Monatshefte für Chemie 132, 279–293 (2001)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Novel 2-Aminothiophene-3-carboxylates by Variations of the *Gewald* Reaction

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Summary. The synthesis of the title compounds through variations of the *Gewald* reaction is presented. *Knoevenagel* condensation of methylketone derivatives with methyl cyanoacetate and subsequent treatment of the α,β-unsaturated nitriles with sulfur and amine resulted in the corresponding 2-aminothiophenes **5** or isomers **9** and **10**. Reaction of methylketone derivatives bearing a leaving group at the methyl group under modified *Gewald* conditions selectively led to the formation of 4-substituted 2-aminothiophenes **9a** and **12**. The introduction of the sulfur atom occurs through nucleophilic displacement with sodium sulfide.

Keywords. 2-Aminothiophenes; *Gewald* reaction; Heterocycles; Methylketones.

Introduction

The couple benzene–thiophene represents one of the most prominent examples of bioisosterism. Whereas the replacement of a benzene ring by a thiophene ring in a pharmacologically active compound has been frequently regarded as a mere case of 'me-too strategy' in drug research, the advent in the market of an increasing number of thiophene containing drugs having no benzene ring predecessor points to the fact that in many cases the specific placement of a thiophene moiety has become the first choice in drug design and is superior to the use of benzene. During the last years our interest in this class of compounds has been focused on their use as precursors to a series of novel inhibitors at the glycine binding-site of the NMDA-receptor such as **1** [1, 2]. For this work we required intermediate **2**. Of particular interest has been the preparation of analogues of **2** bearing various substituents at position 4 (R^2) of the ring system.

The *Gewald* synthesis is probably the most versatile and important reaction for the preparation of biological active compounds and intermediates containing a thiophene moiety. Three major modifications of this method are well known in

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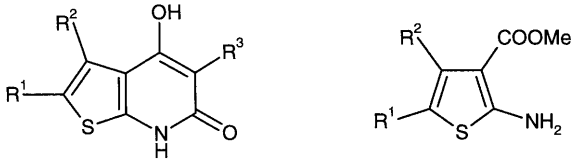
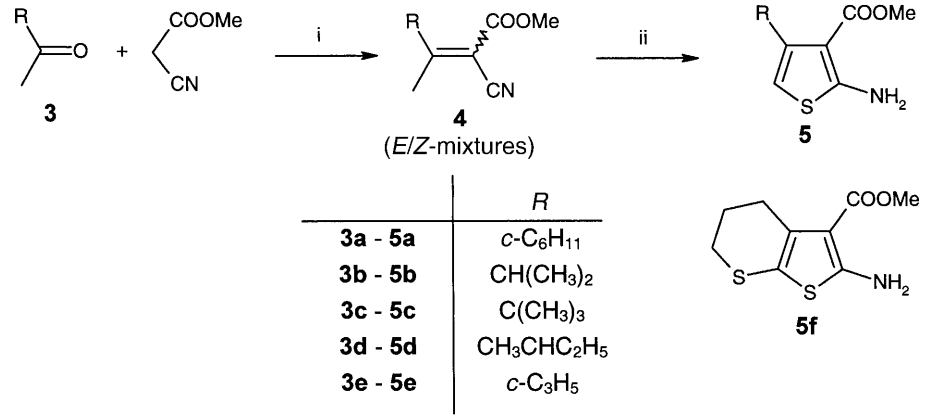


Scheme 1

literature which offer access to various 2-aminothiophenes in a simple fashion [3]. In the first, an α-mercaptoaldehyde or an α-mercaptoketone is treated with an activated nitrile bearing an electron withdrawing group. However, this particular version is less attractive due to a few drawbacks such as utilization of starting compounds which are unstable and difficult to prepare [4–7]. Much more elegant and simple is the one-pot procedure, which includes the condensation of aldehydes, ketones, or 1,3-dicarbonyl compounds with activated nitriles and sulfur in the presence of amines [8–10]. In the third version, a two-step procedure is preferred. It involves the isolation of α,β-unsaturated nitriles from *Knoevenagel* condensation and subsequent conversion of these olefins to the corresponding 2-aminothiophenes by treatment with sulfur and amine. This variation not only gives higher yields, but also allows the conversion of alkyl aryl ketones to thiophenes which is not possible with the one-pot procedure [8, 11–12]. Some time ago, we published a further modification of the *Gewald* reaction which renders 4-*n*-alkyl substituted 2-aminothiophene derivatives accessible not obtainable *via* the classical methods [13]. Herein, we wish to report the results of further investigations on this modification. At the same time we include results on the synthesis of novel methyl 2-aminothiophene-3-carboxylates using the two-step variation of the *Gewald* reaction, particularly of compounds exhibiting a functionalized alkyl group at position 4.

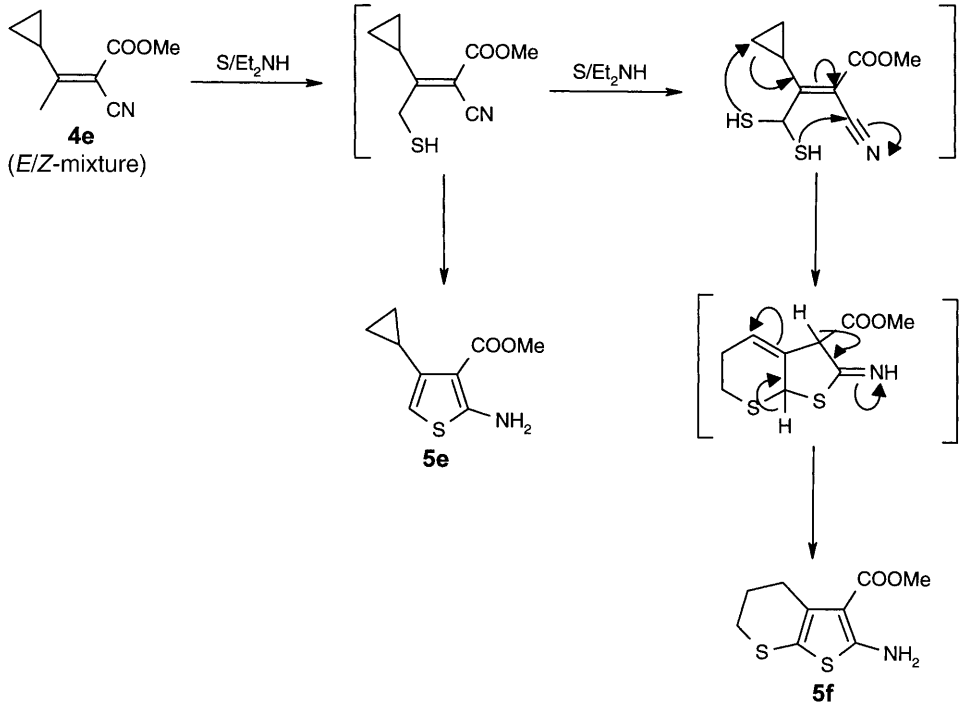
Results and Discussion

The α,β-unsaturated nitriles **4a–e**, in all cases isolated as *E*/*Z*-isomeric mixtures, were obtained by heating of the respective ketones **3a–e** with methyl cyanoacetate in benzene under a constant water separator in the presence of glacial acetic acid and catalytic amounts of ammonium acetate [14, 15]. However, the low reactivity of pinacolone **3c**, due to sterical hindrance by the adjacent methyl groups, required the addition of equimolar amounts of ammonium acetate and extended reaction times to obtain **4c** in at least poor yield [16]. The condensation products **4a–e** were subsequently cyclized with sulfur and diethylamine in methanol to yield **5a–e**. In contrast to *Gewald*, who described the synthesis of **5a** at room temperature but without a yield given [11], we observed that for complete conversion of **4a–e** extended reaction times at 35–40°C were necessary. This indicates that isomerization from *E* to *Z* occurs at elevated temperature and enables the reaction of the *E*-isomer, which is the major condensation product. Depending on the applied amount of sulfur and the course of the reaction the mixtures were worked up according to three different variations, and the final compounds **5a–d** were isolated



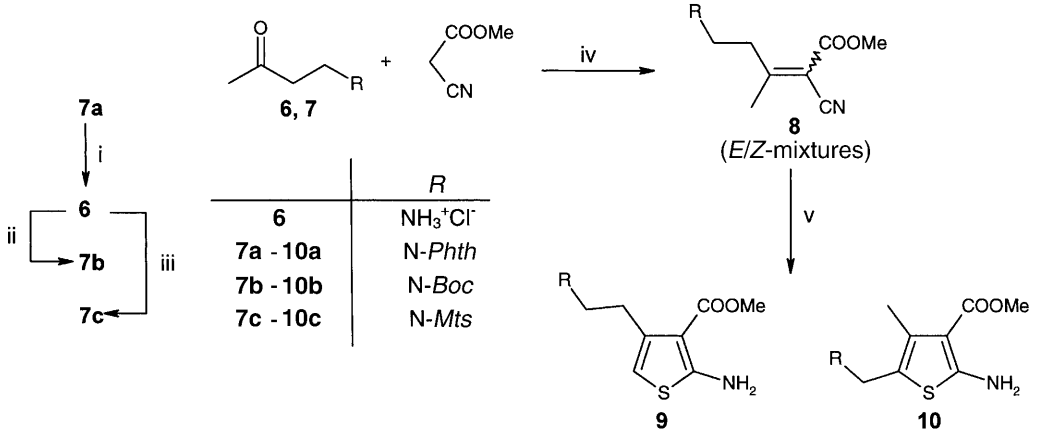
	R
3a - 5a	*c*-C_6H_{11}
3b - 5b	$CH(CH_3)_2$
3c - 5c	$C(CH_3)_3$
3d - 5d	$CH_3CHC_2H_5$
3e - 5e	*c*-C_3H_5

Scheme 2. Reagents and conditions: i) NH_4OAc, AcOH, benzene, reflux; ii) S, Et_2NH, abs. MeOH, 35–40°C



Scheme 3

in moderate to good yields. When compound **4e** was treated as described above, the formation of **5e** along with one byproduct was observed. On the basis of spectroscopic studies, we assigned structure **5f** to this byproduct. Moreover, we assume that the formation of **5f** proceeds *via* the mechanism depicted in Scheme 3. The first step of the formation of both products is an α-thiolation. On the one hand this intermediate cyclizes to the desired thiophene **5e**; on the other hand it is likely that a dithiolation reaction takes place to a certain extent. It is worth mentioning that such dithiolated species have already been decribed as reaction intermediates by

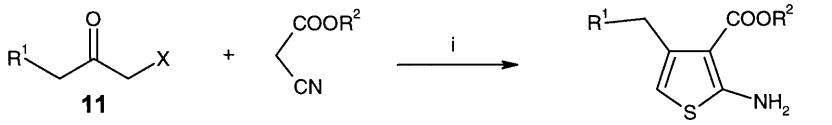


Scheme 4. Reagents and conditions: i) 5 *M* HCl, reflux; ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0°C; iii) *Mts*Cl, Et_3N, CH_2Cl_2, 0°C; iv) NH_4OAc or piperidine, AcOH, benzene, reflux; v) S, Et_2NH, abs. MeOH, 40°C

Asinger [17] as well as *Gewald* [8]. Finally, **5f** is formed by cycloaddition and concurrent nucleophilic opening of the cyclopropyl moiety. It is interesting to note that this side reaction has not been observed during the preparation of the respective ethyl ester [18].

Apart from the described 4-alkyl substituted thiophene derivatives we were interested in 2-aminothiophenes with alkyl groups at position 4 bearing functional groups such as cyano, carboxylic ester, protected amino, and hydroxy groups which allow further synthetic transformations. Thus, we investigated the availability of such compounds *via Gewald* synthesis. Therefore, appropriately substituted methylketones and the corresponding *Knoevenagel* condensation products were required as precursors.

Michael addition of phthalimide to methylvinylketone yielded the ketone **7a** [19], which upon treatment with hydrochloric acid afforded **6**, the key intermediate for the preparation of further protected aminoketones. Thus, the *Boc* and 2,4,6-Trimethylbenzenesulfonyl (*Mts*) protected derivatives **7b** and **7c** were obtained from **6** using standard reaction conditions. Subsequent condensation of **7a–c** with methyl cyanoacetate resulted in *E*/*Z*-mixtures of **8a–c**. In general, the thiolation-heterocyclization reactions of such intermediates to the corresponding aminothiophenes furnish 4-methyl derivatives, because thiolation occurs preferentially at the methylene group and not at the methyl group [11]. However, some reactions have been reported in literature by which thiolation and incorporation of the methyl group led to unexpected aminothiophene derivatives [20]. For this reason, a regioselective thiolation and subsequent formation of the 4-substituted thiophenes could not be expected. Indeed, when compounds **8a–c** were treated with sulfur and diethylamine in methanol at 40°C, mixtures of 4- and 5-substituted isomers **9** and **10** were obtained, which were separated by either chromatography or recrystallization. Unfortunately, in all cases the desired 4-substituted thiophene was the minor reaction product. Nevertheless, this approach gives access to highly substituted thiophenes which could have potential as building blocks in combinatorial chemistry. In order to circumvent the observed selectivity problems we further



	R^1	X
11a	OCH_3	O*Ts*
11b	COOEt	Cl
11c	CN	Br
11d	O*Bz*	O*Ts*
11c	CH_2-N*Phth*	Br

	R^1	R^2
12a	OCH_3	Me
12b	COOEt	Et
12c	CN	Me
12d	O*Bz*	Me
12c	OH	Me
9a	CH_2-N*Phth*	Me

Scheme 5. Reagents and conditions: i) Na_2S nonahydrate, Et_3N, abs. MeOH or EtOH

investigated a modification of the *Gewald* reaction [13] which requires the introduction of a leaving group at the methyl group of methylketone derivatives. This was accomplished by either bromination or total synthesis of the appropriate ketones. Treatment of such ketones under the modified *Gewald* conditions avoids the formation of product mixtures, since the introduction of the sulfur atom occurs through nucleophilic displacement with sodium sulfide. However, reaction of **11e**, which was readily prepared from **7a** through bromination using the conditions described by *Elz* [21], with sodium sulfide in methanol at elevated temperature gave **9a** in a yield similar to that achieved by the foregoing procedure. Despite this unpleasant result, the following examples emphasize the usefulness of this method for the conversion of functionalized alkylmethylketones to 4-substituted thiophenes, particularly in the case of heteroatoms or electron-withdrawing substituents being present, thus rendering the methylene group more acidic than the methyl group. Recent investigations have shown that for such ketones, *e.g.* methoxyacetone, the thiolation-heterocyclization reaction is directed exclusively towards the 5-isomer and generates 5-alkoxy-thiophenes [22]. In contrast to these findings, our modification of the *Gewald* reaction gives acess to the respective 4-isomers.

Monotosylation of 3-methoxypropane-1,2-diol followed by oxidation of the secondary hydroxy group resulted in ketone **11a**, which upon treatment according to the one-pot procedure described above yielded **12a**. Introduction of a cyanomethyl or (ethoxycarbonyl)-methyl residue was achieved in a similar manner using 4-bromo-3-oxo-butanenitrile [23] (**11c**) or commercially available ethyl chloroacetoacetate (**11b**). The precursor **11d** for the synthesis of derivative **12d** was obtained by oxidation of (*R*/*S*)-2-hydroxy-3-(((4-methylbenzene)-sulfonyl)-oxy)-propyl benzoate [24]. Treatment of **11d** under the conditions described above yielded the thiophene **12d**. The deprotected derivative **12e** was isolated in small amounts as well.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. Column chromatography and vacuum flash chromatography (VFC) were performed on silica gel 60 (Merck). Thin layer

chromatography was performed on aluminum sheets, coated with silica gel 60 F_{254} (Merck). Microanalyses were within ±0.4% of theoretical values and were performed by the Institute of Organic Chemistry, University of Frankfurt/Main (CHN-Rapid, Heraeus). 300 MHz ^{1}H NMR spectra were recorded on a Bruker AC 300, 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra on a Bruker AC 200 spectrometer; chemical shifts are reported in ppm relative to internal *TMS*. IR spectra were obtained on a Bruker IFS-48 instrument. UV spectra were recorded on a Varian 300 Bio spectrophotometer. Petroleum ether, diethylether, and CH_2Cl_2 were distilled before use. Other chemicals and solvents were used in standard commerical quality. Abbreviations: *bz*, benzoyl; *chxl*, cyclohexyl; *D*, CH_2Cl_2; *PE*, petroleum ether; *tos*, tosyl; VFC, vacuum flash chromatography.

Compounds **7a** [19] and **11c** [23] were prepared as described in the literature. The synthesis of compound **7b** has also been previously described [25], but an alternative route was used.

Methyl (E/Z)-2-cyano-3-cyclohexyl-2-butenoate (**4a**; $C_{12}H_{17}NO_2$)

Methyl cyanoacetate (15.7 g, 0.16 mol) and 20 g **3a** (0.16 mol) were dissolved in 35 cm^3 dry benzene to which 2.4 g ammonium acetate (31 mmol) and 7.6 g glacial acetic acid (0.13 mol) were added. The mixture was refluxed under a constant water separator until the formation of H_2O ceased. The mixture was cooled, diluted with benzene, and washed with H_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by VFC (300 g silica gel, eluent: *PE*/Et_2O = 20/1) to yield 28.4 g (86.5%) of colourless crystals.

M.p.: 97–101°C (Ref. [11]: m.p.: 96–100°C); R_f (*PE*/Et_2O = 5/1) = 0.27; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.87–3.59/3.03–2.81 (2m, 4H, therein: 3.78 (s, 3H, OCH_3); 1H, CH, *chxl*, *Z*/*E*), 2.26/2.18 (s, CH_3, *E*/*Z*), 1.92–1.0 (m, 10H, *chxl*) ppm.

Methyl (E/Z)-2-cyano-3,4-dimethyl-2-pentenoate (**4b**; $C_9H_{13}NO_2$)

Methyl cyanoacetate (31.4 g, 0.32 mol), 30 g **3b** (0.35 mol), 4.85 g ammonium acetate (63 mmol), and 15.6 g glacial acetic acid (0.26 mol) were dissolved in 60 cm^3 dry benzene and treated for 22 h as described for **4a**. The isolated residue was distilled *in vacuo* to yield 42.7 g (80%) of a colourless liquid.

B.p.: 105–107°C (9–10 mbar) (Ref. [26]: b.p.: 107–108°C (8 mbar)); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 4.06/3.31 (2sept, J = 6.7 Hz, C*H*$(CH_3)_2$, *Z*/*E*), 3.79 (s, OCH_3), 2.25/2.17 (2s, 3-CH_3, *E*/*Z*), 1.12/1.06 (2d, J = 6.7 Hz, CH(C*H*$_3)_2$, *E*/*Z*) ppm.

Methyl (E/Z)-2-cyano-3,4,4-trimethyl-2-pentenoate (**4c**; $C_{10}H_{15}NO_2$)

Methyl cyanoacetate (159.3 g, 1.6 mol), 80.5 g **3c** (0.8 mol), 62 g ammonium acetate (0.8 mol), and 77.2 g glacial acetic acid (1.29 mol) were dissolved in 350 cm^3 dry benzene and treated according to a modified *Knoevenagel* procedure previously described [16]. The residue was distilled *in vacuo* to yield 6.38 g (4.5%) of a colourless liquid.

B.p.: 137–139°C (21 mbar) (Ref. [16]: b.p.: 127–130°C (16 mbar)); R_f (*PE*/Et_2O = 5/1) = 0.36; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.80 (s, OCH_3), 2.26/2.18 (2s, CH_3, *E*/*Z*), 1.36/1.18 (s, C$(CH_3)_3$), *E*/*Z*) ppm.

Methyl (E/Z,R/S)-2-cyano-3,4-dimethyl-2-hexenoate (**4d**; $C_{10}H_{15}NO_2$)

Methyl cyanoacetate (23.7 g, 0.24 mol), 24 g **3d** (0.24 mol), 3.32 g ammonium acetate (43 mmol), and 10.79 g glacial acetic acid (0.18 mol) were dissolved in 40 cm^3 dry benzene and treated for 17 h as described for **4a**. The isolated residue was distilled *in vacuo* to yield 38.5 g (89%) of a colourless liquid.

B.p.: 115–118°C (12 mbar); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 4.0–3.82/3.17–2.96 (2m, 4-CH, *Z*/*E*), 3.78 (s, OCH_3), 2.21/2.13 (2s, 3-CH_3, *E*/*Z*), 1.58–1.33 (m, 5-CH_2), 1.09/1.04 (2d, $J = 6.7$ Hz, 4-CH_3, *E*/*Z*), 0.92–0.75 (m, 6-CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 180.97 (s, 3-C), 162.08/161.66 (2s, COOMe), 115.39/115.03 (2s, CN), 104.64/103.87 (2s, 2-C), 52.0 (q, OCH_3), 44.11/37.38 (2d, 4-C), 27.46/27.22 (2t, 5-C), 18.39/17.75 (2q, 3-CH_3), 15.01 (q, 4-CH_3), 11.52 (q, 6-C) ppm.

Methyl (E/Z)-2-cyano-3-cyclopropyl-2-butenoate (**4e**; $C_9H_{11}NO_2$)

Methyl cyanoacetate (23.56 g, 0.24 mol), 20 g **3e** (0.24 mol), 3.59 g ammonium acetate (46.5 mmol), and 11.4 g glacial acetic acid (0.19 mol) were dissolved in 50 cm^3 dry benzene and treated for 6 h as described for **4a**. The isolated residue was purified by VFC (330 g silica gel, eluent: *PE*/$Et_2O = 9/1$) to yield 28.6 g (73%) of colourless crystals.

M.p.: 74–78°C; R_f (*D*) = 0.38; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 3.82/3.80 (2s, OCH_3, *Z*/*E*), 3.53–3.41/2.46–2.34 (2m, CH, *Z*/*E*), 1.96/1.87 (2s, CH_3, *E*/*Z*), 1.21–1.09 (m, CH_2), 1.07–0.97 (m, CH_2) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 178.87 (s, 3-C), 163.05/162.48 (2s, COOMe), 116.35 (s, CN), 103.58/102.57 (2s, 2-C), 52.25/52.17 (2q, OCH_3), 20.33/16.20 (2d, CH), 17.78/14.01 (2q, 4-C), 10.43/9.36 (2t, CH_2) ppm.

Syntheses of **5a–e**; general procedure

A stirred solution of 0.1 mol **4a–e** in 20–40 cm^3 dry methanol was treated with 0.12–0.2 mol sulfur and 0.07–0.12 mol diethylamine at room temperature and subsequently warmed to 35–40°C. Depending on the applied amount of sulfur and the course of the reaction, the mixtures were worked up according to the following methods:

Method A: The reaction mixture was filtered, diluted with diethyl ether, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by VFC and crystallized by digesting in cold *PE*.

Method B: The reaction mixture was concentrated *in vacuo*. The residue was dissolved in diethyl ether and extracted several times with 6 *M* HCl. The aqueous layer was rendered basic and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was crystallized by digesting in cold *PE* and recrystallized.

Method C: The reaction mixture was concentrated *in vacuo*, and the residue was purified by VFC and crystallized by digesting in cold *PE*.

Methyl 2-amino-4-cyclohexylthiophene-3-carboxylate (**5a**; $C_{12}H_{17}NO_2S$)

Compound **5a** was prepared from 14.4 g **4a** (69.5 mmol), 2.7 g sulfur (84.2 mmol), and 8.75 cm^3 diethylamine (84.2 mmol) in 35 cm^3 dry MeOH as described above. After being stirred for 23 h at 35°C, the reaction mixture was worked up according to method *C* (VFC: 500 g silica gel, eluent: *D*/*PE* = 2/1) to yield 10.6 g (64%) of yellow crystals.

M.p.: 89–90.5°C (Ref. [11]: m.p.: 88–92°C); R_f (*D*) = 0.5; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.0 (s, br, NH_2), 5.86 (s, 5-H), 3.82 (s, OCH_3), 3.1–2.92 (m, CH, *chxl*), 2.01–1.64 (m, 5H, CH_2, *chxl*), 1.48–1.12 (m, 5H, CH_2, *chxl*) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.26 (s, COOMe), 161.35 (s, 2-C), 147.41 (s, 4-C), 105.70 (s, 3-C), 100.65 (d, 5-C), 50.70 (q, OCH_3), 39.34 (d, CH, *chxl*), 34.08 (t, CH_2, *chxl*), 26.98 (t, CH_2, *chxl*), 26.48 (t, CH_2, *chxl*) ppm; IR (KBr): $\tilde{\nu}$ = 3421, 3317, 2947, 2921, 2847, 1651, 1602, 1525, 1476, 1459, 1442, 1287, 1267, 1195, 1119, 1065, 989, 682 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 227 (24293), 300.5 (5340) nm.

Methyl 2-amino-4-isopropylthiophene-3-carboxylate (**5b**; $C_9H_{13}NO_2S$)

Compound **5b** was prepared from 37 g **4b** (0.22 mol), 14.2 g sulfur (0.44 mol), and 17 cm^3 diethylamine (0.16 mol) in 45 cm^3 dry MeOH as described above. After being stirred for 17 h at 40°C,

the reaction mixture was worked up according to method *A* (VFC: 500 g silica gel, eluent: *D*/*PE* = 1/1) to yield 30.9 g (70%) of yellow crystals.

M.p.: 31–32°C; R_f (*D*) = 0.29; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.05 (s, br, NH_2), 5.88 (s, 5-H), 3.81 (s, OCH_3), 3.38 (sept, J = 6.8 Hz, C*H*(CH_3)$_2$), 1.16 (d, J = 6.8 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.23 (s, COOMe), 164.56 (s, 2-C), 148.19 (s, 4-C), 105.63 (s, 3-C), 100.27 (d, 5-C), 50.59 (q, OCH_3), 29.0 (d, CH), 23.16 (q, CH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3441, 3333, 2963, 1674, 1584, 1527, 1475, 1439, 1285, 1260, 1105, 1010, 787, 672 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 227 (24205), 303 (5148) nm.

*Methyl 2-amino-4-*tert*-butylthiophene-3-carboxylate* (**5c**; $C_{10}H_{15}NO_2S$)

Compound **5c** was prepared from 5.66 g **4c** (31.23 mmol), 1.5 g sulfur (46.85 mmol), and 2.43 cm^3 diethylamine (23.42 mmol) in 12 cm^3 dry MeOH as described above. After being stirred for 25 h at 40°C, the reaction mixture was worked up according to method *C* (VFC: 140 g silica gel, eluent: *PE*/Et_2O = 5/1) to yield 1.64 g (25%) of colourless crystals.

M.p.: 56–58°C; R_f (*D*) = 0.44; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 5.97 (s, 5-H), 5.89 (s, br, NH_2), 3.83 (s, OCH_3), 1.33 (s, C(CH_3)$_3$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.21 (s, COOMe), 164.48 (s, 2-C), 149.84 (s, 4-C), 106.80 (s, 3-C), 102.14 (d, 5-C), 50.57 (q, OCH_3), 35.15 (s, *C*(CH_3)$_3$), 30.46 (q, C(*C*H$_3$)$_3$) ppm; IR (KBr): $\tilde{\nu}$ = 3413, 3311, 2950, 1655, 1595, 1513, 1469, 1437, 1293, 1268, 1192, 1119, 998, 782, 728, 675 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 227.5 (22083), 300.5 (5269) nm.

Methyl (R/S)-2-amino-4-(1-methylpropyl)thiophene-3-carboxylate (**5d**; $C_{10}H_{15}NO_2S$)

Compound **5d** was prepared from 35 g **4d** (0.19 mol), 11.15 g sulfur (0.35 mol), and 15 cm^3 diethylamine (0.15 mol) in 40 cm^3 dry MeOH as described above. After being stirred for 23 h at 40°C, the reaction mixture was worked up according to method *B* to yield 25.75 g (65%) of yellow crystals.

M.p.: 54.5–55.5°C (*PE*); R_f (*D*) = 0.52; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.02 (s, br, NH_2), 5.85 (s, 5-H), 3.80 (s, OCH_3), 3.32–3.11 (m, 1′-H), 1.77–1.52 (m, 1H, 2′-CH_2), 1.49–1.22 (m, 1H, 2′-CH_2), 1.15 (d, J = 6.9 Hz, CH-C*H*$_3$), 0.88 (t, J = 7.4 Hz, 3′-CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.32 (s, COOMe), 164.37 (s, 2-C), 147.12 (s, 4-C), 105.90 (s, 3-C), 100.81 (d, 5-C), 50.61 (q, OCH_3), 35.41 (d, 1′-C), 30.27 (t, 2′-C), 20.07 (q, CH-*C*H$_3$), 11.81 (q, 3′-C) ppm; IR (KBr): $\tilde{\nu}$ = 3413, 3311, 2960, 1651, 1605, 1525, 1475, 1459, 1442, 1283, 1194, 671 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 227.5 (26009), 303 (5614) nm.

Methyl 2-amino-4-cyclopropylthiophene-3-carboxylate (**5e**; $C_9H_{11}NO_2S$) *and Methyl 2-amino-5,6-dihydro-4H-thieno[2,3-b]thiopyran-3-carboxylate* (**5f**; $C_9H_{11}NO_2S_2$)

Compound **4e** (28.1 g, 0.17 mol) was treated with 6.5 g sulfur (0.2 mol) and 21.3 cm^3 diethylamine (0.2 mol) in 70 cm^3 dry MeOH as described above. After being stirred for 42 h at 35°C, the reaction mixture was worked up according to method *C* (VFC: 500 g silica gel, eluent: *D*/*PE* = 1/1). The obtained product mixture was digested in diethylether and filtered. The residue was recrystallized from $CHCl_3$ and identified as **5f**. The filtrate was extracted with 6 *M* HCl, the aqueous layer was washed with diethyl ether, rendered basic, and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and crystallized by digesting in *PE*.

5e: 18.4 g (55%) of beige crystals; m.p.: 72–74°C; R_f (*D*) = 0.37; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.0 (s, br, NH_2), 5.69 (s, 5-H), 3.82 (s, OCH_3), 2.25–2.06 (m, CH), 0.87–0.65 (m, CH_2), 0.63–0.44 (m, CH_2) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.51 (s, COOMe), 164.17 (s, 2-C), 142.75 (s, 4-C), 106.75 (s, 3-C), 100.73 (d, 5-C), 50.72 (q, OCH_3), 12.35 (d, CH), 6.87 (t, CH_2) ppm; IR (KBr): $\tilde{\nu}$ = 3425, 3314, 1650, 1596, 1529, 1480, 1441, 1293, 1268, 1013, 784, 664 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 229 (25206), 300.5 (5318) nm.

5f: 2.35 g (6%) of colourless crystals; m.p.: 208.5–209.5°C; R_f (*D*) = 0.33; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 7.29 (s, NH_2), 3.67 (s, OCH_3), 3.03–2.86 (m, 6-CH_2), 2.71 (t, J = 6.4 Hz, 4-CH_2), 2.12–1.90 (m, 5-CH_2) ppm; ^{13}C NMR (50 MHz, δ, *DMSO*-d_6): 164.63 (s, COOMe), 161.76 (s, 2-C), 128.05 (s, 3a-C), 106.27 (s, 3-C), 103.38 (s, 7a-C), 50.29 (q, OCH_3), 27.0 (t, 6-C), 25.54 (t, 4-C), 23.26 (t, 5-C) ppm; IR (KBr): $\tilde{\nu}$ = 3413, 3298, 2941, 2915, 1635, 1582, 1536, 1482, 1442, 1293, 1263, 981, 779 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 232 (23276), 283 (5724), 318.5 (4769) nm.

4-Aminobutan-2-one hydrochloride (**6**; $C_4H_{10}ClNO$)

Compound **7a** [19] (50.30 g, 0.23 mol) was suspended in 200 cm^3 5 *M* HCl and refluxed for 24 h. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was dried *in vacuo* to give 28.1 g (99%) of a yellow hygroscopic solid.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.09 (s, br, H_3N^+), 2.93–2.81 (m, 4H, 4-CH_2/3-CH_2), 2.12 (s, 1-CH_3) ppm; ^{13}C NMR (50 MHz, δ, *DMSO*-d_6): 205.87 (s, 2-C), 39.97 (t, 4-C), 33.54 (t, 3-C), 29.85 (q, 1-C) ppm.

tert-*Butyl (3-oxobutyl)-carbamate* (**7b**; $C_9H_{17}NO_3$)

Di-*tert*-butyldicarbonate (8.83 g, 40.48 mmol) and 12.30 g triethylamine (121.44 mmol) were dissolved in 70 cm^3 CH_2Cl_2 and cooled to 0°C. 5.0 g **6** (40.48 mmol), dissolved in 20 cm^3 *DMSO*, were added dropwise, and the solution was stirred at 0°C until the evolution of gas ceased. The reaction mixture was washed with H_2O (3x). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by VFC (155 g silica gel, eluent: *PE*/Et_2O = 3/1, then 1/1) to give 6.46 g (85%) of a yellowish oil.

R_f (*PE*/Et_2O = 1/2) = 0.26; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 4.92 (t, J = 5.9 Hz, NH), 3.25 (q, J = 5.9 Hz, 1-CH_2), 2.58 (t, J = 5.9 Hz, 2-CH_2), 2.09 (s, 4-CH_3), 1.34 (s, $C(CH_3)_3$) ppm.

2,4,6-Trimethyl-N-(3-oxobutyl)-benzenesulfonamide (**7c**; $C_{13}H_{19}NO_3S$)

2,4,6-Trimethylbenzenesulfonyl chloride (8.80 g, 40.48 mmol) and 12.30 g triethylamine (121.44 mmol) were dissolved in 70 cm^3 CH_2Cl_2 and cooled to 0°C. 5.0 g **6** (40.48 mmol), dissolved in 20 cm^3 *DMF*, were added dropwise, and the solution was stirred at 0°C for 6 h. The reaction mixture was washed with H_2O several times; the organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by VFC (280 g silica gel, eluent: *PE*/ethyl acetate = 10/1, then 2/1) to yield 9.59 g (88%) of a yellowish solid.

M.p.: 57–58°C; R_f (*PE*/ethyl acetate = 1/1) = 0.29; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.97 (s, 2H, H_{arom}), 5.27 (t, J = 6.0 Hz, NH), 3.09 (m, 1′-CH_2), 2.68 (t, J = 5.4 Hz, 2′-CH_2), 2.65 (s, 6H, 2 *o*-CH_3), 2.31 (s, *p*-CH_3), 2.11 (s, 4′-CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 208.0 (s, 3′-C); 142.13 (s, 1-C), 138.94 (s, 4-C), 133.83 (s, 2-C/6-C), 131.96 (d, 3-C/5-C), 42.58 (t, 1′-CH_2), 37.44 (t, 2′-CH_2), 29.97 (q, 4′-CH_3), 22.73 (q, 2 *o*-CH_3), 20.87 (q, *p*-CH_3) ppm.

Methyl (E/Z)-2-cyano-5-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-methyl-2-pentenoate (**8a**; $C_{16}H_{14}N_2O_4$)

Methyl cyanoacetate (7.53 g, 75.5 mmol), 15 g **7a** [19] (69 mmol), 100 mg ammonium acetate (1.3 mmol), and 825 mg glacial acetic acid (13.81 mmol) were dissolved in 80 cm^3 dry benzene and treated for 12 h as described for **4a**. The obtained residue was recrystallized from MeOH to yield 15.5 g (75%) of yellow crystals.

M.p.: 90–92°C; R_f ($CHCl_3$/acetone = 40/1) = 0.16; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.87–7.83 (m, 2H, H_{arom}), 7.76–7.72 (m, 2H, H_{arom}), 4.03–3.91 (m, 5-CH_2), 3.77/3.66 (2s, OCH_3, *E*/*Z*), 3.16/2.96

(2t, $J = 6.6$ Hz, 4-CH_2, *Z*/*E*), 2.50/2.39 (2s, CH_3, *E*/*Z*) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 172.84/172.24 (2s, 3-C), 167.84 (s, 1′-C/3′-C), 161.76/161.65 (2s, COOMe), 134.15/134.06 (2d, 5′-C/6′-C), 131.85/131.79 (2s, 3a′-C/7a′-C), 123.45/123.32 (2d, 4′-C/7′-C), 115.09/114.85 (2s, CN), 107.03/106.39 (2s, 2-C), 52.81/52.59 (2q, OCH_3), 39.54/35.40 (2t, 5-CH_2), 35.05/34.31 (2t, 4-CH_2), 25.35/21.16 (2q, CH_3) ppm.

Methyl (E/Z)-5-((tert-butoxycarbonyl)-amino)-2-cyano-3-methyl-2-pentenoate (**8b**; $C_{13}H_{20}N_2O_4$)

Methyl cyanoacetate (3.42 g, 34.51 mmol), 6.46 g **7b** (34.51 mmol), 59 mg piperidine (0.69 mmol), and 1.04 g glacial acetic acid (17.25 mmol) were dissolved in 30 cm^3 dry benzene and treated for 12 h as described for **4a**. The obtained residue was purified by VFC (170 g silica gel, eluent: *PE*/$Et_2O = 2/1$) to give 7.86 g (85%) of a yellow oil.

R_f (*PE*/$Et_2O = 1/2$) = 0.29; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 4.80/4.71 (2s, br, NH, *Z*/*E*), 3.83/3.82 (2s, OCH_3, *Z*/*E*), 3.43–3.37 (m, 5-CH_2), 3.01/2.77 (2t, $J = 6.75$ Hz, 4-CH_2, *Z*/*E*), 2.45/2.35 (2s, CH_3, *E*/*Z*), 1.43 (s, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 174.64 (s, 3-C), 162.31/162.03 (2s, COOMe), 155.84 (s, $COOC(CH_3)_3$), 115.53/115.27 (2s, CN), 106.22/105.96 (2s, 2-C), 79.76 (s, $C(CH_3)_3$), 52.62/52.46 (2q, OCH_3), 41.57/38.89 (2t, 5-CH_2), 38.40/35.79 (2t, 4-CH_2), 28.30 (q, $C(CH_3)_3$), 25.59/21.36 (2q, CH_3) ppm.

Methyl (E/Z)-2-cyano-3-methyl-5-(((2,4,6-trimethylphenyl)-sulfonyl)-amino)-2-pentenoate (**8c**; $C_{17}H_{22}N_2O_4S$)

Methyl cyanoacetate (2.94 g, 29.7 mmol), 8 g **7c** (29.7 mmol), 50 mg piperidine (0.59 mmol), and 891 mg glacial acetic acid (14.84 mmol) were dissolved in 40 cm^3 dry benzene and treated for 12 h as described for **4a**. The obtained residue was purified by VFC (220 g silica gel, eluent: *PE*/ethyl acetate = 2/1) to yield 7.87 g (76%) of yellow crystals.

M.p.: 159–160°C; R_f (*PE*/ethyl acetate = 1/1) = 0.37; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.01/7.0 (2s, 2H, H_{arom}, *Z*/*E*), 5.13/4.74 (2s, br, NH, *Z*/*E*), 3.87/3.86 (2s, OCH_3, *Z*/*E*), 3.28–3.18 (m, 5-CH_2), 2.96/2.78 (2t, $J = 6.75$ Hz, 4-CH_2, *Z*/*E*), 2.67/2.66 (2s, 6H, 2 *o*-CH_3, *E*/*Z*), 2.35 (s, *p*-CH_3), 2.33/2.20 (2s, CH_3, *E*/*Z*) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 173.19/172.99 (2s, 3-C), 162.59/161.70 (2s, COOMe), 142.57/142.46 (2s, 1′-C), 139.09/139.03 (2s, 4′-C), 133.34 (s, 2′-C/6′-C), 132.05 (d, 3′-C/5′-C), 115.33/114.82 (2s, CN), 106.99/106.59 (2s, 2-C), 52.93/52.59 (2q, OCH_3), 40.66/40.54 (2t, 5-C), 40.23/34.87 (2t, 4-C), 24.93/22.92 (2q, CH_3), 22.89 (q, 2 *o*-CH_3), 20.90 (q, *p*-CH_3) ppm.

Methyl 2-amino-4-(2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-ethyl)-thiophene-3-carboxylate (**9a**; $C_{16}H_{14}N_2O_4S$) *and Methyl 2-amino-5-((1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl)-4-methylthiophene-3-carboxylate* (**10a**; $C_{16}H_{14}N_2O_4S$)

A solution of 4.88 g **8a** (16 mmol), 513 mg sulfur (16 mmol), and 836 mg diethylamine (11 mmol) in 50 cm^3 dry MeOH was stirred at 40°C for 12 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The obtained product mixture was separated by repeated recrystallization from MeOH.

9a: 710 mg (14%) of yellow needles; m.p.: 160–163°C; R_f (Et_2O) = 0.6; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.86–7.81 (m, 2H, H_{arom}), 7.74–7.69 (m, 2H, H_{arom}), 6.11 (s, br, NH_2), 5.93 (s, 5-H), 3.97–3.80 (m, 5H, N-CH_2-CH_2, OCH_3), 3.06 (t, $J = 7.3$ Hz, C-CH_2-CH_2) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 168.18 (s, 1′-C/3′-C), 166.09 (s, COOMe), 164.60 (s, 2-C), 136.60 (s, 3-C), 133.80 (d, 5′-C/6′-C), 132.14 (s, 3a′-C/7a′-C), 123.10 (d, 4′-C/7′-C), 105.66 (s, 4-C), 104.73 (d, 5-C), 50.93 (q, OCH_3), 38.28 (t, N-CH_2-CH_2), 30.72 (t, C-CH_2-CH_2) ppm; IR (KBr): $\tilde{\nu} = 3448$, 3318, 2934, 1770, 1700, 1672, 1575, 1482, 1447, 1393, 1365, 1274, 1111, 1067, 1010, 870, 736, 720 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon) = 221$ (60703), 300 (7392) nm.

10a: 1.87 g (37%) of colourless crystals; m.p.: 211–215°C; R_f (Et_2O) = 0.6; ^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 7.88–7.81 (m, 4H, H_{arom}), 7.30 (s, br, NH_2), 4.65 (s, CH_2), 3.67 (s, OCH_3), 2.29 (s, CH_3) ppm; ^{13}C NMR (50 MHz, δ, *DMSO*-d_6): 167.31 (s, 1′-C/3′-C), 165.20 (s, COOMe), 163.89 (s, 2-C), 134.56 (d, 5′-C/6′-C), 133.27 (s, 3-C), 131.37 (s, 3a′-C/7a′-C), 123.14 (d, 4′-C/7′-C), 112.43 (s, 4-C), 103.12 (s, 5-C), 50.34 (q, OCH_3), 33.46 (t, CH_2), 14.55 (q, CH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3432, 3320, 2924, 2853, 1767, 1698, 1660, 1577, 1481, 1438, 1400, 1269, 1128, 728 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 225.5 (36580), 267.5 (4832), 296 (4815) nm.

*Methyl 2-amino-4-((2-(*tert*-butoxycarbonyl)-amino)-ethyl)-thiophene-3-carboxylate* (**9b**; $C_{13}H_{20}N_2O_4S$) *and Methyl 2-amino-5-(((*tert*-butoxycarbonyl)-amino)-methyl)-4-methylthiophene-3-carboxylate* (**10b**; $C_{13}H_{20}N_2O_4S$)

A solution of 5.0 g **8b** (18.6 mmol), 775 mg sulfur (24.18 mmol), and 935 mg diethylamine (12.78 mmol) in 40 cm^3 dry MeOH was stirred at 40°C for 12 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The obtained product mixture was separated by VFC (70 g silica gel, eluent: *PE*/Et_2O = 2/1).

9b: 890 mg (16%) of yellowish crystals; m.p.: 117–118°C; R_f (*PE*/Et_2O = 1/2) = 0.33; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.15 (s, br, NH_2), 6.0 (s, 5-H), 4.52 (s, br, NH), 3.75 (s, OCH_3), 3.27 (m, N-CH_2-CH_2), 2.80 (t, J = 6.5 Hz, C-CH_2-CH_2), 1.36 (s, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.0 (s, COOMe), 164.65 (s, 2-C), 155.91 (s, *C*OOC$(CH_3)_3$), 137.62 (s, 4-C), 105.57 (s, 3-C), 104.17 (d, 5-C), 79.08 (s, *C*$(CH_3)_3$); 50.84 (q, OCH_3), 40.34 (t, N-*C*H_2-CH_2), 32.15 (t, C-*C*H_2-CH_2), 28.42 (q, C(*C*$H_3)_3$) ppm; IR (KBr): $\tilde{\nu}$ = 3401, 3304, 2977, 1693, 1649, 1596, 1531, 1486, 1447, 1270, 1167, 1139, 1063, 960, 794, 698 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 227 (25077), 300 (5707) nm.

10b: 1.84 g (33%) of colourless crystals; m.p.: 133–134°C; R_f (*PE*/Et_2O = 1/2) = 0.4; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.08 (s, br, NH_2), 4.70 (s, br, NH), 4.28 (d, J = 5.3 Hz, CH_2), 3.85 (s, OCH_3), 2.26 (s, CH_3), 1.49 (s, $C(CH_3)_3$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.39 (s, COOMe), 162.59 (s, 2-C), 155.48 (s, *C*OOC$(CH_3)_3$), 132.96 (s, 5-C), 116.17 (s, 4-C), 106.61 (s, 3-C), 79.64 (s, *C*$(CH_3)_3$), 50.71 (q, OCH_3), 36.96 (t, CH_2), 28.37 (q, C(*C*$H_3)_3$), 14.80 (q, CH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3435, 3325, 2970, 2946, 1666, 1583, 1522, 1485, 1271, 1165, 1120, 1052, 783 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 228 (29081), 262.5 (4670), 305.5 (5089) nm.

Methyl 2-amino-4-(2-(((2,4,6-trimethylphenyl)-sulfonyl)-amino)-ethyl)-thiophene-3-carboxylate (**9c**; $C_{17}H_{22}N_2O_4S_2$) *and Methyl 2-amino-4-methyl-5-((((2,4,6-trimethyl-phenyl)-sulfonyl)-amino)-methyl)-thiophene-3-carboxylate* (**10c**; $C_{17}H_{22}N_2O_4S_2$)

A solution of 5.0 g **8c** (14.26 mmol), 457 mg sulfur (14.26 mmol), and 706 mg diethylamine (9.66 mmol) in 40 cm^3 dry MeOH was stirred at 40°C for 12 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The obtained product mixture was separated by column chromatography (75 g silica gel, eluent: *PE*/Et_2O = 2/1).

9c: 709 mg (13%) of colourless crystals; m.p.: 115–117°C; R_f (*PE*/Et_2O = 1/2) = 0.21; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.89 (s, 2H, H_{arom}), 6.34 (s, 5-H), 6.12 (s, br, NH_2), 4.49 (s, br, NH), 3.72 (s, OCH_3), 3.13 (m, N-CH_2-CH_2), 2.92 (t, J = 6.4 Hz, C-CH_2-CH_2), 2.55 (s, 6H, 2 *o*-CH_3), 2.28 (s, *p*-CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 165.22 (s, COOMe), 162.99 (s, 2-C), 142.42 (s, 1′-C), 139.34 (s, 4′-C), 139.06 (s, 2′-C/6′-C), 134.46 (s, 4-C), 131.88 (d, 3′-C/5′-C), 115.23 (d, 5-C), 113.17 (s, 3-C), 50.78 (q, OCH_3), 39.08 (t, N-*C*H_2-CH_2), 22.90 (q, 2 *o*-CH_3), 22.83 (t, C-*C*H_2-CH_2), 20.93 (q, *p*-CH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3414, 3320, 3312, 2943, 1652, 1608, 1536, 1482, 1444, 1323, 1276, 1158, 1082, 784, 658 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 205 (51409), 226.5 (30634), 301.5 (5623) nm.

10c: 2.13 g (39%) of colourless needles; m.p.: 151–152°C; R_f (*PE*/Et_2O = 1/2) = 0.26; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.98 (s, 2H, H_{arom}), 6.06 (s, br, NH_2), 4.52 (s, br, NH), 4.03 (d, J = 5.7 Hz, CH_2), 3.80 (s, OCH_3), 2.65 (s, 6H, 2 *o*-CH_3), 2.32 (s, *p*-CH_3), 2.09 (s, CH_3) ppm; ^{13}C NMR (50 MHz,

δ, $CDCl_3$): 165.24 (s, COOMe), 162.89 (s, 2-C), 142.32 (s, 1′-C), 139.33 (s, 4′-C), 139.08 (s, 2′-C/6′-C), 131.98 (s, 5-C), 131.87 (d, 3′-C/5′-C), 128.12 (s, 4-C), 113.17 (s, 3-C), 50.78 (q, OCH_3), 39.06 (t, CH_2), 22.90 (q, 2 *o*-CH_3), 20.93 (q, *p*-CH_3), 14.75 (q, CH_3) ppm; IR (KBr): $\tilde{\nu} = 3424$, 3374, 3309, 3201, 2937, 1641, 1575, 1485, 1443, 1334, 1276, 1151, 1033, 1021, 675 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon) = 206.5$ (41884), 229.5 (34261), 269.5 (6014), 303 (4708) nm.

1-Methoxy-3-(((4-methylbenzene)-sulfony)-oxy)-2-propanone (**11a**; $C_{11}H_{14}O_5S$)

a) 3-Methoxypropane-1,2-diol (11.04 g, 103.8 mmol) and 16.78 cm^3 pyridine (207.6 mmol) were dissolved in 55 cm^3 dry CH_2Cl_2 at room temperature. The solution was cooled to −10°C, and 19.82 g *p*-toluenesulfonyl chloride (103.8 mmol) were added. After stirring for 8 h at −10°C, the reaction mixture was washed with 5% $NaHCO_3$ solution (3x) and 2 *M* HCl (2x). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The obtained product mixture was separated by VFC (300 g silica gel, eluent: $Et_2O/PE = 1/1$, then $Et_2O/PE = 3/1$) to yield 16.35 g (60%) 1-tosylate.

Colourless oil; R_f (MeOH/*D* = 1/5) = 0.5; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.79 (d, $J = 8.2$ Hz, 2H, H_{arom}), 7.30 (d, $J = 8.2$ Hz, 2H, H_{arom}), 4.15–3.92 (m, 3H, 1′-CH_2, 2′-H), 3.39 (m, 3′-CH_2), 3.30 (s, OCH_3), 2.56 (d, $J = 5.3$ Hz, OH), 2.42 (s, CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 145.02 (s, 1-C), 132.64 (s, 4-C), 129.90 (d, 3-C/5-C), 127.97 (d, 2-C/6-C), 72.48 (t, 1′-C), 70.62 (t, 3′-C), 68.19 (d, 2′-C), 59.19 (q, OCH_3), 21.61 (q, CH_3) ppm.

The second VFC fraction consisted of 9.47 g (22%) 1,2-*bis*-tosylate (colourless oil).

b) To a stirred solution of 16.29 g 1-tosylate (62.6 mmol) in 26 cm^3 diethyl ether, 31.4 cm^3 $Na_2Cr_2O_7$ solution [27] were added dropwise such that the reaction temperature was kept between 20–30°C. After stirring for 3 h, further 15.6 cm^3 of $Na_2Cr_2O_7$ solution were added, and the reaction mixture was stirred for additional 7.5 h at 20–30°C. The phases were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ silution, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by VFC (150g silica gel, eluent: *D*, then $Et_2O/PE = 2/1$) to give 7 g (43%) of colourless crystals.

M.p.: 35–37°C; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 8.84 (d, $J = 8.2$ Hz, 2H, H_{arom}), 7.35 (d, $J = 8.2$ Hz, 2H, H_{arom}), 4.76 (s, 1-CH_2), 4.16 (s, 3-CH_2), 3.41 (s, OCH_3), 2.47 (s, CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 200.07 (s, 2-C), 145.47 (s, 1′-C), 132.36 (s, 4′-C), 130.0 (d, 3′-C/5′-C), 128.06 (d, 2′-C/6′-C), 75.97 (t, 1-C), 70.79 (t, 3-C), 59.55 (q, OCH_3), 21.66 (q, CH_3) ppm.

3-(((4-Methylbenzene)-sulfonyl)-oxy)-2-oxopropyl benzoate (**11d**; $C_{17}H_{16}O_6S$)

To a stirred solution of 10 g (*R*/*S*)-2-hydroxy-3-(((4-methylbenzene)-sulfonyl)-oxy)-propyl benzoate [24] (28.54 mmol) in 100 cm^3 diethyl ether, 61 cm^3 $Na_2Cr_2O_7$ solution [27] were added dropwise in four portions every 6 h, and the solution was stirred for additional 6 h after the last addition. The phases were separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by VFC (200 g silica gel, eluent: *D*/*n*-hexane = 50/1) to give 5.0 g (50%) of a colourless solid.

M.p.: 83–85°C; R_f (*D*) = 0.25; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 8.05 (d, $J = 7.4$ Hz, 2H, H_{arom}, *bz*), 7.83 (d, $J = 8.15$ Hz, 2H, H_{arom}, *tos*), 7.60 (t, $J = 7.4$ Hz, 1H, H_{arom}, *bz*), 7.46 (t, $J = 7.4$ Hz, 2H, H_{arom}, *bz*), 7.38 (d, $J = 8.15$ Hz, 2H, H_{arom}, *tos*), 5.08 (s, 1′-CH_2), 4.69 (s, 3′-CH_2), 2.46 (s, CH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 196.74 (s, 2′-C), 165.65 (s, *C*$OOCH_2$), 145.83 (s, 4-C, *tos*), 133.63 (d, 4-C, *bz*), 131.85 (s, 1-C, *tos*), 130.17 (d, 2-C/6-C, *tos*), 129.93 (d, 2-C/6-C, *bz*), 128.77 (s, 1-C, *bz*), 128.53 (d, 3-C/5-C, *bz*), 128.14 (d, 3-C/5-C, *tos*), 70.69 (t, 1′-CH_2), 66.76 (t, 3′-CH_2), 21.71 (q, CH_3) ppm.

2-(4-Bromo-3-oxobutyl)-1,3-dihydro-2H-isoindol-1,3-dione (**11e**; $C_{12}H_{10}BrNO_3$)

7a (13.72 g, 63.19 mmol) was dissolved in 120 cm^3 dry MeOH/*n*-butanol = 1/1 to which a solution of 10.19 g bromine (63.19 mmol) in 120 cm^3 dry MeOH/dioxane = 1/1 was added at 50°C. The solution

was stirred at 50°C until complete decolourization, poured onto water, and kept at 4°C overnight. The precipitate was collected by filtration and purified by repeated recrystallization to yield 7.81 g (42%) of colourless needles.

M.p.: 120°C; R_f (*PE*/$Et_2O = 2/1$) = 0.05; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.88–7.82 (m, 2H, H_{arom}), 7.76–7.70 (m, 2H, H_{arom}), 3.96 (t, $J = 7.1$ Hz, 1′-CH_2), 3.95 (s, 4′-CH_2), 3.12 (t, $J = 7.1$ Hz, 2′-CH_2) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 199.56 (s, 3′-C), 167.93 (s, 1-C/3-C), 134.09 (d, 5-C/6-C), 131.95 (s, 3a-C/7a-C), 123.35 (d, 4-C/7-C), 37.99 (t, 1′-C), 33.70 (t, 4′-C), 33.09 (t, 2′-C) ppm.

Methyl 2-amino-4-(methoxymethyl)-thiophene-3-carboxylate (**12a**; $C_8H_{11}NO_3S$)

Methyl cyanoacetate (0.355 g, 3.6 mmol) and 861 mg Na_2S nonahydrate (3.6 mmol) were dissolved in 5 cm^3 dry methanol to which 926 mg **11a** (3.6 mmol) dissolved in 5 cm^3 dry MeOH were added at 0°C. The cooling bath was removed, and 0.5 cm^3 triethylamine (3.6 mmol) were added. After stirring for 2.5 h at room temperature the reaction mixture was evaporated to dryness, and the residue was partitioned between H_2O and diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by VFC (7 g silica gel, eluent: *PE*/$Et_2O = 6/1$) to yield 310 mg (43%) of colourless crystals.

M.p.: 82–83°C; R_f (*PE*/$Et_2O = 3/1$) = 0.14; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.21 (s, 5-H), 6.06 (s, br, NH_2), 4.52 (s, CH_2), 3.83 (s, $COOCH_3$), 3.46 (s, OCH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 165.87 (s, COOMe), 164.48 (s, 2-C), 137.52 (s, 3-C), 104.57 (s, 4-C), 103.82 (d, 5-C), 71.42 (t, CH_2), 58.62 (q, COO*C*H_3), 50.89 (q, OCH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3422, 3320, 1653, 1606, 1544, 1483, 1440, 1114, 1051, 967, 780, 737 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 224.5 (24468), 298.5 (5804) nm.

Ethyl 2-amino-4-((ethoxycarbonyl)-methyl)-thiophene-3-carboxylate (**12b**; $C_{11}H_{15}NO_4S$)

Ethyl cyanoacetate (7.44 g, 66 mmol) and 15.8 g Na_2S nonahydrate (66 mmol) were dissolved in 54 cm^3 dry EtOH to which 10.8 g ethyl chloroacetoacetate (66 mmol) dissolved in 22 cm^3 EtOH were added at 0°C. The cooling bath was removed, and 9.2 cm^3 triethylamine (66 mmol) were added. The solution was stirred for 1 h at room temperature and for additional 3 h at 40°C. The reaction mixture was evaporated to dryness, and the residue was treated with H_2O and extracted with diethyl ether. The combined organic layers were extracted with 6 *M* HCl. The aqueous layer was rendered basic and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by VFC (170 g silica gel, eluent: *PE*/$Et_2O = 5/1$) to yield 3.45 g (20%) of colourless crystals.

M.p.: 63–65°C; R_f (*D*) = 0.16; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.10 (s, br, NH_2), 6.03 (s, 5-H), 4.30–4.12 (m, 4H, 2 OC*H*$_2$CH$_3$), 3.70 (s, CH_2), 1.35–1.20 (m, 6H, 2 OCH_2C*H*$_3$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 171.45 (s, 2-C), 165.37 (s, COOEt), 164.19 (s, COOEt), 132.46 (s, 4-C), 106.04 (d, 5-C), 105.88 (s, 3-C), 60.51 (t, OCH_2), 59.65 (t, OCH_2), 37.53 (t, CH_2), 14.22 (q, OCH_2*C*H_3), 14.17 (q, OCH_2*C*H_3) ppm; IR (KBr): $\tilde{\nu}$ = 3401, 3302, 3099, 2976, 1725, 1667, 1598, 1541, 1491, 1440, 1279, 1187, 1071, 1025, 721 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 225 (24541), 266 (3642), 299.5 (5985) nm.

Methyl 2-amino-4-(cyanomethyl)-thiophene-3-carboxylate (**12c**; $C_8H_8N_2O_2S$)

Methyl cyanoacetate (1.24 g, 12.52 mmol) and 3.03 g Na_2S nonahydrate (12.6 mmol) were dissolved in 10 cm^3 dry MeOH to which 2.03 g 4-bromo-3-oxo-butyronitrile [23] (12.5 mmol) dissolved in 20 cm^3 MeOH were added within 1 h at −20°C. The cooling bath was removed, and 1.74 cm^3 triethyl amine (12.52 mmol) were added. After stirring for 16 h at room temperature the reaction mixture was concentrated *in vacuo*, diluted with H_2O, and extracted with CH_2Cl_2 (4x). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by VFC (35 g silica gel, eluent: *D*) to give 320 mg (13%) of colourless crystals.

M.p.: 139–140°C; R_f (D) = 0.5; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.27 (s, 5-H), 6.10 (s, br, NH_2), 3.85 (s, OCH_3), 3.79 (s, CH_2) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 165.2 (s, COOMe), 164.8 (s, 2-C), 128.0 (s, 3-C), 117.7 (s, CN), 105.9 (d, 5-C), 104.5 (s, 4-C), 51.1 (q, OCH_3), 20.9 (t, CH_2) ppm; IR (KBr): $\tilde{\nu}$ = 3429, 3410, 3305, 3084, 2946, 2242, 1674, 1600, 1539, 1488, 1442, 1331, 1276, 1040, 778, 744, 696 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 223 (26971), 296 (6962) nm.

Methyl 2-amino-4-((benzoyloxy)-methyl)-thiophene-3-carboxylate (**12d**; $C_{14}H_{13}NO_4S$) *and Methyl 2-amino-4-(hydroxymethyl)-thiophene-3-carboxylate* (**12e**; $C_7H_9NO_3S$)

Methyl cyanoacetate (569 mg, 5.74 mmol) and 1.4 g Na_2S nonahydrate (5.74 mmol) were dissolved in 20 cm^3 dry MeOH to which 2 g **11b** (5.74 mmol) dissolved in 20 cm^3 dry MeOH were added at 0°C. The cooling bath was removed, and 581 mg triethylamine (5.74 mmol) were added. After stirring for 3 h at room temperature the reaction mixture was evaporated to dryness. The residue was partitioned between H_2O and diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The obtained product mixture was separated by VFC (20 g silica gel, eluent: Et_2O/*PE* = 1/2).

12d: 237 mg (14%) of colourless crystals; m.p.: 130–132°C; R_f (Et_2O/*PE* = 1/1) = 0.53; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 8.05 (d, J = 7.4 Hz, 2H, H_{arom}, *bz*), 7.54 (t, J = 7.4 Hz, 1H, H_{arom}, *bz*), 7.42 (t, J = 7.4 Hz, 2H, H_{arom}, *bz*), 6.24 (s, 5-H), 6.11 (s, br, NH_2), 5.39 (s, CH_2), 3.77 (s, OCH_3) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 166.24 (s, 2-C), 165.82 (s, *C*$OOCH_2$), 164.68 (s, COOMe), 134.69 (s, 4-C), 132.97 (d, 4′-C, *bz*), 130.21 (s, 1′-C, *bz*), 129.60 (d, 2′-C/6′-C, *bz*), 128.38 (d, 3′-C/5′-C, *bz*), 105.24 (d, 5-C), 104.56 (s, 3-C), 63.40 (t, CH_2), 51.05 (q, OCH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3454, 3335, 2958, 2929, 2872, 1716, 1673, 1618, 1511, 1460, 1445, 1273, 1124, 1066, 704 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 224 (29507), 297.5 (5220) nm.

12e: 63 mg (6%) of yellow crystals; m.p.: 117–119°C; R_f (Et_2O/*PE* = 1/1) = 0.15; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 6.24 (s, 5-H), 6.11 (s, br, NH_2), 4.52 (d, J = 5.5 Hz, CH_2), 3.85 (s, OCH_3), 3.33 (s, br, OH) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 165.67 (s, 2-C), 164.72 (s, COOMe), 140.52 (s, 4-C), 105.68 (d, 5-C), 104.82 (s, 3-C), 61.47 (t, CH_2), 51.38 (q, OCH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3416, 3304, 1650, 1597, 1528, 1482, 1455, 1281, 1068, 999, 972, 782, 685 cm^{-1}; UV (MeOH): $\lambda_{max}(\varepsilon)$ = 225.5 (21315), 297.5 (5219) nm.

Methyl 2-amino-4-(2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-ethyl)-thiophene-3-carboxylate (**9a**; $C_{16}H_{14}N_2O_4S$)

Methyl cyanoacetate (321 mg, 3.24 mmol) and 778 mg Na_2S nonahydrate (3.24 mmol) were dissolved in 30 cm^3 dry MeOH to which 960 mg **11e** (3.24 mmol) were added in small portions at 0°C. After complete addition the cooling bath was removed, and 328 mg triethylamine (3.24 mmol) were added. After stirring for 12 h at 50°C the reaction mixture was evaporated to dryness. The residue was partitioned between H_2O and diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by VFC (10 g silica gel, eluent: Et_2O/*PE* = 1/1) to yield 120 mg (11%) of yellow needles.

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Received July 5, 2000. Accepted (revised) August 23, 2000