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A Synthetic Approach to Methyl Thieno[2,3-*d*][1,2,3]thiadiazole Carboxylates *via* Diazotation

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Summary. A route to methyl thieno[2,3-*d*][1,2,3]thiadiazole carboxylates **3** as highly potent inducers of systemic acquired resistance (SAR) is reported. The construction of the appropriately substituted thiophene precursors is elaborated. Cyclization towards the thiadiazole ring system was carried out using diazotation techniques.

Keywords. Plant activators; Systemic acquired resistance; Diazotation.

Ein Syntheseweg zu Thieno[2,3-*d*][1,2,3]thiadiazolcarbonsäuremethylestern über Diazotierungsreaktionen

Zusammenfassung: Eine Herstellungsmethode von Thieno[2,3-*d*][1,2,3]thiadiazolcarbonsäuremethylestern **3** als hochwirksame Induktoren für chemisch induzierte Resistenz (SAR) wird beschrieben. Der Aufbau von entsprechend substituierten Thiophenvorstufen wird beschrieben. Der Ringschluß zum Thiadiazolringsystem erfolgte über Diazotierungstechniken.

Introduction

In many cases the local infection of a plant leads to the development of resistance to subsequent challenges by a variety of pathogens. The phenomenon of systemic acquired resistance (SAR) can also be induced by heterocyclic compounds called plant activators like 2,6-dichloroisonicotinic acid **1** or various 1,2,3-benzothiadiazole-7-carboxylic acid derivatives such as **2** (Scheme 1). Both approaches lead to the same biochemical reactions within the plant strongly correlating with the expressions of PR-proteins. As a result, the whole plant develops a general resistance against a large variety of different pathogens [1]. This strategy was successfully introduced as a new concept in plant protection chemistry recently by *Novartis* with compound **2** representing the first commercial product called Bion® [2].

Based on the bioisosteric effect [3] of thiophene and benzene rings, we became interested in the development of synthetic routes to thieno [2,3,-*d*][1,2,3]thiadiazole-6-carboxylic esters **3** as potential activators for SAR [4].

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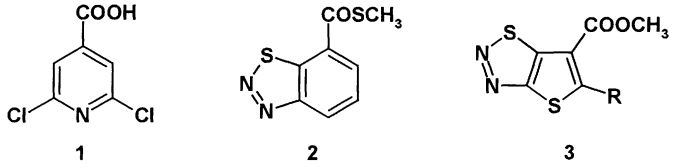
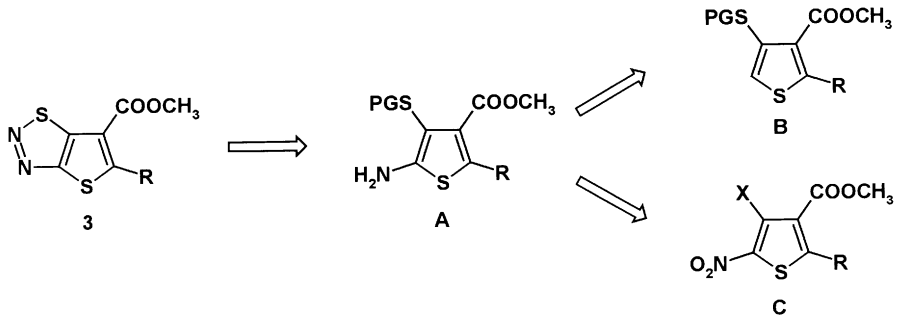


Scheme 1



Scheme 2

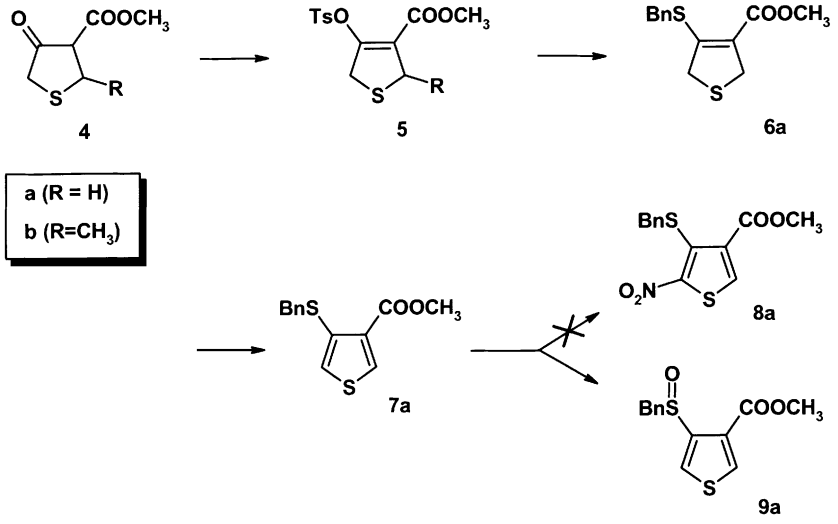
Diazotation of amine precursors and trapping of the ionic intermediate by an adjacent sulfur functionality represents a general route to 1,2,3-thiadiazole ring systems [5]. The retrosynthetic analysis suggested two straightforward approaches to the construction of the key species **A**: introduction of the nitrogen functionality could be achieved either after (**B**) or before (**C**) implementation of the protected sulfur moiety into the required substitution pattern (Scheme 2).

Results and Discussion

Following the first route towards the intermediate of type **B**, the enol form of the easily accessible compound **4** [6] was trapped with tosyl chloride to give **5** (Scheme 3). Introduction of the protected sulfur substituent was carried out by an addition/elimination process with benzylthiol. The obtained dihydro compound **6a** could be aromatized according to a general procedure by treatment with SO_2Cl_2 [7]. Electrophilic chlorination followed by elimination led to **7a**.

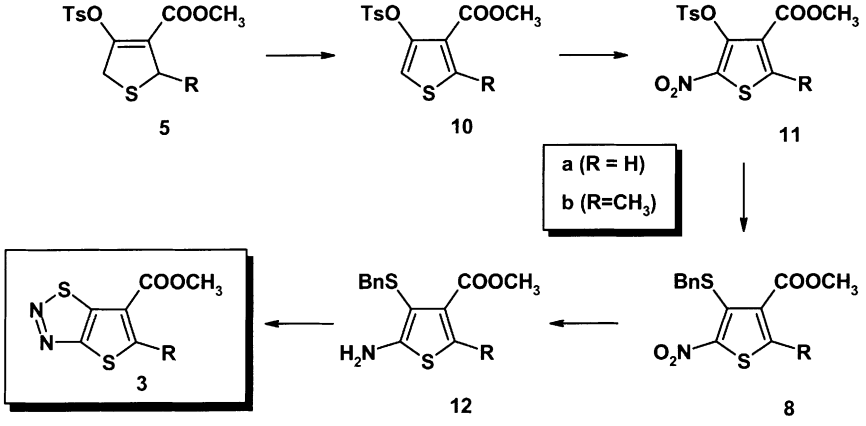
For completion of the construction of the substitution pattern, we wanted to utilize the electronic effects present in product **7a**. However, the attempted nitration reaction with HNO_3/H_2SO_4 did not lead to the expected compound **8a** but gave the sulfoxide **9a** instead. Several different nitration procedures failed to give substitution in position 5, but all led to oxidation of the sulfur group. In order to prove the nature of **9a** the compound was deliberately synthesized from **7a** by treatment with *m*-chloroperbenzoic acid.

Changing our approach towards the heterocyclic system **3** we aromatized compound **5** to obtain **10** (Scheme 4). On this route, the following nitration gave the expected product **11** with the tosyloxy moiety as highly activated leaving group for a nucleophilic substitution reaction with benzylthiol. Reduction of the NO_2 group in **8** was performed with iron/AcOH.

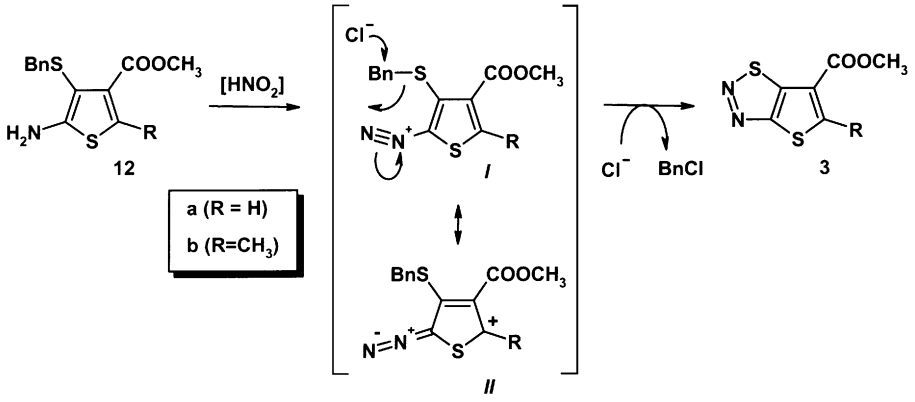


Scheme 3

Cyclization to **3** under acidic diazotation conditions gave only a very poor yield (16%) in the case of amine **12a**. Further optimization efforts changing several reaction parameters including the nitrosation source failed. However, when using the fully substituted precursor **12b**, the yield of cyclized product **3b** was improved substantially. We attribute this different behavior to the fact that the intermediate ionic species **I** is also activated at position 2 as shown in the mesomeric structure **II** (Scheme 5). As a consequence, side reactions such as nitrosations, azo-coupling reactions, and polymerizations can occur in the case of an unsubstituted position 2 in precursor **12a** resulting in a low yield of **3a**. A similar effect was observed in the synthesis of thieno[2,3-*d*]triazinones *via* diazotation techniques [8]. Blocking position 2 by introducing a methyl group as in **12b** prevents the side reactions, and the required ring system **3b** is accessible in good yields.



Scheme 4



Scheme 5

Experimental

General

All solvents were distilled prior to use. Dry CH_2Cl_2 was prepared by distillation from P_2O_5 and dry MeOH by distillation from Mg. Commercially available dry *DMF* was treated with molecular sieves (4 Å). TLC was performed on Merck precoated silica gel plates (5554), and flash column chromatography on silica gel 60 from E. Merck (40–63 µm, 9385). Melting points were determined using a Reichert micro hot stage apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory, University of Vienna. The results are in good agreement with the calculated values. The NMR spectra were recorded in $CDCl_3$ solution with a Bruker AC 200 (200 MHz) spectrometer; chemical shifts are reported in ppm relative to *TMS* as internal standard.

2,5-Dihydro-2-methyl-4-((4-methylphenyl)sulfonyl)oxy-3-thiophenecarboxylic acid methyl ester (**5b**; $C_{14}H_{16}O_5S_2$)

To a suspension of NaH (0.17 g, 7.00 mmol) in 10 ml of dry *DMF*, compound **4b** (1.11 g, 6.37 mmol) in 10 ml of dry *DMF* was added dropwise. After addition stirring was continued for 20 min at room temperature then solid *p*-toluenesulfonyl chloride (1 eq) was added slowly. When TLC indicated complete conversion, the reaction mixture was hydrolyzed with water and extracted with diethyl ether. The combined organic layers were repeatedly washed with water to remove *DMF*, dried over Na_2SO_4, filtered, and evaporated to dryness to give 1.53 g (73%) of crude **5b** as a brown oil. According to TLC and NMR, the isolated material was sufficiently pure and was therefore directly used in the next step due to the instability of the compound.

^{1}H NMR (200 MHz, δ, $CDCl_3$): 1.45 (d, $J = 7$ Hz, 3H), 2.47 (s, 3H), 3.60 (s, 3H), 3.85 (dd, $J_1 = 3$ Hz, $J_2 = 16$ Hz, 1H), 4.02 (dd, $J_1 = 5$ Hz, $J_2 = 16$ Hz, 1H), 4.25–4.42 (m, 1H), 7.39 (d, $J = 7$ Hz, 2H), 7.87 (d, $J = 7$ Hz, 2H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 21.6 (q), 23.8 (q), 35.1 (t), 43.2 (d), 51.6 (q), 125.5 (s), 128.1 (d), 129.7 (d), 132.4 (s), 145.8 (s), 151.3 (s), 162.1 (s) ppm.

2,5-Dihydro-4-(phenylmethyl)thio-3-thiophenecarboxylic acid methyl ester (**6a**; $C_{13}H_{14}O_2S_2$)

Benzylthiol (5.92 g, 47.7 mmol) was added to a solution of NaOH (1 eq) in a mixture of MeOH/water = 8/1 and stirred until the emulsion became homogeneous. Compound **5a** (15.00 g, 47.7 mmol) was dissolved in 100 ml of acetone and treated with the prepared solution of thiolate at 0°C. After the

addition was complete, the reaction mixture was warmed to room temperature, and stirring was continued for 20 h. The solution was concentrated, hydrolyzed with water, and extracted with diethyl ether. The combined organic layers were washed with 2 *N* NaOH and water, dried over Na_2SO_4, filtered, and evaporated. Recrystallization of the crude product gave 11.43 g (90%) of pure **6a** as colorless crystals.

M.p.: 71–74°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.40 (s, 3H), 3.92–4.02 (m, 2H), 4.06–4.21 (m, 4H), 7.20–7.43 (m, 5H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 36.2 (t), 37.7 (t), 41.2 (t), 51.5 (q), 121.3 (s), 127.5 (d), 128.6 (d), 128.7 (d), 136.2 (s), 153.5 (s), 164.3 (s) ppm.

Aromatization of compounds **5** *and* **6** *using* SO_2Cl_2

A 10% solution of dihydro compound **5** or **7** (1 eq) in dry CH_2Cl_2 was treated with a 10% solution of SO_2Cl_2 (1 eq) in dry CH_2Cl_2 below 25°C. The mixture was stirred at room temperature until TLC indicated complete conversion. After hydrolysis with ice/water the organic layer was washed with water and satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to give the crude aromatized product.

4-(Phenylmethyl)thio-3-thiophenecarboxylic acid methyl ester (**7a**; $C_{13}H_{12}O_2S_2$)

Compound **6a** (4.50 g, 16.89 mmol) was treated with SO_2Cl_2 to give 3.47 g (78%) of **7a** as beige crystals after recrystallization from diisopropyl ether.

M.p.: 100–102°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.87 (s, 3H), 4.15 (s, 2H), 6.81 (d, $J = 3$ Hz, 1H), 7.20–7.46 (m, 5H), 8.17 (d, $J = 3$Hz, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 38.1 (t), 51.7 (q), 118.5 (d), 127.2 (d), 128.5 (d), 128.8 (d), 130.7 (s), 134.4 (d), 135.4 (s), 136.3 (s), 162.4 (s) ppm.

4-((4-Methylphenyl)sulfonyl)oxy-3-thiophenecarboxylic acid methyl ester (**10a**; $C_{13}H_{12}O_5S_2$)

Treatment of **5a** (5.00 g, 15.90 mmol) according to the above procedure for aromatization afforded 4.64 g (94%) of **10a** as colorless crystals after recrystallization from diisopropyl ether.

M.p.: 88–89°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.44 (s, 3H), 3.74 (s, 3H), 7.06 (d, $J = 4$ Hz, 1H), 7.33 (d, $J = 8$ Hz, 2H), 7.78 (d, $J = 8$ Hz, 2H), 8.00 (d, $J = 4$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 21.5 (q), 51.6 (q), 116.0 (d), 125.8 (s), 128.5 (d), 129.5 (d), 132.0 (s), 132.8 (d), 143.2 (s), 145.5 (s), 160.8 (s) ppm.

2-Methyl-4-((4-methylphenyl)sulfonyl)oxy-3-thiophenecarboxylic acid methyl ester (**10b**; $C_{14}H_{14}O_5S_2$)

Compound **5b** (2.94 g, 8.95 mmol) was treated with SO_2Cl_2 to give 2.07 g (71%) of **10b** as yellow oil after purification by flash column chromatography (silica gel: substance = 15:1, petroleum ether/ethyl acetate = 10/1) which slowly crystallized.

M.p.: 89–92°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.45 (s, 3H), 2.62 (s, 3H), 3.76 (s, 3H), 6.67 (s, 1H), 7.32 (d, $J = 7$ Hz, 2H), 7.78 (d, $J = 7$ Hz, 2H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 16.6 (q), 21.6 (q), 51.3 (q), 111.3 (d), 121.8 (s), 128.4 (d), 129.5 (d), 132.2 (s), 142.7 (s), 145.3 (s), 148.1 (s), 162.1 (s) ppm.

4-(Phenylmethyl)sulfinyl-3-thiophenecarboxylic acid methyl ester (**9a**; $C_{13}H_{12}O_3S_2$)

Compound **7a** (0.50 g, 1.89 mmol) was dissolved in 10 ml of dry CH_2Cl_2, cooled to −60°C, and treated with a solution of *MCPBA* (1 eq) in 10 ml dry CH_2Cl_2. After the addition was completed, the reaction mixture was warmed to room temperature and stirred for 3 h. The solution was washed with

satd. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated to give 0.32 g (60%) of pure **9a** as colorless crystals after flash column chromatography (silica gel: substance = 40:1, petroleum ether/ethyl acetate = 1/1).

M.p.: 85–88°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.92 (s, 3H), 4.01 (d, $J = 13$ Hz, 1H), 4.38 (d, $J = 13$ Hz, 1H), 7.01–7.14 (m, 2H), 7.19–7.31 (m, 3H), 7.50 (d, $J = 4$ Hz, 1H), 8.22 (d, $J = 4$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 52.4 (q), 61.1 (t), 128.0 (d), 128.1 (d), 128.3 (d), 128.9 (s), 130.0 (s), 130.4 (d), 136.0 (d), 144.2 (s), 162.2 (s) ppm.

Nitration of compounds **10a**,**b**

A 10% solution of **10** (1 eq) in Ac_2O was cautiously treated with a mixture of fuming HNO_3 (3 eq) and conc. H_2SO_4 (3 eq) keeping the temperature below + 40°C. After the highly exothermic reaction ceased the solution was stirred at room temperature until completion (TLC control), hydrolyzed with ice/water, and alkalized with solid $NaHCO_3$. After extraction with diethyl ether the combined organic layers were washed with satd. $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered, and evaporated to dryness.

4-((4-Methylphenyl)sulfonyl)oxy-5-nitro-3-thiophenecarboxylic acid methyl ester (**11a**; $C_{13}H_{11}NO_7S_2$)

Compound **10a** (1.99 g, 6.37 mmol) gave 1.37 g (60%) of pure **11a** as faint yellow crystals according to the above procedure after recrystallization from diisopropyl ether.

M.p.: 122–124°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.48 (s, 3H), 3.80 (s, 3H), 7.36 (d, $J = 8$ Hz, 2H), 7.80 (d, $J = 8$ Hz, 2H), 8.17 (s, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 21.9 (q), 52.5 (q), 128.1 (s), 128.8 (d), 130.0 (d), 132.5 (s), 133.8 (d), 140.0 (s), 141.3 (s), 146.6 (s), 160.0 (s) ppm.

2-Methyl-4-((4-methylphenyl)sulfonyl)oxy-5-nitro-3-thiophenecarboxylic acid methyl ester (**11b**; $C_{14}H_{13}NO_7S_2$)

Compound **10b** (2.00 g, 6.13 mmol) gave 1.50 g (66%) of **11b** as faint yellow crystals according to the above procedure after recrystallization from diisopropyl ether. In order to get an analytically pure sample, a small amount was purified by flash column chromatography (silica gel: substance = 50:1, petroleum ether/ethyl acetate = 5/1).

M.p.: 82–85°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.45 (s, 3H), 2.72 (s, 3H) 3.81 (s, 3H), 7.35 (d, $J = 7$ Hz, 2H), 7.78 (d, $J = 7$ Hz, 2H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 16.6 (q), 21.6 (q), 52.0 (q), 124.6 (s), 128.3 (d), 129.9 (d), 132.2 (s), 136.7 (s), 139.7 (s), 146.3 (s), 150.0 (s), 161.2 (s) ppm.

Nucleophilic substitution of **11** *with benzylthiol*

A 10% solution of benzylthiol (1 eq) in dry *DMF* was treated with K_2CO_3 (1 eq) at 0°C. To this mixture, a 10% solution of **11** (1 eq) in dry *DMF* was added maintaining the temperature below 0°C. After TLC indicated complete conversion, hydrolysis was carried out with ice/water and the mixture was extracted with diethyl ether. The combined organic layers were washed with 2 *N* HCl, satd. $NaHCO_3$, and water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

5-Nitro-4-(phenylmethyl)thio-3-thiophenecarboxylic acid methyl ester (**8a**; $C_{13}H_{11}NO_4S_2$)

Precursor **11a** (0.89 g, 2.49 mmol) gave 0.46 g (60%) of **8a** after purification by flash column chromatography (silica gel: substance = 30:1, petroleum ether/ethyl acetate = 5/1).

M.p.: 75–77°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.92 (s, 3H), 4.26 (s, 2H), 7.13–7.30 (m, 5H), 8.09 (s, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 40.1 (t), 52.4 (q), 127.5 (d), 128.5 (d), 128.9 (d), 134.4 (s), 135.6 (d), 135.8 (s), 136.4 (s), 150.0 (s), 161.2 (s) ppm.

2-Methyl-5-nitro-4-(phenylmethyl)thio-3-thiophenecarboxylic acid methyl ester (**8b**; $C_{14}H_{13}NO_4S_2$)

Compound **11b** (0.54 g, 1.45 mmol) gave 0.40 g (85%) of **8b** as yellow crystals after purification by flash column chromatography (silica gel: substance = 40:1, petroleum ether/ethyl acetate = 10/1).

M.p.: 97–100°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.56 (s, 3H), 3.90 (s, 3H), 4.16 (s, 3H), 7.15–7.32 (m, 5H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 15.7 (q), 39.9 (t), 52.3 (q), 127.6 (d), 128.5 (d), 129.0 (d), 133.1 (s), 135.7 (s), 136.4 (s), 145.8 (s), 148.6 (s), 163.0 (s) ppm.

Reduction to amines **12**

Iron powder (4 eq) was added slowly to a 10% solution of compound **8** (1 eq) in acetic acid, keeping the reaction temperature below 30°C. After TLC indicated complete conversion the mixture was hydrolyzed with ice/water and extracted with diethyl ether. The combined organic layers were washed with satd. $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered, and concentrated.

5-Amino-4-(phenylmethyl)thio-3-thiophenecarboxylic methyl ester (**12a**; $C_{13}H_{13}NO_2S_2$)

8a (6.00 g, 19.39 mmol) gave 4.45 g (82%) of **12a** as red oil following the above protocol. Crude **16a** was sufficiently pure for the following conversion according to TLC and NMR.

B.p.: 198–203°C (0.05 mbar, *Kugelrohr* distillation with partial decomp.); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.86 (s, 3H), 3.90 (s, 2H), 4.10 (bs, 2H), 7.04–7.13 (m, 2H), 7.16–7.25 (m, 3H), 7.31 (s, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 40.4 (t), 51.5 (q), 105.3 (s), 118.7 (d), 126.7 (d), 128.1 (d), 128.7 (d), 132.7 (s), 138.6 (s), 156.5 (s), 162.8 (s) ppm.

5-Amino-2-methyl-4-(phenylmethyl)thio-3-thiophenecarboxylic acid methyl ester (**12b**; $C_{14}H_{15}NO_2S_2$)

Compound **8b** (400 mg, 1.24 mmol) gave 150 mg (42%) of **12b** as orange oil according to the general reduction procedure after purification by flash column chromatography (silica gel: substance = 30:1, petroleum ether/ethyl acetate = 10/1).

^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.45 (s, 3H), 3.77–3.95 (2s and bs, 7H), 7.03–7.30 (m, 5H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 15.2 (q), 40.7 (t), 51.3 (q), 105.2 (s), 126.7 (d), 128.2 (d), 128.8 (d), 129.3 (s), 131.7 (s), 138.8 (s), 152.8 (s), 164.4 (s) ppm.

Cyclization to **3**

An approx. 3% solution of the precursor **12a**,**b** (1 eq) in a 1:1 mixture of acetic acid and conc. HCl was cooled below 10°C and slowly treated with an approx. 10% solution of $NaNO_2$ (1.1 eq) in water. The progress of the reaction was monitored by TLC. After hydrolysis with ice/water the mixture was extracted either with diethyl ether or CH_2Cl_2. The combined organic layers were washed with satd. $NaHCO_3$ solution and water, treated with charcoal, dried over Na_2SO_4, filtered, and evaporated *in vacuo*.

Thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methyl ester (**3a**; $C_6H_4N_2O_2S_2$)

Amino compound **12a** (3.14 g, 11.24 mmol) gave 0.35 g (16%) **3a** as colorless crystals after flash column chromatography (silica gel: substance = 30:1, petroleum ether/ethyl acetate = 5/1) and recrystallization from diisopropyl ether.

M.p.: 140–142°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.98 (s, 3H), 8.57 (s, 1H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 52.7 (q), 122.3 (s), 141.3 (d), 145.8 (s), 161.0 (s), 163.1 (s) ppm.

5-Methyl-thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid methyl ester (**3b**; $C_7H_6N_2O_2S_2$)

Precursor **12b** (150 mg, 0.51 mmol) gave 60 mg (55%) of **3b** as colorless crystals after purification by flash column chromatography (silica gel: substance = 60:1, petroleum ether/ethyl acetate = 10/1) according to the general cyclization procedure.

M.p.: 89–91°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 2.95 (s, 3H), 3.98 (s, 3H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 17.4 (q), 52.4 (q), 118.1 (s), 147.5 (s), 158.0 (s), 160.3 (s), 161.8 (s) ppm.

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