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Synthesis of 4-Isobutyl Substituted Thiophenes by *Gewald* Reaction[#]

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Summary. The *Gewald* reaction of 4-methyl-2-pentanone with alkyl cyanoacetates was investigated. Alkyl 2-amino-4-isobutylthiophene-3-carboxylates (**4**) were formed, together with *bis*-(2-amino-3-alkoxycarbonyl-4-isobutyl-5-thienyl)-disulfides (**5**) and alkyl 2-amino-4-isobutyl-5-morpholinothiophene-3-carboxylates (**6**). The absence of any 4-methyl substituted aminothiophene in the product mixtures came up highly unexpected. The mechanism of the reaction is discussed with respect to previously reported suggestions.

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

Synthese von 4-isobutylsubstituierten Thiophenen durch *Gewald*-Reaktion

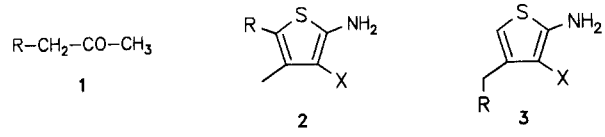
Zusammenfassung. Die *Gewald*-Reaktion von 4-Methyl-2-pentanon mit Cyanessigsäurealkylestern wurde untersucht. Dabei entstehen die 2-Amino-4-isobutylthiophen-3-carbonsäurealkylester **4** als Hauptprodukte sowie die *bis*-(2-Amino-3-alkoxycarbonyl-4-isobutyl-5-thienyl)-disulfide **5** und die 2-Amino-4-isobutyl-5-morpholinothiophen-3-carbonsäurealkylester **6**. 4-Methylsubstituierte Aminothiophene wurden überraschenderweise in den Produktgemischen nicht aufgefunden. Der Reaktionsmechanismus wird im Zusammenhang mit bereits publizierten Vorstellungen diskutiert.

Introduction

The chemistry of 2-aminothiophenes has received much attention; this is almost entirely due to their convenient availability through the versatile synthesis introduced by *Gewald* [1]. In its simplest version, aldehydes, ketones, and 1,3-dicarbonyl compounds are reacted with elemental sulfur and an acetonitrile molecule bearing an electron-withdrawing group in the presence of an organic base. The products of the *Gewald* reaction are substituted 2-aminothiophenes with an electron-attracting group at position 3. A number of methylketones (**1**, Scheme 1) were converted to the corresponding aminothiophenes [2]. Typically, these thiolation-heterocyclization reactions furnish 4-methyl-derivatives (**2**). Products **2** are indeed to be expected, since the thiolation of the postulated initially formed *Knoevenagel* condensation products occur preferentially at the methylene group and not at the methyl group [3]. However, methyl ketones without a methylene group also undergo the *Gewald*

[#] Dedicated to Professor Dr. *Karl Gewald* on the occasion of his 65th birthday

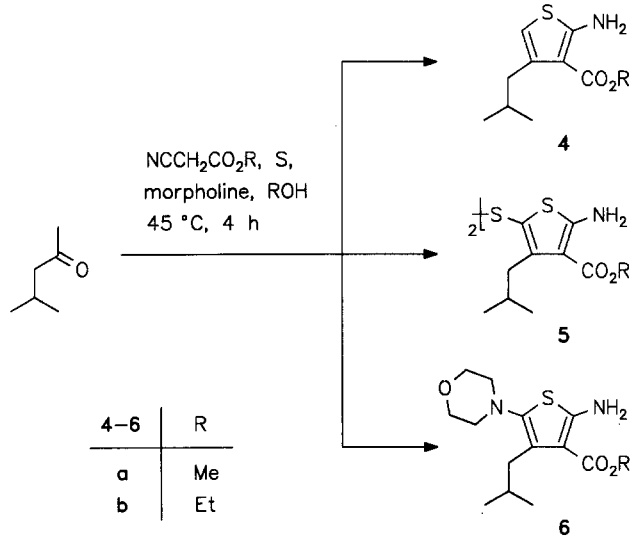
reaction to 2-amino-4-substituted derivatives with a free 5-position. In the latter case, the methyl group is incorporated into the thiophene ring. With respect to the reaction of methylketones **1**, this might lead to the formation of thiophenes **3**, at least as by-products. However, according to the literature, for more than twenty different aminothiophenes prepared from methylketones **1** by *Gewald* synthesis, structure **2** was assigned. The only exception, the preparation of **3** ($R = CH(CH_3)_2$, $X = CO_2Et$) [4] is not further discussed in the literature. This prompted us to study the *Gewald* reaction of the commercially available 4-methyl-2-pentanone (**1**, $R = CH(CH_3)_2$) with alkyl cyanoacetates.



Scheme 1

Results and Discussion

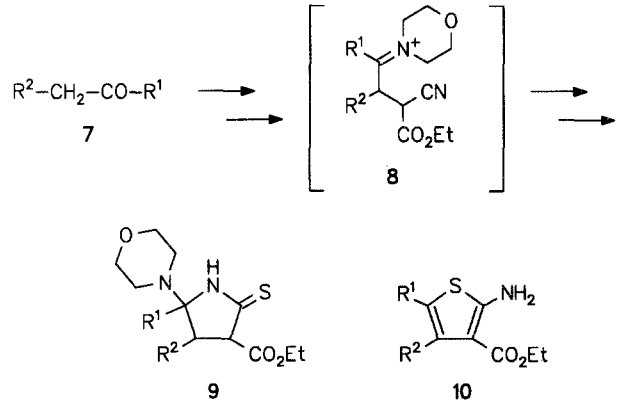
4-Methyl-2-pentanone was reacted with methyl cyanoacetate and sulfur according to the one-pot version of the *Gewald* synthesis (Scheme 2). The reaction was carried out in methanol with morpholine as the amine base. A mixture of three aminothiophenes, as indicated by the reaction with 4-dimethylaminobenzaldehyde (*Ehrlich*'s reagent) on TLC, was formed. However, using column chromatography, we were able to separate the pure components and establish their structures as the 4-isobutyl substituted aminothiophenes **4a**, **5a**, and **6a**. When 4-methyl-2-pentanone and ethyl cyanoacetate were subjected to the *Gewald* conditions, a corresponding product mixture was obtained. Similar work-up gave **4b**, **5b**, and **6b**. Structural elucidation of the products of both reactions made obvious that only



Scheme 2

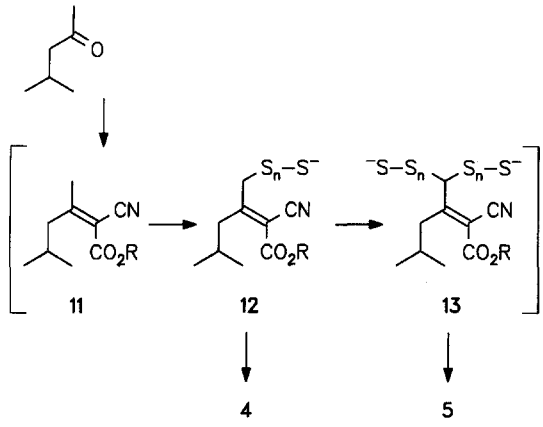
4-isobutyl substituted aminothiophenes were formed. Surprisingly, the 1-methyl group of 4-methyl-2-pentanone was always found to be incorporated into the thiophene ring. Alkyl 2-amino-5-isopropyl-4-methylthiophenecarboxylates (which correspond to structure **2**, Scheme 1) were not even formed as by-products. The main products **4** (which correspond to structure **3**, Scheme 1) are accompanied by the disulfides **5** and the morpholino derivatives **6**.

Previously, *Peet* and coworkers [5] have reported the formation of an unexpected morpholino derivative resulting from the *Gewald* reaction (Scheme 3): When cyclopentanone was treated with ethyl cyanoacetate and sulfur in the presence of morpholine, the pyrrole derivative **9** ($R^1R^2 = (CH_2)_3$) was formed. On the other hand, cyclohexanone gave the expected thiophene **10** ($R^1R^2 = (CH_2)_4$). On the basis of this observation, a mechanism for the morpholine catalyzed one-pot *Gewald* reaction was proposed by *Peet* and coworkers as depicted in Scheme 3. From the initially formed morpholinyl enamines, the final products **10** are produced *via* **8**. However, the authors have not discussed a consequence of this proposal: In comparison with the common assignments, the positions of the residues R^1 and R^2 on the final aminothiophenes **10** would be exchanged. Of course, this is not relevant for the cycloaliphatic ketones studied by *Peet*, but for several aminothiophenes with different R^1 and R^2 residues already published. In our case, for example, we would have obtained 5-isobutyl substituted aminothiophenes. To clarify this, we have prepared two isomeric thiophenes (ethyl 2-amino-4-phenyl-3- thiophenecarboxylate [6] and ethyl 2-amino-5-phenyl-3-thiophenecarboxylate [7]). On the basis of the ^{13}C NMR data of these compounds, the chemical shifts for the C-4 and C-5 carbons of **4–6** were calculated using substituent parameters. The experimental data satisfactorily correlate with the calculation for the assigned structures **4–6**, but not with the calculation for the exchanged ones.



Scheme 3

Final evidence to confirm structures **4–6** came from the following experiment. The *Koevenagel* adduct **11** (R = Et) [9] (Scheme 4) was prepared and treated under similar conditions with sulfur and morpholine in ethanol. This reaction gave identical products **4b**, **5b**, and **6b**. Their spectroscopic data and physical constants were identical in all respects to those of the material obtained by the reaction of 4-methyl-2-pentanone.



Scheme 4

It is therefore to be concluded, that **4**, **5**, and **6** are formed from 4-methyl-2-pentanone *via* the intermediate *Knoevenagel* adducts **11**. The postulated mechanism is outlined in Scheme 4. Thiolation occurs exclusively at the methyl group of **11**. The methylene group is obviously less activated and/or sterically shielded by the adjacent isopropyl group. Monothiolation gives α-mercapto intermediates **12** ($n = 0$), resulting from the degradation [5] of an initially formed polysulfide **12** ($n = 7$). Subsequent cyclization and prototropic rearrangement produces **4**.

With respect to the formation of **5**, it should be noted that *Gewald* and *Schinke* [3] have reported an analog disulfide as the main product in the reaction of acetone with ethyl cyanoacetate and sulfur in the presence of triethylamine. Accordingly, the formation of **5** is assumed to proceed *via* the dithiolated intermediates **13** which cyclize to intermediate 2-amino-5-mercaptothiophenes and are subsequently oxidized to the disulfides **5** [10].

In order to explain the formation of the morpholino derivatives **6**, compound **5a** was treated with morpholine and methanol using our standard conditions. However, the formation of **6a** was not observed, and unchanged starting material was obtained. This indicates, in contrast to our initial expectation, that the disulfides **5** are no intermediates for the formation of **6**. Possibly, a nucleophilic attack of morpholine at the intermediate **13** ($n = 7$) could explain the generation of **6**.

As already mentioned, the synthesis of **4b** by the reaction of 4-methyl-2-pentanone with ethyl cyanoacetate and sulfur in the presence of morpholine has been claimed in a European patent [4]. Unfortunately, no yield and no spectral data are given therein. Our investigation confirms the reported structure. We have repeated the preparation of **4b** following the procedure and the work-up described. But, in contrast to the report, we were unable to isolate **4b** from the reaction mixture without using column chromatography.

In conclusion, we have examined the unexpected formation of three different 4-isobutyl substituted aminothiophenes from 4-methyl-2-pentanone subjected to the conditions of the *Gewald* reaction. Synthetic applications of the thiophenes **4** as precursors for potential enzyme inhibitors are currently under investigations in our laboratory.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 16 PC FTIR spectrometer. ^{13}C NMR (75 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on a Varian Gemini 300 NMR spectrometer. ^{13}C NMR signals were assigned on the basis of APT (*a*ttached *p*roton *t*est) and HETCOR (heteronuclear correlation) experiments. ^{1}H NMR data of the disulfides **5** are expressed for the corresponding monomer units. Mass spectra (70 eV) were obtained using a Varian MAT CH6 spectrometer. Analytical TLC was performed on aluminium sheets, silica gel 60 F_{254} (Merck). The TLC spots were detected with *UV*, I_2, and 4-dimethylaminobenzaldehyde (*Ehrlich*'s reagent). R_f values were calculated from TLC in ethyl acetate/*n*-hexane (3:7) in a saturated chamber. Column chromatography was performed on silica gel 60 (Merck) 70–230 mesh, using ethyl acetate/*n*-hexane (1:4).

Gewald reaction with 4-methyl-2-pentanone and methyl cyanoacetate

A mixture of 4-methyl-2-pentanone (30 g, 300 mmol), sulfur (9.6 g, 300 mmol), methyl cyanoacetate (29.7 g, 300 mmol), and methanol (75 ml) was stirred at 45 °C. Morpholine (26.1 g, 300 mmol) was added dropwise. The mixture was stirred at 45 °C for 4 h, cooled, poured into 0.4 *M* AcOH (1.25 l) and extracted with diethyl ether (4 × 200 ml). The organic layer was washed with water (2 × 200 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue was chromatographed on a silica gel column with ethyl acetate/*n*-hexane (1:4). Three fractions were collected, and the solvents were evaporated *in vacuo* to obtain **4a**, **5a**, and **6a**.

Methyl 2-Amino-4-(2-methylpropyl)-thiophene-3-carboxylate (**4a**)

4a (14.5 g, 23%) was obtained as a yellow semisolid and recrystallized from petroleum ether to give pale yellow prisms. M.p.: 64.5–65.5 °C; R_f (ethyl acetate/*n*-hexane 3:7) = 0.45; IR (KBr): $\nu(cm^{-1})$ = 1652 (C=O); ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (d, 6 H, $J = 6.7$ Hz, $CHCH_3$), 1.73–1.90 (m, 1 H, CH), 2.53 (d, 2 H, $J = 6.8$ Hz, CH_2CH), 3.81 (s, 3 H, OCH_3), 5.81 (s, 1 H, H-5), 5.90 (s, br, 2 H, NH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.6$ ($CHCH_3$), 28.4 (CH), 41.1 (CH_2CH), 50.7 (OCH_3), 103.5 (C-5), 105.9 (C-3), 140.3 (C-4), 164.5 (C-2), 166.4 (C=O) ppm; MS (70 eV): *m/z* (%) = 213 (M^+, 56), 171 (M^+-C_3H_6, 100); calcd. for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 5.67; S, 15.03; found: C, 56.50; H, 6.98; N, 6.59; S, 15.44.

bis-(2-Amino-3-methoxycarbonyl-4-(2-methylpropyl)-5-thienyl)-disulfide (**5a**)

5a (8.1 g, 11%) was obtained as yellow crystals which were collected and washed with cold *n*-hexane. M.p.: 164–165 °C; R_f (ethyl acetate/*n*-hexane 3:7) = 0.28; IR (KBr): ν (cm^{-1}) 1654 (C=O); ^{1}H NMR (acetone-d_6): $\delta = 0.84$ (d, 6 H, $J = 6.7$ Hz, $CHCH_3$), 1.68–1.86 (m, 1 H, CH), 2.60 (d, 2 H, $J = 7.0$ Hz, CH_2CH), 3.83 (s, 3 H, OCH_3), 7.56 (s, 2 H, NH_2) ppm; ^{13}C NMR (acetone-d_6): $\delta = 23.1$ ($CHCH_3$), 30.8 (CH), 38.3 (CH_2CH), 51.4 (OCH_3), 106.6 (C-3), 110.8 (C-5), 151.3 (C-4), 166.8 (C-2), 169.8 (C=O) ppm; MS (70 eV): *m/z*(%) = 488 (M^+, 6), 245 ($M^+/2 + H$, 100); calcd. for $C_{20}H_{28}N_2O_4S_4$: C, 49.16; H, 5.78; N, 5.73; S, 26.24; found: C, 49.07; H, 6.02; N, 6.09; S, 26.44.

Methyl 2-Amino-4-(2-methylpropyl)-5-morpholinothiophene-3-carboxylate (**6a**)

6a (2.5 g, 3%) was obtained as colourless needles which were collected and washed with cold *n*-hexane. M.p.: 125–127 °C; R_f (ethyl acetate/*n*-hexane 3:7) = 0.34; IR (KBr): ν (cm^{-1}) = 1670 (C=O); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (d, 6 H, $J = 6.7$ Hz, $CHCH_3$), 1.68–1.86 (m, 1 H, CH), 2.59 (d, 2 H, $J = 6.8$ Hz, CH_2CH), 2.75 (t, 4 H, $J = 4.6$ Hz, NCH_2), 3.77 (t, 4 H, $J = 4.6$ Hz, OCH_2), 3.79 (s, 3 H, OCH_3), 6.09 (s,

2 H, NH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.1$ ($CHCH_3$), 29.5 (CH), 37.1 (CH_2CH), 51.1 (OCH_3), 55.7 (NCH_2), 67.6 (OCH_2), 103.5 (C-3), 132.4 (C-4), 136.3 (C-5), 160.9 (C-2), 167.1 (C=O) ppm; MS (70 eV): m/z(%) = 298 (M^+, 100), 255 (M^+-C_3H_7, 90); calcd. for $C_{14}H_{22}N_2O_3S$: C, 56.35; H, 7.43; N, 9.39; S, 10.74; found: C, 56.45; H, 7.47; N, 9.59; S, 11.07.

Gewald reaction with 4-methyl-2-pentanone and ethyl cyanoacetate

4-Methyl-2-pentanone, sulfur, ethyl cyanoacetate, and morpholine were reacted in ethanol according to the procedure outlined above. Upon column chromatography, three fractions were collected to obtain **4b**, **5b**, and **6b**.

Ethyl 2-Amino-4-(2-methylpropyl)-thiophene-3-carboxylate (**4b**)

4b (18.4 g, 27%) was obtained as a yellow semisolid and recrystallized from petroleum ether to give pale yellow prisms. M.p.: 63–64 °C (Ref. [4]: M.p.: 65 °C); R_f (ethyl acetate/*n*-hexane 3:7) = 0.48; IR (KBr): ν (cm^{-1}) = 1652 (C=O); ^1H NMR ($CDCl_3$): $\delta = 0.86$ (d, 6 H, $J = 6.6$ Hz, $CHCH_3$), 1.36 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.76–1.93 (m, 1 H, CH), 2.54 (d, 2 H, $J = 6.9$ Hz, CH_2CH), 4.28 (q, 2 H, $J = 7.1$ Hz, CH_2CH_3), 5.80 (s, 1 H, H-5), 5.90 (s, br, 2 H, NH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.4$ (CH_2CH_3), 22.5 ($CHCH_3$), 28.3 (CH), 41.1 (CH_2CH), 59.6 (CH_2CH_3), 103.6 (C-5), 106.3 (C-3), 140.3 (C-4), 164.4 (C-2), 166.2 (C=O) ppm; MS (70 eV): m/z(%) = 227 (M^+, 78), 185 (M^+-C_3H_6, 100); calcd. for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16; S, 14.10; found: C, 58.11; H, 7.51; N, 6.31; S, 14.05.

bis-(2-Amino-3-ethoxycarbonyl-4-(2-methylpropyl)-5-thienyl)-disulfide (**5b**)

5b (5.4 g, 7%) was obtained as a yellow semisolid and recrystallized from diethyl ether/*n*-hexane to give yellow crystals. M.p.: 146–149 °C; R_f (ethyl acetate/*n*-hexane 3:7) = 0.28; IR (KBr): ν (cm^{-1}) = 1652 (C=O); ^1H NMR ($CDCl_3$): $\delta = 0.83$ (d, 6 H, $J = 6.6$ Hz, $CHCH_3$), 1.36 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.69–1.87 (m, 1 H, CH), 2.61 (d, 2 H, $J = 7.1$ Hz, CH_2CH), 4.28 (q, 2 H, $J = 7.1$ Hz, CH_2CH_3), 6.44 (s, 2 H, NH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.4$ (CH_2CH_3), 22.4 ($CHCH_3$), 29.5 (CH), 37.6 (CH_2CH), 59.9 (CH_2CH_3), 106.8 (C-3), 111.5 (C-5), 149.5 (C-4), 165.9 (C-2), 167.4 (C=O) ppm; MS (70 eV): m/z(%) = 516 (M^+, 28), 258 ($M^+/2$, 100); calcd. for $C_{22}H_{32}N_2O_4S_4$: C, 51.14; H, 6.24; N, 5.42; S, 24.82; found: C, 51.42; H, 6.50; N, 5.67; S, 24.38.

Ethyl 2-Amino-4-(2-methylpropyl)-5-morpholinothiophene-3-carboxylate (**6b**)

6b (1.9 g, 2%) was obtained as colourless needles which were collected and washed with cold *n*-hexane. M.p.: 145–147 °C; R_f (ethyl acetate/*n*-hexane 3:7) = 0.41; IR (KBr): ν (cm^{-1}) = 1660 (C=O); ^1H NMR ($CDCl_3$): $\delta = 0.87$ (d, 6 H, $J = 6.6$ Hz, $CHCH_3$), 1.34 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.72–1.90 (m, 1 H, CH), 2.59 (d, 2 H, $J = 7.1$ Hz, CH_2CH), 2.74 (t, 4 H, $J = 4.6$ Hz, NCH_2), 3.76 (t, 4 H, $J = 4.6$ Hz, OCH_2), 4.25 (q, 2 H, $J = 7.1$ Hz, CH_2CH_3), 6.16 (s, 2 H, NH_2) ppm; ^{13}C NMR ($CDCl_3$); $\delta = 14.4$ (CH_2CH_3), 22.6 ($CHCH_3$), 28.9 (CH), 36.6 (CH_2CH), 55.2 (NCH_2), 59.5 (CH_2CH_3), 67.2 (OCH_2), 103.0 (C-3), 131.8 (C-4), 135.7 (C-5), 160.5 (C-2), 166.4 (C=O) ppm; MS (70 eV): m/z(%) = 312 (M^+, 100), 269 (M^+-C_3H_7, 82); calcd. for $C_{15}H_{24}N_2O_3S$: C, 57.67; H, 7.74; N, 8.97; S, 10.26; found: C, 57.72; H, 7.92; N, 8.76; S, 10.68.

Gewald reaction with (E/Z)-2-cyano-3,5-dimethyl-2-hexenoic acid ethyl ester

Compound **11** [9] (3.9 g, 20 mmol), sulfur (640 mg, 20 mmol), and morpholine (1.74 g, 20 mmol) were reacted in ethanol (5 ml) according to the standard procedure outlined above. On column chromatography, three fractions were collected to obtain **4b** (1.75 g, 38%), **5b** (360 mg, 7%), and **6b** (130 mg, 2%).

References

[1] Gewald K, Schinke E, Böttcher H (1966) Chem Ber **99**: 94

[2] For recent reviews, see: [a] Rudorf W-D, Methoden Org Chemie, 4th edn. (Houben-Weyl) 1994, vol. E 6a, pp 186–555; [b] Sabnis RW (1994) Sulfur Reports **16**: 1

[3] Gewald K, Schinke E (1966) Chem Ber **99**: 2712

[4] Dickore K, Luerssen K (Bayer AG), EP 4931, 1979; CA (1980) **92**: P110837k

[5] Peet NP, Sunder S, Barbuch RJ, Vinogradoff AP, (1986) J Heteocycl Chem **12**: 129

[6] Ethyl 2-amino-4-phenyl-3-thiophenecarboxylate was prepared from the corresponding *Knoevenagel* adduct according to Ref. [1]. ^{1}H NMR (*DMSO*-d_6): $\delta = 0.89$ (t, 3 H, $J = 7.1$ Hz, CH_3), 3.94 (q, 2 H, $J = 7.1$ Hz, CH_2), 6.15 (s, 1 H, H-5), 7.21–7.30 (m, 5 H, arom.), 7.37 (s, 2 H, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.7$ (CH_3), 58.6 (CH_2), 103.0 (C-3), 105.1 (C-5), 126.4 (C-4′), 127.1 (C-2′), 128.6 (C-3′), 138.2 and 140.5 (C-4 and C-1′), 164.7 (C-2), 165.1 (C=O) ppm

[7] Ethyl 2-amino-5-phenyl-3-thiophenecarboxylate was prepared from phenylacetaldehyde according to Ref. [1]. ^{1}H NMR (*DMSO*-d_6): $\delta = 1.28$ (t, 3 H, $J = 7.1$ Hz, CH_3), 4.21 (q, 2 H, $J = 7.1$ Hz, CH_2), 7.14–7.21 (m, 1 H, H-4′), 7.24 (s, 1 H, H-4), 7.29–7.36 (m, 2 H, H-3′), 7.42–7.47 (m, 2 H, H-2′), 7.48 (s, 2 H, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 14.4$ (CH_3), 59.1 (CH_2), 105.0 (C-3), 121.0 (C-4), 122.2 (C-5), 123.9 (C-2′), 126.2 (C-4′), 128.9 (C-3′), 133.7 (C-1′), 163.4 (C-2), 164.3 (C=O) ppm; ^{13}C NMR values were in accordance with Ref. [8]

[8] Gewald K, Hain U, Gruner M (1988) Chem Ber **121**: 573

[9] Julia S, Torrent J, Olle J, Ramio J, Sanz M (1974) Affinidad **31**: 117

[10] When performing the Gewald reaction with 4-methyl-2-pentanone and ethyl cyanoacetate under argon or, otherwise, under a weak air stream, the formation of **5b** was not remarkably affected. This may indicate that sulfur has acted as oxidizing agent.

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