grateful to Mrs. Silvia Markusová for IR spectra measurements.

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