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 \textbf{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, and was later commercialized as S-methyl ester 3 under the brand Bion© (Figure 1).

![Chemical structures for plant activators 1-3.](image)

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 as well as thieno[3,2-d][1,2,3]thiadiazoles 5 were prepared and the latter was identified as an alternative lead with comparable activity to compound 2. Moreover, the benzene ring was also substituted by pyrrole leading to various pyrrolothiadiazoles (e.g., of type 6). Further structural variations included compounds of type 8 and 9. 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 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 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 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\textsubscript{2}) or it can act as directing group for metalation into position 5 followed by CO\textsubscript{2}H 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). 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 AlCl₃ were used in dry dichloromethane 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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{41}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{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°.}
\end{figure}

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
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).

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 K₂CO₃ 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 Et₃N 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.

**Figure 5.** Conformational requirements for cyclization.

**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 \(-10^\circ\text{C}\), 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°.
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 diethyl ether 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).

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 CO2) 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). AlCl₃ (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 NaHCO₃ solution, dried (Na₂SO₄) and the solvent was evaporated. The crude product was purified by column chromatography (LP/EtOAc, 20:1) to give 18a (0.38 g, 63%) as yellow oil. ¹H NMR (200 MHz, CDCl₃): δ 2.44 (s, 3H), 2.79 (s, 3H), 7.58 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): 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 C₇H₇BrOS₂: 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). AlCl₃ (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 NaHCO₃ solution, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.32 (s, 3H), 7.48 (t, 7J Hz, 2H), 7.56 (t, 7J Hz, 1H), 7.58 (s, 1H), 7.84 (d, 7J Hz, 2H). ¹³C NMR (50 MHz, CDCl₃): 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 C₁₂H₉BrOS₂: 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 NaHCO₃ solution, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.49 (s, 3H), 7.74 (s, 1H), 10.19 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 19.6 (q), 118.9 (s), 131.7 (d), 142.6 (s), 143.7 (s), 183.5 (d). Anal. Calcd. for C₆H₂BrOS₂: 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 NaHCO₃ solution, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.55 (s, 3H), 7.79 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 19.0 (q), 116.0 (q, 1JCF 291 Hz), 119.9 (s), 130.1 (s), 131.9 (d), 147.5 (s), 171.7 (q, 2JCF 37 Hz). Anal. Calcd. for C₇H₄BrF₃OS₂: 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), NH₂OH 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. ¹H NMR (200 MHz, DMSO-d₆): δ 2.32 (s, 3H), 2.35 (s, 3H), 7.79 (s, 1H), 11.65 (s, 1H). ¹³C NMR (50 MHz, DMSO-d₆): 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 C₇H₈BrNOS₂: 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 NaHCO₃, dried (Na₂SO₄) 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: ¹H NMR (200 MHz, CDCl₃): δ 2.08 (s, 3H), 7.31-7.60 (m, 6H), 9.34 (bs, 1H). ¹³C NMR (50 MHz, CDCl₃): 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: ¹H NMR (200 MHz, CDCl₃): δ 2.25 (s, 3H), 7.31-7.60 (m, 6H), 9.34 (bs, 1H). ¹³C NMR (50 MHz, CDCl₃): 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 C₁₂H₁₀BrNOS₂: 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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, DMSO-d₆): δ 2.30 (s, 3H), 7.79 (s, 1H), 8.41 (s, 1H), 11.68 (s, 1H). ¹³C NMR (50 MHz, DMSO-d₆): 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. ¹H NMR (200 MHz, DMSO-d₆): δ 2.31 (s, 3H), 7.97 (s, 1H), 8.11 (s, 1H), 12.50 (s, 1H). ¹³C NMR (50 MHz, DMSO-d₆): δ 19.5 (q), 117.1 (s), 128.1 (d), 132.9 (s), 133.6 (s), 138.5 (d). Anal. Calcd. for C₆H₆BrNOS₂: 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 (1.57 g, 15.96 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 NaHCO₃, dried (Na₂SO₄) 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: ¹H NMR (200 MHz, CDCl₃): δ 2.35 (s, 3H), 7.56 (s, 1H), 9.28 (bs, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 18.2 (q), 117.7 (s), 119.7 (q, ¹JCF 274 Hz), 126.4 (d), 126.8 (s), 136.3 (s), 141.6 (q, ²JCF 35 Hz). Z-isomer: ¹H NMR (200 MHz, CDCl₃): δ 2.35 (s, 3H), 7.49 (s, 1H), 9.05 (bs, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 18.6 (q), 117.2 (q, ¹JCF 282 Hz), 118.0 (s), 125.3 (d), 132.1 (s), 135.9 (s), 142.3 (q, ²JCF 34 Hz). Anal. Calcd. for C₇H₃BrF₃NOS₂: 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 NaHCO₃ solution, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.60 (s, 3H), 7.49 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 17.9 (q), 100.9 (s), 130.5 (d), 137.4 (s), 157.8 (s), 159.6 (s). Anal. Calcd. for C₆H₄BrNS: 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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 7.44-7.58 (m, 3H), 7.59 (s, 1H), 8.00-8.10 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): 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 C₁₁H₆BrNS₂: 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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 7.57 (s, 1H), 8.68 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 100.4 (s), 131.2 (d), 137.7 (s), 148.6 (d), 159.9 (s). Anal. Calcd. for C₆H₂BrNS₂: 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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 7.64 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 100.3 (s), 119.0 (q, ¹JC₃F
273 Hz), 132.8 (d), 134.7 (s), 148.0 (q, $^2\text{J}_{\text{CF}}$ 40 Hz), 162.5 (s). Anal. Calcd. for C$_6$HBrF$_3$NS$_2$: 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$_2$SO$_4$) 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$_3$): $\delta$ 2.68 (s, 3H), 7.53 (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 19.8 (q), 112.9 (s), 115.7 (s), 129.2 (d), 131.8 (s), 145.4 (s). Anal. Calcd. for C$_8$H$_4$BrNS$_2$: 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-methylsulfonyloxime (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$_3$): $\delta$ 2.42 (s, 3H), 3.30 (s, 3H), 7.67, (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 18.1 (q), 37.0 (q), 118.3 (s), 118.8 (q, $^1\text{J}_{\text{CF}}$ = 277 Hz), 124.5 (s), 127.8 (d), 138.0 (s), 148.4 (q, $^2\text{J}_{\text{CF}}$ = 36 Hz). Anal. Calcd. for C$_7$H$_5$BrF$_3$NS$_2$: 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$_2$SO$_4$). The product 20a (0.37 g, 57%) was obtained as colorless crystals. decomposition at 226 °C. $^1$H NMR (200 MHz, DMSO-d$_6$): $\delta$ 2.57 (s, 3H), 8.68 (s, 1H). $^{13}$C NMR (50 MHz, DMSO-d$_6$): $\delta$ 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$_7$H$_5$NO$_2$S$_2$: 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$_2$SO$_4$). The product 22b (0.13g, 52%) was obtained as colorless crystals. decomposition at 243 °C. $^1$H NMR (200 MHz, DMSO-d$_6$): $\delta$ 7.40-7.67 (m, 3H), 7.89-8.06 (m, 2H, 8.79 (s, 1H). $^{13}$C NMR (50 MHz, DMSO-d$_6$): $\delta$ 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$_2$SO$_4$). The product 22c (0.26 g, 55%) was obtained as beige crystals. decomposition at 191 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 8.73 (s, 1H), 8.90 (s, 1H). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 124.5 (s), 138.0 (s), 141.3 (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$_2$SO$_4$ (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$_2$SO$_4$). 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$_3$): $\delta$ 2.63 (s, 3H), 3.96 (s, 3H), 8.38 (s, 1H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 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$_8$H$_7$NO$_2$S$_2$: 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$_2$SO$_4$ (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$_2$SO$_4$) 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_9$NO$_2$S$_2$: 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$_2$SO$_4$ (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$_2$SO$_4$) 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$_3$): $\delta$ 3.95 (s, 3H), 8.38 (s, 1H), 8.61 (s, 1H). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 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$_7$H$_5$NO$_2$S$_2$: 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 (Na₂SO₄). Product 25 (0.44 g, 83%) was obtained as colorless solid. mp 133-135 °C. ¹H NMR (200 MHz, DMSO-d₆): δ 2.60 (s, 3H). ¹³C NMR (50 MHz, DMSO-d₆): 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 C₇H₄BrNO₂S₂: 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. H₂SO₄ (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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.62 (s, 3H), 3.98 (s, 3H). ¹³C NMR (50 MHz, CDCl₃): 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 C₈H₈BrNO₂S₂: 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 NaHCO₃, dried (Na₂SO₄) and the solvent was evaporated. The product 27 (0.50 g, 74%) was obtained as colorless oil by column chromatography (LP/EtOAc, 100:1). ¹H NMR (200 MHz, CDCl₃): δ 2.62 (s, 3H), 7.27 (d, J 5 Hz, 1H), 7.61 (d, J 5 Hz, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 17.9 (q), 117.8 (d), 133.6 (d), 138.4 (s), 156.9 (s), 158.8 (s). Anal. Calcd. for C₆H₅NS₂: 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 (Na₂SO₄). The product 27 (0.53 g, 88%) was obtained as colorless crystals. mp: decomposition at 228 °C. ¹H NMR (200 MHz, DMSO-d₆): δ 2.58 (s, 3H), 8.12 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): 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 C₇H₅NO₂S₂: 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 dispensed in dry MeOH (20 mL). Conc. H₂SO₄ (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 NaHCO₃, dried (Na₂SO₄) 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. ¹H NMR (200 MHz, CDCl₃): δ 2.67 (s, 3H), 3.94 (s, 3H), 7.96 (s, 1H). ¹³C NMR (50 MHz, CDCl₃): 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 C₈H₇NO₂S₂: 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 F² 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**: C₆H₅BrNOS₂, Mᵣ = 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) Å³, Z = 1 (Z′ = 2), μ = 4.44 mm⁻¹, dₓ = 1.750 g cm⁻³, T = 295 K, 4355 independent reflections (θ_max = 27°). Final R indices (I > 2σ(I)): R₁ = 0.0350, wR₂ = 0.0821, 220 parameters. CCDC-165803.¹⁸

**E-19c**: C₆H₅BrNOS₂, Mᵣ = 252.15, monoclinic, space group P2₁/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) Å³, Z = 4, μ = 5.09 mm⁻¹, dₓ = 1.906 g cm⁻³, T = 296 K, 2531 independent reflections (θ_max = 30°). Final R indices (I > 2σ(I)): R₁ = 0.0294, wR₂ = 0.0637, 106 parameters. CCDC-165802.¹⁸

**Z-22**: C₆H₅BrF₃NO₅S₃, orthorhombic, space group Pbcₐ (no. 61), Mᵣ = 398.24, a = 10.492(4) Å, b = 8.792(4) Å, c = 31.402(9) Å, V = 2897(2) Å³, Z = 8, μ = 3.30 mm⁻¹, dₓ = 1.826 g cm⁻³, T = 298 K, 2555 independent reflections (θ_max = 25°). Final R indices (I > 2σ(I)): R₁ = 0.0427, wR₂ = 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](http://www.ccdc.cam.ac.uk/data_request/cif).