Synthesis of substituted thieno[2,3-*d*]isothiazoles as potential plant activators

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Abstract
Thieno[2,3-*d*]isothiazoles were synthesized as potential plant activators. Based on previously reported thienothiadiazole plant activators, one ring nitrogen was eliminated from the bicyclic motif in order to extend structure activity relationship information. Thieno[2,3-*d*]isothiazoles bearing different functional groups were prepared starting from readily available 3,4-dibromothiophene. Introduction of an oxime and a methylthio group in positions 1 and 2 of the thiophene system set the stage for cyclization, which occurred spontaneously after converting the oxime into the more reactive oxime ester in the presence of methanesulfonyl chloride.

Keywords: Thieno[2,3-*d*]isothiazoles, cyclization, chemical induced resistance, plant activator, oxime

Introduction

In modern agriculture, plant protection agents play an important role to defend crops against infections by bacteria or fungi and against harmful insects in order to increase crop yield.[1-10] Traditional approaches aim at a rapid intervention in case a pest starts to affect a crop either by repeated administration of topical products or by single use of systemic control agents. An alternative strategy aims at strengthening the intrinsically present resistance of the plant itself against certain pathogens. In the early stages, this immunization was activated via non-pathogenic bacteria or fungi.[11-16] Furthermore, compounds such as oxalate or phosphate salts were known to induce a certain immune response.[17,18] In 1991 2,6-dichloroisonicotinic acid **1** was described as the first synthetic product that was able to induce resistance in crops.[19] Further studies by Ciba-Geigy AG and later Syngenta led to the discovery of 1,2,3-benzothiadiazole-7-

carboxylic acid **2** as a potent lead structure to induce such systemic acquired resistance,[20] and was later commercialized as S-methyl ester **3** under the brand Bion© (Figure 1).

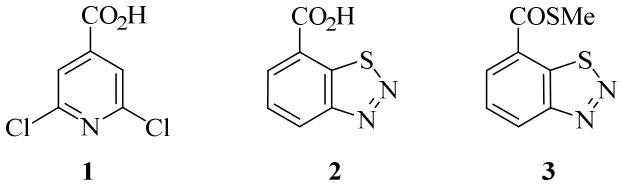


Figure 1. Chemical structures for plant activators **1-3**.

Based on compounds **2** and **3**, different modifications on the ring system have been performed by our group in order to carry out structure activity relationship studies (Figure 2). Initially, the benzene ring was substituted by bioisosteric thiophene. Both thieno[2,3-*d*][1,2,3]thiadiazoles **4**[21-26] as well as thieno[3,2-*d*][1,2,3]thiadiazoles **5**[27] were prepared and the latter was identified as an alternative lead with comparable activity to compound **2**.[21-31] Moreover, the benzene ring was also substituted by pyrrole leading to various pyrrolo-thiadiazoles (*e.g.*, of type **6**).[28,29] Further structural variations included compounds of type **8**[30] and **9**[31]. Within a follow-up generation of structural targets, it was investigated whether both nitrogens of the thiadiazole ring were necessary for biological activity. Initially, the thieno[2,3-*d*]thiazole derivatives[32] **7** were prepared, however, biological studies indicated a significant loss in activity. Hence, it was concluded that the nitrogen in position 2 was important for biological activity.

Within this study, we further investigated deletions of nitrogen from the parent scaffold. Synthesis of the isomeric thieno[2,3-*d*]isothiazole system and various carboxylic acids as well as esters (Figure 2, **10**) became of interest in connection with their potential as plant activators.

Results and Discussion

Little is known about the synthesis of the thieno[2,3-*d*]isothiazole system. Paulmier and coworkers[33] synthesized the title compound **12** by cyclization of 3-(methylthio)thiophene-2-carbaldehyde oxime **11** with phosphorus pentoxide in phosphoric acid (Scheme 1, upper part). The group of Scrowston[34] performed the cyclization using ketoximes **13a** and **13b** as starting materials in acetic acid and acetic anhydride leading to compound **14**. Moreover, they reported a cyclization method using 4-nitrobenzoic acid ester as a leaving group on the oxime (Scheme 1 lower part).

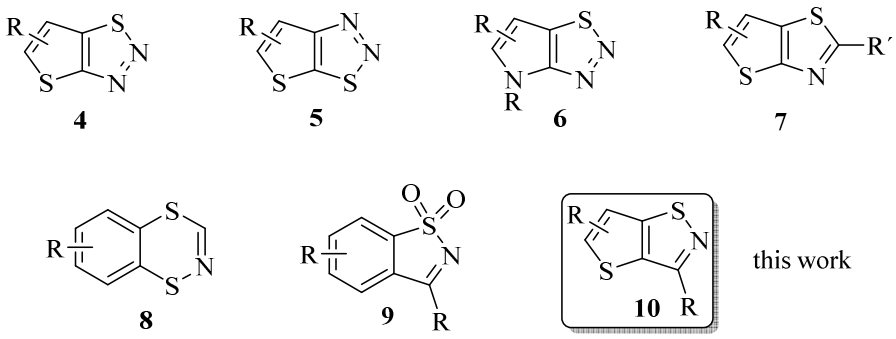
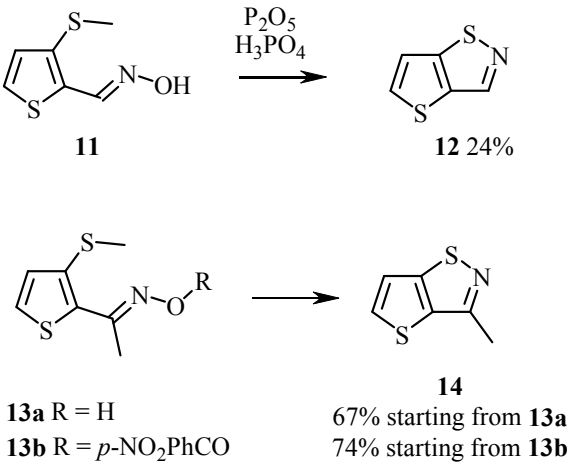
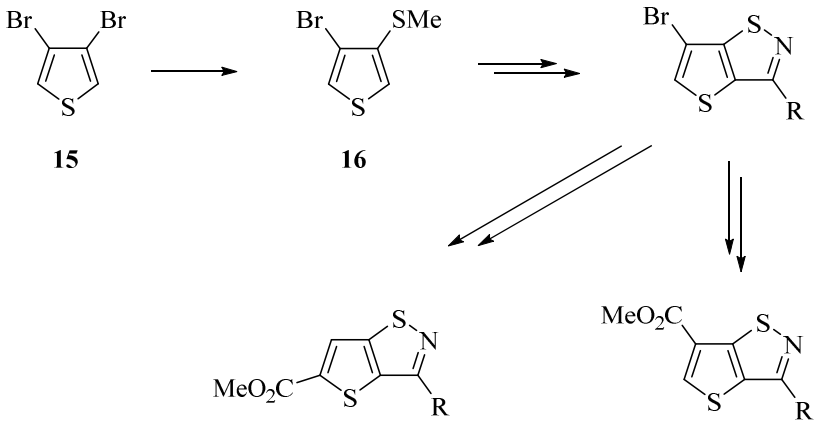


Figure 2. Structural modifications based on **2** and **3**.



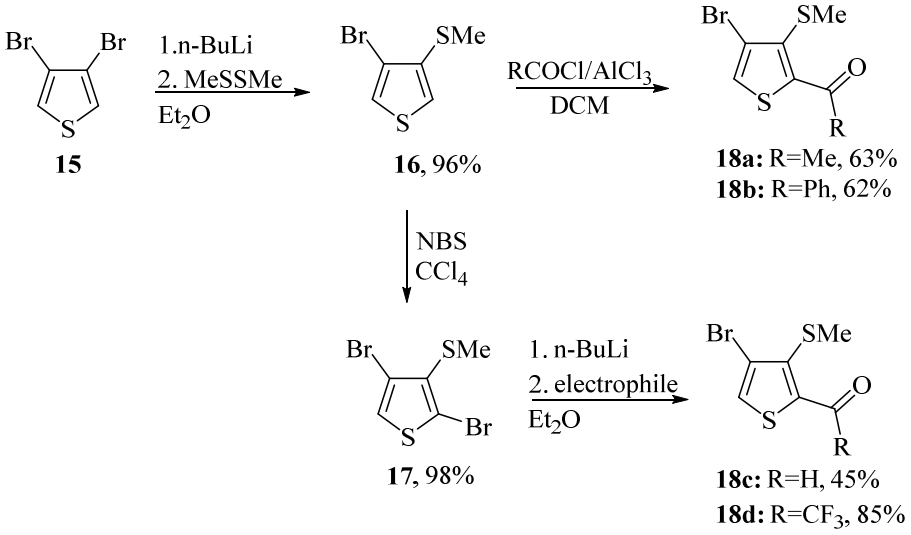
Scheme 1. Paulmier's and Scrowston´s synthesis of thienoisothiazoles.

To synthesize thieno[2,3-*d*]isothiazoles carrying carboxylic acid functionalities in positions 5 or 6 a starting material was required to enable subsequent introduction of the acid functionality. During the planning phase of our approach, it was important to find a substrate which allowed functionalization in both positions 5 and 6 in order to develop a modular synthesis for the design of a focused compound library at a later stage. 3,4-Dibromothiophene **15** was identified as suitable starting material which is additionally cost efficient and easily available. According to our synthetic strategy (Scheme 2) one bromine is used to install the sulfur center of the isothiazole; after cyclization the remaining bromine can either react in a metal-halogen exchange reaction to give a carboxylic acid in position 6 (after quenching with CO_2) or it can act as directing group for metalation into position 5 followed by CO_2H introduction.



Scheme 2. Synthetic strategy.

Starting from 3,4-dibromothiophene **15** a methylthio group was introduced in excellent yield using two equivalents of *n*-butyllithium and two equivalents of dimethylsulfide according to a procedure of Bäuerle *et al.* (Scheme 3).[35] Next, an oxime has to be introduced in position 5 of the thiophene ring which initially requires introduction of a ketone or aldehyde function in this position. This can be carried out via a Friedel-Crafts acylation since the methylthio group in 4 position selectively activates the adjacent 5 position due to its +M effect. To obtain the methyl ketone **18a**, 1.2 equivalents acetylchloride and 1.2 equivalents of $AlCl_3$ were used in dry dichloromethane[36] and **18a** was obtained in 63% yield (Scheme 3). Compound **18b** was obtained via the same protocol using benzoylchloride as the acylation reagent in 62% yield. The synthesis of the aldehyde **18c** was less efficient under Friedel-Crafts conditions[37] and led only to 44% isolated yield after some optimization efforts. Additionally, the reaction workup was tedious owing to the formation of an emulsion caused by the metal salts formed in the workup process.



Scheme 3. Synthesis of carbonyl substrates **18a-d**.

Hence, a lithiation strategy was investigated for **18c** and **18d**.[38,39] Again taking advantage of the aryl activation by the SMe group, **16** was brominated with *N*-bromosuccinimide to give 2,4-dibromo-3-(methylthio)thiophene **17**.[38] Then, metal-halogen-exchange was performed using *n*-butyllithium, followed by quenching with dimethylformamide as electrophile. Unfortunately, the desired aldehyde **18c** was obtained in only 45% yield also via this route. However, the workup procedure of this two-step process was much more convenient and fast compared to the Friedel-Crafts acylation reaction. Trifluoromethyl ketone **18d** was synthesized also via this sequence using *N*,*N*-diethyl-trifluoroacetamide as electrophile; in this case a high yield of 85% was obtained for **18d** (Scheme 3).

The carbonyl functions of all analogs were converted to the corresponding oximes using hydroxylamine hydrochloride and sodium acetate as a base in dry methanol at room temperature.[40] Starting from the methyl ketone **18a**, the oxime compound **19a** could be obtained with 89% yield (Scheme 4). According to NMR data and melting point (only 2 °C interval) only one stereoisomer was formed. To determine the structure of this product, single crystal X-ray-crystallography was used. It was revealed that the hydroxyl group of the oxime is *trans* to the thiophene ring representing the *E*-isomer. Moreover, it could be shown that the oxime nitrogen is close to the thiophene sulfur atom but is not coplanar with the ring (Figure 3). This is in accordance with work from Farell and coworkers.[41]

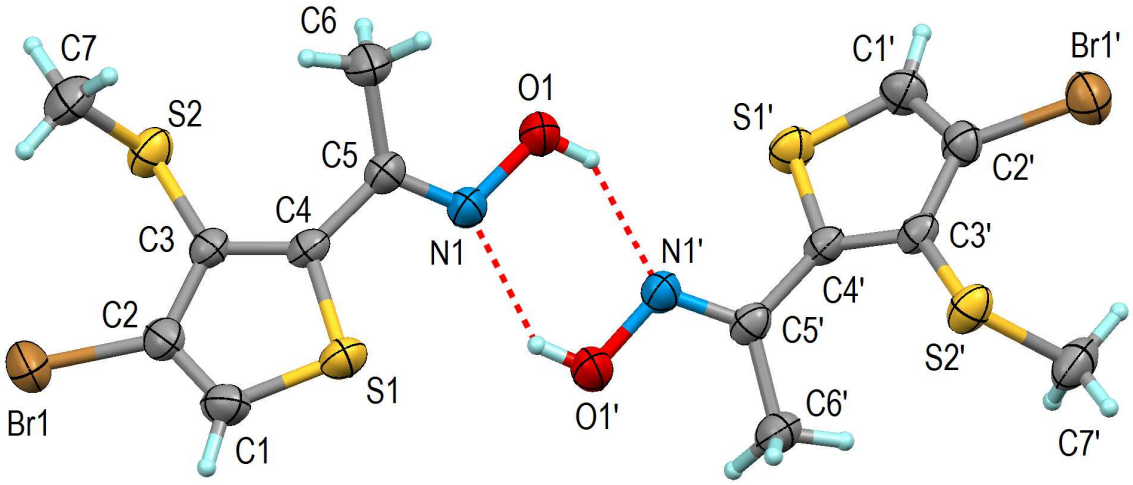
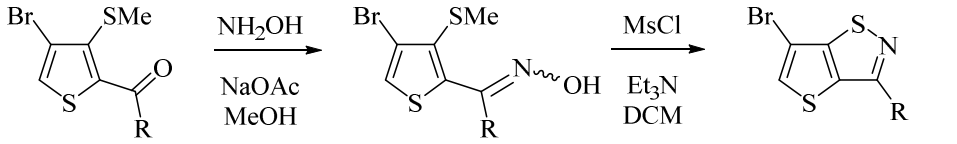


Figure 3. X-ray analysis of ***E*-19a** showing the two inequivalent molecules of the structure linked by a pair of O-H···N hydrogen bonds (O1···N1 = 2.79 Å, O1'···N1' = 2.85 Å). N1-O1 = 1.399 Å, N1-C5 = 1.281 Å, O1-N1-C5 = 112.7°, S1-C4-C5-N1 = 42.7°, S1'-C4'-C5'-N' = -38.3°.

The formation of the aldoxime **19c** could be performed with 83% yield via the same protocol. This time, two stereoisomers were detected in a 1:1 mixture by NMR spectroscopy. The two compounds could not be separated entirely but pure amounts of both of them were obtained. The

compound with the larger R_f value in a light petroleum/ethyl acetate mixture was analyzed by X-ray crystallography and identified as the *E*-isomer (Figure 4). As for the methyl ketoxime **19a**, the oxime group points to the sulfur atom of the thiophene ring. The molecule is mostly planar with only the S-methyl group pointing out of the plane. The mixture of the two isomers could be isomerized to the *Z*-isomer by heating in acetic acid for one hour. Isomerization occurs also during storage at room temperature after a few days.



18a: R=Me
18b: R=Ph
18c: R=H
18d: R=CF_3

19a: R=Me, 89%, *E*-isomer
19b: R=Ph, 75%, *E*:*Z*=1:5
19c: R=H, 83%, *E*:*Z*=1:1
19d: R=CF_3, 71%, *E*:*Z*=1:1

20a: R=Me, 68%
20b: R=Ph, 21%
20c: R=H, 75%
20d: R=CF_3, 11%

Scheme 4. Oxime formation and cyclization.

The synthesis of the phenyl ketoxime **19b** took longer owing to deactivation at the carbonyl center; the product was formed in 75% in a 1:5 mixture of *E/Z* isomers (Scheme 4). To decrease the reaction time (3 days), the reaction was performed in dry ethanol under reflux in the presence of 2.5 equivalents of base to inhibit isomerization to the *Z*-isomer. With this protocol, complete conversion was achieved overnight and the product obtained with 68% yield in an *E/Z* mixture of 1:2.5 (not shown).

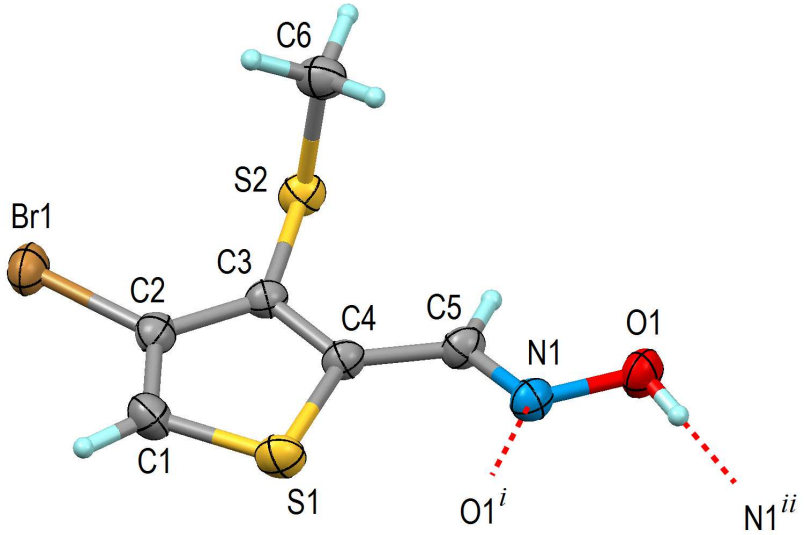


Figure 4. X-ray analysis of ***E*-19c**. Dashed lines indicate O-H···N hydrogen bonds with two neighboring molecules (O···N = 2.85 Å). N1-O1 = 1.403 Å, N1-C5 = 1.278 Å, O1-N1-C5 = 110.4°, S1-C4-C5-N1 = 7.7°

The reaction with the trifluoromethyl ketone **19d** at room temperature showed no conversion overnight. Therefore, the reaction mixture was also heated to reflux and after two days conversion was completed. The reason for the long reaction time might be that the initial intermediate formed from the nucleophilic attack of the hydroxyl amine at the carbonyl group is quite stable due to the electron withdrawing effect of the trifluoromethyl group. Hence, elimination of water is hindered. Nevertheless the product was isolated in 71% yield with an *E*/*Z* mixture of 1:1 (Scheme 4). Regarding the nomenclature of the isomers it should be considered, that due to the higher priority of the trifluoromethyl group, the thiophene substituent is *cis* to the hydroxyl group in the *E*-isomer.

For the cyclization to the thienoisothiazoles, the oximes **19** were first converted to the corresponding oxime esters by reaction with *p*-nitrobenzoyl chloride or methanesulfonyl chloride. These activated oxime esters were not isolated since they were expected to spontaneously cyclize to the desired products, provided that the correct stereochemistry is established. Attack of the sulfur nucleophile can only occur if the leaving group X adopts a *trans* configuration relative to the thiophene ring; otherwise, the leaving group impedes the nucleophilic attack on the nitrogen due to steric hindrance (Figure 5).

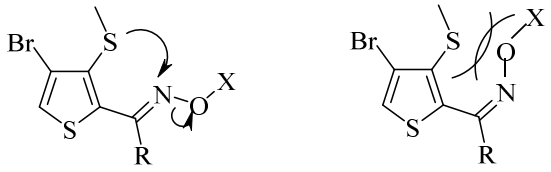
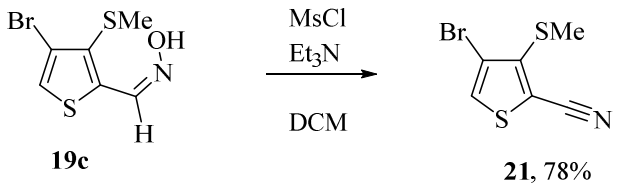


Figure 5. Conformational requirements for cyclization.

As a result, *E*-oximes are preferred for cyclization reactions. In a first experiment oxime **19a** was reacted with *p*-nitrobenzoyl chloride in the presence of K_2CO_3 in dry dichloromethane. After workup the cyclization product was isolated in 55% yield. To further facilitate the process, the reaction was performed using methanesulfonyl chloride and Et_3N as base again in dry dichloromethane as solvent. After 30 minutes stirring at room temperature **20a** was isolated in an improved 68% yield. Since X-ray analysis of **19a** revealed that the oxime nitrogen points towards the thiophene sulfur, rotation around the thiophene-oxime bond seems possible in solution and cyclization can indeed take place.



Scheme 5. Nitrile formation from ***Z*-19c**.

The cyclization reaction of the aldoxime **19c** was repeated using methanesulfonyl chloride as activating agent. Using the pure *E*-isomer of **19c**, 75% of the cyclized product **20c** was isolated accompanied by 10% of nitrile **21** formed upon elimination of water from the oxime. On the other hand, when the pure *Z*-oxime of **19c** was submitted to the same reaction conditions only formation of the nitrile **21** (Scheme 5, 78% isolated yield) was observed which is in accordance to literature.[42] When the 1:1 mixture of isomers was converted at room temperature overnight, the main product was again nitrile **21** and only traces of cyclization product were detected. When the experiment was repeated at -10 °C, 15% of the cyclized product **20c** was isolated but still, the nitrile was the main product.

For the formation of the phenyl analog **20b**, the 1:2.5 mixture of isomers **19b** was used. Only 21% of cyclization product was isolated. Considering the amount of *E*-isomer, which is the only one that can cyclize, this represents an effective yield of 53%.

The protocol was also applied on the 1:1 isomeric mixture of the trifluoromethyl ketoxime **19d**. The reaction yielded thienothiazole product **20d** in 11%. Moreover, 70% of oxime ester **22** was isolated and analyzed by X-ray crystallography (Figure 6). It revealed to be the *Z*-isomer which is the unreactive isomer towards cyclization. The low yield may be attributed to isomerisation of the *E*- to the *Z*-isomer in solution or upon storage.

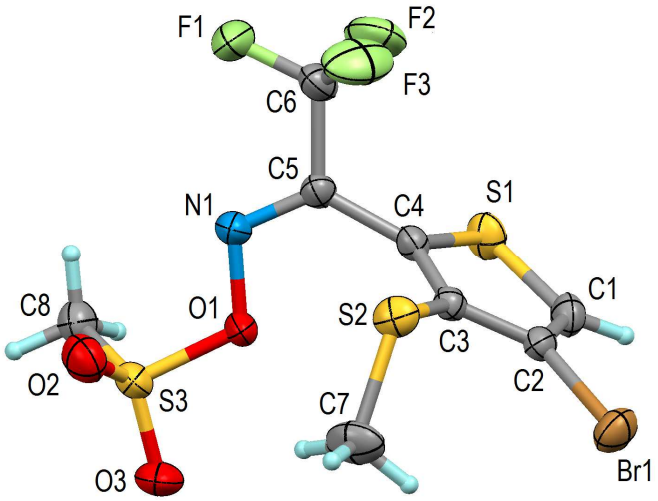
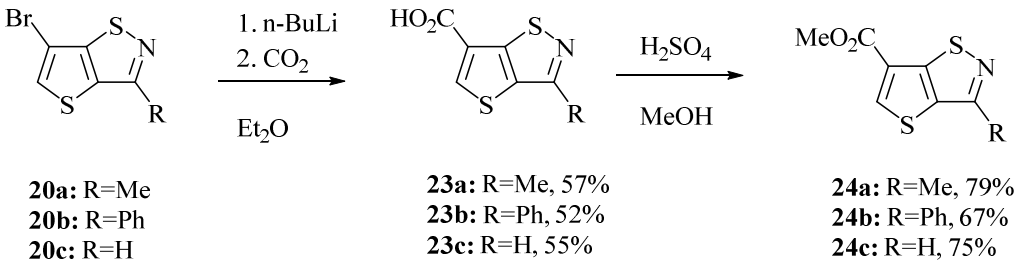


Figure 6. X-ray analysis of the oxime ester **22**. N1-O1 = 1.410 Å, N1-C5 = 1.269 Å, O1-N1-C5 = 110.0°, S1-C4-C5-N1 = 103.9°, C4-C5-N1-O1 = -2.4°, C5-N1-O1-S3 = 175.5°.



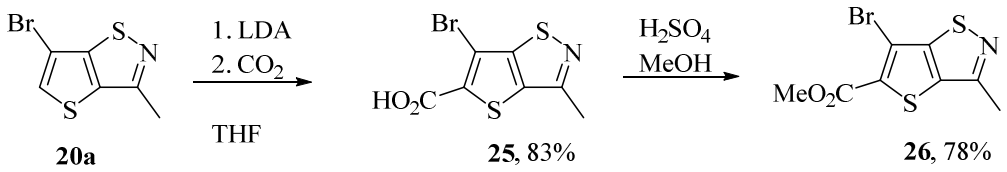
20a: R=Me
20b: R=Ph
20c: R=H

23a: R=Me, 57%
23b: R=Ph, 52%
23c: R=H, 55%

24a: R=Me, 79%
24b: R=Ph, 67%
24c: R=H, 75%

Scheme 6. Acid and ester introduction on substrates **20a-c**.

The last step of the synthesis was the introduction of an ester group on the ring system in position 6. First, a metal-halogen-exchange with *n*-butyllithium in dry diethylether at -70 °C was performed and then dry carbon dioxide was used as an electrophile at -100 °C (Scheme 6). The reaction resulted in good yields for the thienoisothiazole **23c** and its methyl and phenyl analogs **23a** and **23b**. The electrophilic attack of carbon dioxide on the trifluoromethyl compound **20d** resulted in decomposition of the ring system. Even lower temperatures did not inhibit this reaction. The resulting carboxylic acids **23a-c** were esterified using concentrated sulfuric acid in dry methanol under reflux. All three compounds **24a-c** were obtained in good yields (Scheme 6). To access the isomeric isothiazolo-5-carboxylate, substrate **20a** was lithiated with LDA in tetrahydrofuran at -50 °C followed by quenching with dry carbon dioxide at -100 °C. The carboxylic acid **25** was esterified with sulfuric acid in dry methanol to give **26** in 78% yield (Scheme 7).



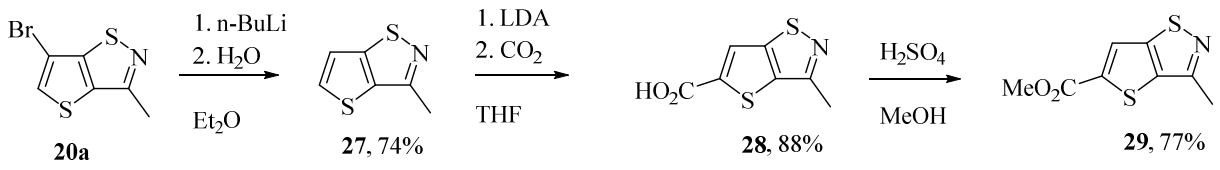
20a

25, 83%

26, 78%

Scheme 7. Ester introduction in position 5 of **20a**.

In an alternative approach towards the non-halogenated 5-carboxylate, unsubstituted 3-methylthienoisothiazole **27** was synthesized starting from 6-bromo-3-methylthienoisothiazole **20a**. A metal-halogen-exchange was performed with *n*-butyllithium and water was added as electrophile. The carboxy group was introduced in 5 position in the same manner as above (LDA, then CO_2) to give **28** in 88% yield. Finally, esterification in dry methanol with sulfuric acid gave **29** in 77% (Scheme 8).



Scheme 8. Debromination and ester introduction on **20a**.

Conclusions

A series of thieno[2,3-*d*]isothiazoles was synthesized from a common, cheap and readily available 3,4-dibromothiophene. It was demonstrated that only the *E*-isomers can cyclize to the target compounds. The *Z*-isomer is either converted to a nitrile such as **21**, or can be isolated as oxime ester intermediate. X-ray analysis was carried out on key compounds to confirm their structure and to corroborate the observed reactivities. Finally, methods to introduce an acid or ester functionality in 5 and 6 positions of the isothiazole core were developed. The compounds are submitted to biological testing and the results will be reported in due course.

Experimental Section

General. Flash column chromatography was performed on silica gel 60 (40-63 µm), obtained from Merck. Melting points were determined using a Kofler type Leica Galen III micro hot stage microscope and are uncorrected. NMR spectra were recorded on a Bruker AC 200 spectrometer and chemical shifts are reported in parts per million, using TMS as internal standard. Combustion analysis was carried out at the Microanalytic Laboratory, University of Vienna.

1-[4-Bromo-3-(methylthio)thiophen-2-yl]ethanone (18a). $AlCl_3$ (0.38 g, 2.87 mmol) was dispersed in dry MeOH (10 mL). The mixture was cooled to 0 °C and acetyl chloride (0.18 mL, 2.87 mmol) was added dropwise. Then, precursor **16** (0.50 g, 2.39 mmol) was dissolved in dry MeOH (10 mL) and slowly added to the reaction solution. The reaction was stirred at 0 °C for 2 h, then poured into 2N HCl, and extracted with dichloromethane. The combined organic phases were washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **18a** (0.38 g, 63%) was as yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.79 (s, 3H), 7.58 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5 (q), 29.3 (q), 119.9 (s), 129.2 (d), 136.9 (s), 145.3 (s), 190.6 (s). Anal. Calcd. for $C_7H_7BrOS_2$: C, 33.47; H, 2.81. Found: C, 33.69; H, 2.76.

1-[4-Bromo-3-(methylthio)thiophen-2-yl]-1-phenyl-methanone (18b). $AlCl_3$ (7.65 g, 57.40 mmol) was dispersed in dry MeOH (150 mL). The mixture was cooled to 0 °C and benzoyl chloride (8.10 g, 57.40 mmol) was added in portions. Then, precursor **16** (10.00 g, 47.80 mmol)

was dissolved in dry MeOH (50 mL) and slowly added to the reaction solution. The reaction was stirred at 0 °C for 1 h and at room temperature for 5 h. The reaction mixture was poured on 2N HCl and extracted with dichloromethane. The combined organic phases were washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **18b** (9.35 g, 62%) as yellow solid. mp 62-64 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.48 (t, *J* 7 Hz, 2H), 7.56 (t, *J* 7 Hz, 1H), 7.58 (s, 1H), 7.84 (d, *J* 7 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3 (q), 118.2 (s), 127.2 (d), 128.2 (s), 128.3 (d), 129.7 (d), 133.3 (d), 137.6 (s), 140.8 (s), 188.3 (s). Anal. Calcd. for $C_{12}H_9BrOS_2$: C, 46.01; H, 2.90. Found: C, 45.72; H, 2.72.

4-Bromo-3-(methylthio)thiophene-2-carbaldehyde (18c). Compound **17** (13.26 g, 46.04 mmol) was dissolved in dry diethyl ether (200 mL) under nitrogen atmosphere and cooled to -80 °C. *n*-BuLi (18.87 mL, 46.04 mmol, 2.44N) was added dropwise and stirred. After 1 h, dry DMF (4.04 g, 53.25 mmol) was added slowly. After another hour, the mixture was allowed to warm to room temperature, poured onto 2N HCl and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **18c** (4.94 g, 45%) as yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.49 (s, 3H), 7.74 (s, 1H), 10.19 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.6 (q), 118.9 (s), 131.7 (d), 142.6 (s), 143.7 (s), 183.5 (d). Anal. Calcd. for $C_6H_5BrOS_2$: C, 30.29; H, 2.13. Found: C, 30.20; H, 2.15.

1-[4-Bromo-3-(methylthio)thiophen-2-yl]-2,2,2-trifluoroethanone (18d). Compound **17** (13.55 g, 47.04 mmol) was dissolved under nitrogen atmosphere in dry diethyl ether (100 mL) and cooled to -80 °C. *n*-BuLi (19.68 mL, 47.04 mmol, 2.39N) was added dropwise and stirred. After 1 h, *N*,*N*-diethyl trifluoracetamide (8.75 g, 51.75 mmol) was added slowly. After 2 h, the mixture was allowed to warm to room temperature, poured onto 2N HCl and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **18d** (12.21 g, 85%) as yellow solid. mp 66-67 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.79 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0 (q), 116.0 (q, $^1J_{CF}$ 291 Hz), 119.9 (s), 130.1 (s), 131.9 (d), 147.5 (s), 171.7 (q, $^2J_{CF}$ 37 Hz). Anal. Calcd. for $C_7H_4BrF_3OS_2$: C, 27.55; H, 1.32. Found: C, 27.58; H, 1.35.

***E*-1-[4-Bromo-3-(methylthio)thiophen-2-yl]-ethanone oxime (19a).** A mixture of **18a** (6.91 g, 27.51 mmol), NH_2OH HCl (2.29 g, 33.01 mmol) and NaOAc (2.71 g, 33.01 mmol) in dry MeOH (100 mL) were stirred at room temperature overnight. The reaction solution was concentrated in vacuo and poured onto water. The precipitate was filtered and dried in vacuo. Product **19a** (6.54 g, 89%) was obtained as colorless solid by column chromatography (LP/EtOAc, 20:1). mp 99-101 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.35 (s, 3H), 7.79 (s, 1H), 11.65 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.1 (q), 19.4 (q), 117.4 (s), 124.1 (d), 129.6 (s), 143.0 (s), 150.0 (s). Anal. Calcd. for $C_7H_8BrNOS_2$: C, 31.59; H, 3.03; N, 5.26. Found: C, 31.89; H, 2.84; N, 5.15.

***E/Z*-1-[4-Bromo-3-(methylthio)thiophen-2-yl]-1-phenyl-methanone oxime (19b).** Compound **18b** (5.00 g, 15.96 mmol), hydroxylamine hydrochloride (1.33 g, 19.15 mmol) and sodium acetate (1.57 g, 19.15 mmol) were dispersed in dry methanol (80 mL) and stirred for 3 d. The mixture was concentrated in vacuo, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 10:1) to give **19b** (3.93 g, 75%) as colorless solid and was a 1:5 mixture of *E/Z* isomers. mp 120-124 °C. ***E*-18b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3H), 7.31-7.60 (m, 6H), 9.34 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.8 (q), 118.6 (s), 124.1 (d), 127.9 (d), 129.5 (d), 129.7 (d), 132.1 (s), 133.2 (s), 140.7 (s), 152.1 (s). ***Z*-18b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 3H), 7.31-7.60 (m, 6H), 9.34 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 (q), 117.2 (s), 124.9 (d), 127.0 (d), 128.5 (d), 129.9 (d), 133.4 (s), 134.2 (s), 134.9 (s), 151.0 (s). Anal. Calcd. for $C_{12}H_{10}BrNOS_2$: C, 43.91; H, 3.07; N, 4.27. Found: C, 43.99; H, 2.96; N, 4.18.

***E/Z*-4-Bromo-3-(methylthio)thiophene-2-carbaldehyde oxime (19c).** Compound **18c** (0.93 g, 3.92 mmol), hydroxylamine hydrochloride (0.33 g, 4.71 mmol) and sodium acetate (0.39 g, 4.71 mmol) were dispersed in dry methanol (100 mL) and stirred overnight. The mixture was concentrated in vacuo, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **19c** (0.82 g, 83%) as colorless solid and was a 1:1 mixture of *E/Z* isomers. *E*-isomer: mp 129-131 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.79 (s, 1H), 8.41 (s, 1H), 11.68 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 19.3 (q), 116.7 (s), 124.7 (d), 132.6 (s), 139.4 (s), 150.0 (d). Z-isomer: mp 145-147 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.31 (s, 3H), 7.97 (s, 1H), 8.11 (s, 1H), 12.50 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 19.5 (q), 117.1 (s), 128.1 (d), 132.9 (s), 133.6 (s), 138.5 (d). Anal. Calcd. for $C_6H_6BrNOS_2$: C, 28.58; H, 2.40; N, 5.55. Found: C, 28.83; H, 2.43; N, 5.49.

***E/Z*-1-[4-Bromo-3-(methylthio)thiophen-2-yl]-2,2,2-trifluoroethanone oxime (19d).** Compound **18d** (6.36 g, 20.84 mmol), hydroxylamine hydrochloride (1.84 g, 26.44 mmol) and sodium acetate trihydrate (3.40 g, 35.01 mmol) were dispersed in dry methanol (100 mL) and heated to reflux for 2 d. The mixture was concentrated in vacuo, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **19d** (4.75 g, 71%) as yellow oil and was a 1:1 mixture of *E/Z* isomers. *E*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.56 (s, 1H), 9.28 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q), 117.7 (s), 119.7 (q, $^1J_{CF}$ 274 Hz), 126.4 (d), 126.8 (s), 136.3 (s), 141.6 (q, $^2J_{CF}$ 35 Hz). Z-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.49 (s, 1H), 9.05 (bs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.6 (q), 117.2 (q, $^1J_{CF}$ 282 Hz), 118.0 (s), 125.3 (d), 132.1 (s), 135.9 (s), 142.3 (q, $^2J_{CF}$ 34 Hz). Anal. Calcd. for $C_7H_5BrF_3NOS_2$: C, 26.26; H, 1.57; N, 4.37. Found: C, 26.52; H, 1.63; N, 4.31.

6-Bromo-3-methylthieno[2,3-*d*]isothiazole (20a). Compound **19a** (0.30 g, 1.13 mmol) and triethylamine (0.23 g, 2.25 mmol) were dissolved in dry MeOH (20 mL). Methanesulfonyl chloride (0.10 mL, 1.35 mmol) was added dropwise. The reaction was stirred for 30 min at room temperature. Then the mixture was washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent was evaporated. Product **20a** (0.15 g, 68%) was obtained as pale yellow solid by column chromatography (LP/EtOAc, 20:1). mp 103-105 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.49 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (q), 100.9 (s), 130.5 (d), 137.4 (s), 157.8 (s), 159.6 (s). Anal. Calcd. for $C_6H_4BrNS_2$: C, 30.78; H, 1.72; N, 5.98. Found: C, 30.97; H, 1.75; N, 5.92.

6-Bromo-3-phenylthieno[2,3-*d*]isothiazole (20b). Compound **19b** (0.38 g, 1.16 mmol, *E:Z*=1:2.5) was dissolved in dry dichloromethane (20 mL). Methanesulfonyl chloride (0.15 g, 1.39 mmol) and triethylamine (0.14 g, 1.39 mmol) were added and the reaction was stirred at room temperature over night. The mixture was poured onto water and extracted with dichloromethane. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **20b** (0.07 g, 21%) as colorless solid. mp 122-124 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44-7.58 (m, 3H), 7.59 (s, 1H), 8.00-8.10 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 100.8 (s), 127.0 (d), 129.0 (d), 129.8 (d), 131.0 (d), 133.4 (s), 135.0 (s), 158.2 (s), 161.0 (s). Anal. Calcd. for $C_{11}H_6BrNS_2$: C, 44.60; H, 2.04; N, 4.73. Found: C, 44.73; H, 2.09; N, 4.63.

6-Bromothieno[2,3-*d*]isothiazole (20c). Compound **19c** (0.55 g, 2.18 mmol, *E*-isomer) was dissolved in dry dichloromethane (20 mL) and cooled to -10 °C. Methanesulfonyl chloride (0.30 g, 2.62 mmol) was added and the reaction turned yellow. Triethylamine (0.26 g, 2.62 mmol) was added dropwise and the reaction was stirred over night at room temperature. The mixture was poured onto water and extracted with dichloromethane. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 15:1) and recrystallised from diisopropyl ether to give **20c** (0.36 g, 75%) as colorless crystals. mp 97-99 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.57 (s, 1H), 8.68 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 100.4 (s), 131.2 (d), 137.7 (s), 148.6 (d), 159.9 (s). Anal. Calcd. for $C_5H_2BrNS_2$: C, 27.28; H, 0.92; N, 6.36. Found: C, 27.58; H, 1.10; N, 6.35.

6-Bromo-3-(trifluoromethyl)thieno[2,3-*d*]isothiazole (20d). Compound **19d** (1.40 g, 4.37 mmol, *E:Z*=1:1) was dissolved in dry dichloromethane and cooled to -10 °C. Methanesulfonyl chloride (0.60 g, 5.25 mmol) and triethylamine (0.53 g, 5.25 mmol) were added and the reaction was stirred for 2 d at room temperature. The mixture was poured onto water and extracted with dichloromethane. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **20d** (0.14 g, 11%) as colorless solid. mp 72-74 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 100.3 (s), 119.0 (q, $^1J_{CF}$

273 Hz), 132.8 (d), 134.7 (s), 148.0 (q, $^2J_{CF}$ 40 Hz), 162.5 (s). Anal. Calcd. for $C_6HBrF_3NS_2$: C, 25.01; H, 0.35; N, 4.86. Found: C, 24.97; H, 0.53; N, 4.79.

4-Bromo-3-(methylthio)thiophene-2-carbonitrile (21). Compound **19c** (0.40 g, 1.59 mmol) and triethylamine (0.19 g, 1.90 mmol) were added to acetic anhydride (10 mL) and heated to reflux for 30 min. The mixture was allowed to cool to room temperature, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **21** (0.29 g, 78%) as beige solid. mp 78-80 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.68 (s, 3H), 7.53 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8 (q), 112.9 (s), 115.7 (s), 129.2 (d), 131.8 (s), 145.4 (s). Anal. Calcd. for $C_6H_4BrNS_2$: C, 30.78; H, 1.72; N, 5.98. Found: C, 31.05; H, 1.74; N, 5.76.

(*Z*)-1-[4-Bromo-3-(methylthio)thiophen-2-yl]-2,2,2-trifluoroethanone *O*-methylsulfonyl oxime (22). Compound **22** was obtained as side-product in the synthesis of **20d** as colorless solid. mp 95-97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.30 (s, 3H), 7.67, (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1 (q), 37.0 (q), 118.3 (s), 118.8 (q, $^1J_{CF}$ = 277 Hz), 124.5 (s), 127.8 (d), 138.0 (s), 148.4 (q, $^2J_{CF}$ = 36 Hz). Anal. Calcd. for $C_8H_7BrF_3NO_3S_3$: C, 56.71; H, 3.29; N, 5.09. Found: C, 56.51; H, 3.32; N, 4.97.

3-Methylthieno[2,3-*d*]isothiazole-6-carboxylic acid (23a). Precursor **20a** (0.76 g, 3.25 mmol) was dissolved in dry diethyl ether (50 mL) under nitrogen atmosphere, cooled to -80 °C, and treated dropwise with *n*-BuLi (1.47 mL, 3.57 mmol, 2.43N). After 30 min the reaction was cooled to -110 °C and dry carbon dioxide gas was introduced for 20 min. Then the solution was allowed to warm to room temperature and the reaction mixture was poured on ice water. The aqueous phase was extracted with diethyl ether and acidified with concentrated HCl. The precipitate was filtered, washed with water and dried (Na_2SO_4). The product **20a** (0.37 g, 57%) was obtained as colorless crystals. decomposition at 226 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.57 (s, 3H), 8.68 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 17.4 (q), 125.3 (s), 137.3 (s), 142.0 (d), 157.1 (s), 157.8 (s, C 3*), 162.5 (s). Anal. Calcd. for $C_7H_5NO_2S_2$: C, 42.20; H, 2.53; N, 7.03. Found: C, 42.30; H, 2.58; N, 6.89.

3-Phenylthieno[2,3-*d*]isothiazole-6-carboxylic acid (23b). Compound **20b** (0.28 g, 0.95 mmol) was dispensed under nitrogen atmosphere in dry diethyl ether (25 mL), cooled to -75 °C and treated dropwise with *n*-BuLi (0.39 mL, 0.95 mmol, 2.41N). After 30 min, the reaction mixture was cooled to -90 °C and dry carbon dioxide gas was introduced for 20 min. The reaction was allowed to warm to room temperature, poured onto ice water and extracted with diethyl ether. The organic phase was acidified with conc. HCl and the precipitate was filtered, washed with water and dried (Na_2SO_4). The product **22b** (0.13g, 52%) was obtained as colorless crystals. decomposition at 243 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.40-7.67 (m, 3H), 7.89-8.06 (m, 2H,, 8.79 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 125.3 (s), 126.8 (d), 129.3 (d), 130.1 (d), 132.8 (d), 134.5 (s), 142.5 (d), 157.0 (s), 159.4 (s), 162.5 (s).

Thieno[2,3-*d*]isothiazole-6-carboxylic acid (23c). Compound **20c** (0.56 g, 2.54 mmol) was dispensed under nitrogen atmosphere in dry diethyl ether (50 mL), cooled to -80 °C and treated

dropwise with *n*-BuLi (1.14 mL, 2.78 mmol, 2.44N). After one hour, the reaction mixture was cooled to -100 °C and dry carbon dioxide gas was introduced for 20 min. The reaction was allowed to warm to room temperature, poured onto ice water and extracted with diethyl ether. The organic phase was acidified with conc. HCl and the precipitate was filtered, washed with water and dried (Na_2SO_4). The product **22c** (0.26 g, 55%) was obtained as beige crystals. decomposition at 191 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.90 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 124.5 (s), 138.0 (s), 143.1 (d), 149.7 (d), 157.5 (s), 162.5 (s).

Methyl 3-methylthieno[2,3-*d*]isothiazole-6-carboxylate (24a). Acid **23a** (0.40 g, 2.01 mmol) was dissolved in dry MeOH (20 mL) and conc. H_2SO_4 (0.22 g, 2.21 mmol) was added dropwise. The reaction was heated to reflux and stirred overnight. After cooling to room temperature the reaction was concentrated in vacuo and poured onto ice water. The precipitate was collected by filtration, washed with water and dried (Na_2SO_4). Column chromatography (LP/EtOAc, 15:1) afforded **24a** (0.34 g, 79%) as colorless solid. mp 92-94 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.96 (s, 3H), 8.38 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.6 (q), 52.3 (q), 124.4 (s), 137.3 (s), 140.1 (d), 156.7 (s), 157.9 (s), 161.5 (s). Anal. Calcd. for $C_8H_7NO_2S_2$: C, 45.05; H, 3.31; N, 6.57. Found: C, 44.98; H, 3.20; N, 6.36.

Methyl 3-phenylthieno[2,3-*d*]isothiazole-6-carboxylate (24b). Acid **23b** (0.09 g, 0.34 mmol) and conc. H_2SO_4 (0.03 g, 0.34 mmol) were added to dry MeOH (20 mL) and heated to reflux overnight. The reaction was allowed to warm to room temperature, concentrated in vacuo, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **24b** (0.06 g, 67%) as colorless solid. mp 147-148 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.46-7.60 (m, 3H), 8.02-8.11 (m, 2H), 8.45 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.5 (q), 124.3 (s), 127.1 (d), 129.0 (d), 129.8 (d), 133.4 (s), 135.1 (s), 140.5 (d), 157.5 (s), 159.3 (s), 161.7 (s). Anal. Calcd. for $C_{13}H_9NO_2S_2$: C, 56.71; H, 3.29; N, 5.09. Found: C, 56.51; H, 3.32; N, 4.97.

Methyl thieno[2,3-*d*]isothiazole-6-carboxylate (24c). Acid **23c** (0.26 g, 1.40 mmol) and conc. H_2SO_4 (0.14 g, 1.40 mmol) were added to dry MeOH (30 mL) and heated to reflux overnight. The reaction was allowed to warm to room temperature, poured onto water and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 15:1) to give **24c** (0.21 g, 75%) as colorless crystals. mp 111-113 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95 (s, 3H), 8.38 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.4 (q), 122.7 (s), 138.1 (s), 143.3 (d), 149.5 (d), 156.9 (s), 161.2 (s). Anal. Calcd. for $C_7H_5NO_2S_2$: C, 42.20; H, 2.53; N, 7.03. Found: C, 41.99; H, 2.74; N, 6.93.

6-Bromo-3-methylthieno[2,3-*d*]isothiazole-5-carboxylic acid (25). Dry diisopropylamine (0.21 g, 2.11 mmol) was added to dry THF (20 mL), cooled to -50 °C and treated dropwise with *n*-BuLi (1.06 mL, 2.11 mmol, 2N). After 30 min the reaction was cooled to -80 °C. Compound **20a** (0.45 g, 1.92 mmol) was dissolved in dry THF (10 mL) and added to the reaction solution. The reaction was stirred at -70 °C for 1 h. Then the reaction was cooled to -100 °C and dry carbon

dioxide gas was introduced for 15 min. The reaction was allowed to warm to room temperature and concentrated in vacuo. The mixture was poured onto ice water and extracted with diethyl ether. The organic phase was acidified with conc. HCl and the precipitate was filtered, washed with water and dried (Na_2SO_4). Product **25** (0.44 g, 83%) was obtained as colorless solid. mp 133-135 °C ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.60 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 17.7 (q), 105.2 (s), 135.8 (s), 136.3 (s), 159.1 (s), 159.9 (s), 161.7 (s). Anal. Calcd. for $C_7H_4BrNO_2S_2$: C, 30.23; H, 1.45; N, 5.04. Found: C, 30.43; H, 1.66; N, 4.94.

Methyl 6-bromo-3-methylthieno[2,3-*d*]isothiazole-5-carboxylate (26). Acid **25** (0.44 g, 1.58 mmol) was dispersed in dry MeOH (20 mL), conc. H_2SO_4 (0.17 g, 1.74 mmol) was added dropwise and the reaction was heated to reflux for 48 h. After cooling to room temperature the reaction was concentrated in vacuo and poured onto ice water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1). Product **26** (0.36 g, 78%) was obtained as colorless crystals. mp 133-135 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.0 (q), 52.7 (q), 106.7 (s), 133.5 (s), 137.0 (s), 158.3 (s), 160.8 (s), 161.3 (s). Anal. Calcd. for $C_8H_6BrNO_2S_2$: C, 32.89; H, 2.07; N, 4.79. Found: C, 33.06; H, 1.95; N, 4.68.

3-Methylthieno[2,3-*d*]isothiazole (27). Dry diisopropylamine (0.34 g, 3.33 mmol) was added to dry diethyl ether (50 mL), cooled to -70 °C, and treated dropwise with *n*-BuLi (2.42 mL, 4.84 mmol, 2N). After 1 h a mixture of THF and water (3:1) was added and the reaction was allowed to warm to room temperature The mixture was poured onto 2N HCl and extracted with diethyl ether. The combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The product **27** (0.50 g, 74%) was obtained as colorless oil by column chromatography (LP/EtOAC, 100:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 3H), 7.27 (d, *J* 5 Hz, 1H), 7.61 (d, *J* 5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (q), 117.8 (d), 133.6 (d), 138.4 (s), 156.9 (s), 158.8 (s). Anal. Calcd. for $C_6H_5NS_2$: C, 46.42; H, 3.25; N, 9.02. Found: C, 46.67; H, 3.25; N, 8.88.

3-Methylthieno[2,3-*d*]isothiazole-5-carboxylic acid (28). Dry diisopropylamine (0.34 g, 3.33 mmol) was added to dry THF (20 mL), cooled to -50 °C and treated dropwise with *n*-BuLi (1.67 mL, 3.33 mmol, 2N). After 30 min the reaction was cooled to -70 °C and **27** (0.47 g, 3.03 mmol) was added. The reaction was stirred for 2 h at -60 °C, then cooled to -100 °C and dry carbon dioxide gas was introduced for 15 min. The reaction was allowed to warm to room temperature and concentrated in vacuo. The mixture was poured onto ice water and the aqueous phase was extracted with diethyl ether. The organic phase was acidified with conc. HCl and the precipitate was filtered, washed with water and dried (Na_2SO_4). The product **27** (0.53 g, 88%) was obtained as colorless crystals. mp: decomposition at 228 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.58 (s, 3H), 8.12 (s, 1H).^{13}C NMR (50 MHz, $CDCl_3$): δ 17.7 (q), 124.3 (d), 139.6 (s), 142.0 (s), 157.6 (s), 157.7 (s), 163.3 (s). Anal. Calcd. for $C_7H_5NO_2S_2$: C, 42.20; H, 2.53; N, 7.03. Found: C, 42.29; H, 2.65; N, 6.92.

Methyl 3-methylthieno[2,3-*d*]isothiazole-5-carboxylate (29). Compound **28** (0.28 g, 1.41 mmol) was dispended in dry MeOH (20 mL). Conc. H_2SO_4 (0.15 g, 1.54 mmol) was added dropwise and the reaction was heated to reflux overnight. After cooling to room temperature the reaction was concentrated in vacuo and poured onto ice water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give **28** (0.23 g, 77%) as colorless crystals. mp 120-121 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.67 (s, 3H), 3.94 (s, 3H), 7.96 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9 (q), 52.7 (q), 123.1 (d), 140.6 (s), 140.7 (s), 157.2 (s), 157.7 (s), 162.6 (s). Anal. Calcd. for $C_8H_7NO_2S_2$: C, 45.05; H, 3.31; N, 6.57. Found: C, 45.07; H, 3.07; N, 6.55.

X-ray structure determination

X-ray diffraction data were collected at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and 0.3° ω-scan frames. After data integration corrections for absorption were applied with the multi-scan method. The structures were solved with direct methods and refined on F^2 using SHELXTL. Hydrogen atoms were placed in calculated positions and thereafter treated as riding. Proprietary software (programs SMART, SAINT, SADABS and SHELXTL) of Bruker AXS Inc., Madison, WI, was used. Selected crystallographic data are:

***E*-19a**: $C_7H_8BrNOS_2$, M_r = 266.17, triclinic, space group *P*-1 (no. 2), a = 8.559(3) Å, b = 10.688(4) Å, c = 12.596(5) Å, α = 95.75(1)°, β = 104.63(1)°, γ = 111.85(1)°, V = 1010.3(7) Å^3, Z = 4 (Z' = 2), μ = 4.44 mm^{-1}, d_x = 1.750 g cm^{-3}, T = 295 K, 4355 independent reflections (θ_{max} = 27°). Final R indices ($I > 2\sigma(I)$): R_1 = 0.0350, wR_2 = 0.0821, 220 parameters. CCDC-165803.[18]

***E*-19c**: $C_6H_6BrNOS_2$, M_r = 252.15, monoclinic, space group $P2_1/c$ (no. 14), a = 14.679(5) Å, b = 4.802(2) Å, c = 13.547(4) Å, β = 113.08(2)°, V = 878.5(5) Å^3, Z = 4, μ = 5.09 mm^{-1}, d_x = 1.906 g cm^{-3}, T = 296 K, 2531 independent reflections (θ_{max} = 30°). Final R indices ($I > 2\sigma(I)$): R_1 = 0.0294, wR_2 = 0.0637, 106 parameters. CCDC-165802.[18]

***Z*-22**: $C_8H_7BrF_3NO_3S_3$, orthorhombic, space group *P*bca (no. 61), M_r = 398.24, a = 10.492(4) Å, b = 8.792(4) Å, c = 31.402(9) Å, V = 2897(2) Å^3, Z = 8, μ = 3.30 mm^{-1}, d_x = 1.826 g cm^{-3}, T = 298 K, 2555 independent reflections (θ_{max} = 25°). Final R indices ($I > 2\sigma(I)$): R_1 = 0.0427, wR_2 = 0.0867, 175 parameters. CCDC-165804.[43]

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43. CCDC 165802 – 165804 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

