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Perfluoroalkyl-Substituted Thiophenes and Pyrroles from Donor–Acceptor Cyclopropanes and Heterocumulenes: Synthesis and Exploration of their Reactivity

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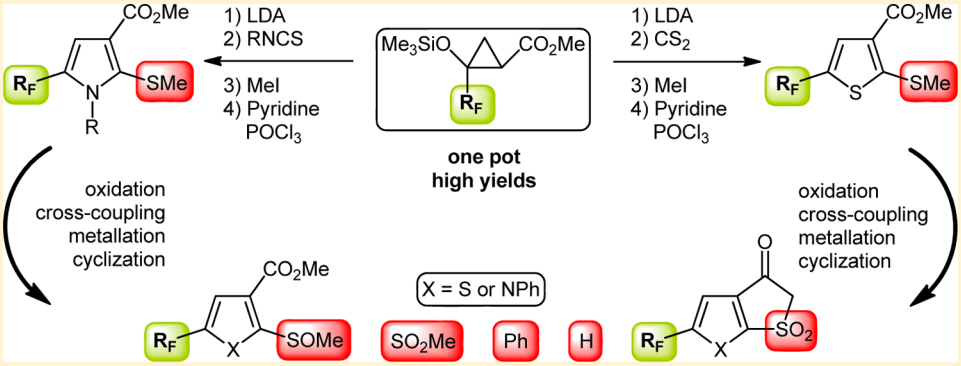
Supporting Information



ABSTRACT: A methyl 2-trifluoromethyl-2-siloxycyclopropanecarboxylate was smoothly deprotonated by lithium diisopropylamide and reacted with carbon disulfide and methyl iodide to afford a dihydrothiophene derivative. The crucial step in this transformation is a ring-expansion of the anionic intermediate by [1,3] sigmatropic rearrangement. The dihydrothiophene was converted into the corresponding 5-trifluoromethylthiophene derivative by phosphoryl chloride in refluxing pyridine. A one-pot version of the reaction sequence efficiently provided the thiophene in good yield. Analogously, aryl- and alkyl-substituted isothiocyanates instead of carbon disulfide afforded the corresponding trifluoromethyl-substituted pyrroles in moderate to very good overall yields. Explorative reactivity studies with the methylthio-substituted thiophene and pyrrole derivatives demonstrate that they are precursors of a range of interesting trifluoromethyl-substituted products, including new members from the thienothiophene and thienopyrrole class.

INTRODUCTION

In the constantly growing field of heterocyclic compounds, specifically substituted thiophenes and pyrroles have diverse biological activities[1] and have found frequent applications in medicine,[2] agriculture,[3] and material science.[4] Prominent examples are the broad-spectrum insecticide Chlorfenapyr,[5] the multitargeted receptor tyrosine kinase (RTK) inhibitor Sutent,[6] and the cholesterol lowering blockbuster drug Lipitor.[7] This importance renders the need for new methods for the synthesis of these heterocycles.[8] Traditional reactions for the preparation of thiophenes are the Fiesselmann, Gewald, Hinsberg, or Paal–Knorr reactions, whereas pyrroles are commonly prepared by protocols according to Knorr, Hantzsch, Piloty–Robinson, Madelung, Bischler–Möhlau, Nenitzescu, Brunner, and Graebe–Ullmann.[9] In recent years, organosulfur-[10] and trifluoromethyl-substituted[11] pyrroles and thiophenes received great attention. It is well-established that the incorporation of fluorine atoms into organic molecules leads to new and often superior biological, chemical, and physical properties that are highly desirable in pharmaceutical, agrochemical, and materials research and industry.[12] This dramatic influence originates from the high electronegativity, small volume, hydrophobicity, and small polarizability of the fluorine atom and from its very strong bond to carbon atoms.[13]

The activation of cyclopropane derivatives, strained three-membered rings, by suitable electron-donating and electron-withdrawing substituents in a vicinal relationship makes these compounds valuable building blocks in organic synthesis. After introducing the concept of donor–acceptor cyclopropanes,[14,15] our group and others reported a broad range of interesting reactions of this class of compounds. Recent efforts were devoted to [3 + 2] and [3 + 3] cycloadditions; however, many reactions with nucleophiles, electrophiles, or radicals are also feasible.[16] In this context, Lewis acid mediated cycloadditions of donor–acceptor cyclopropanes affording five-membered heterocycles have been described.[17,18]

We demonstrated that deprotonation of alkyl 2-siloxycyclopropanecarboxylates and reaction of the generated ester enolates with carbon disulfide or aryl isothiocyanates provides substituted thiophene[19] or pyrrole[20] derivatives in a one-pot fashion. The crucial step of this transformation was an

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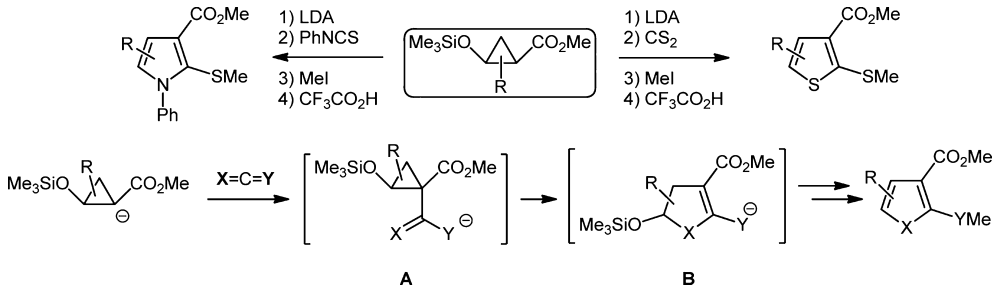
Scheme 1. One-Pot Transformations of Alkyl 2-Siloxycyclopropanecarboxylates Yielding Pyrroles and Thiophenes



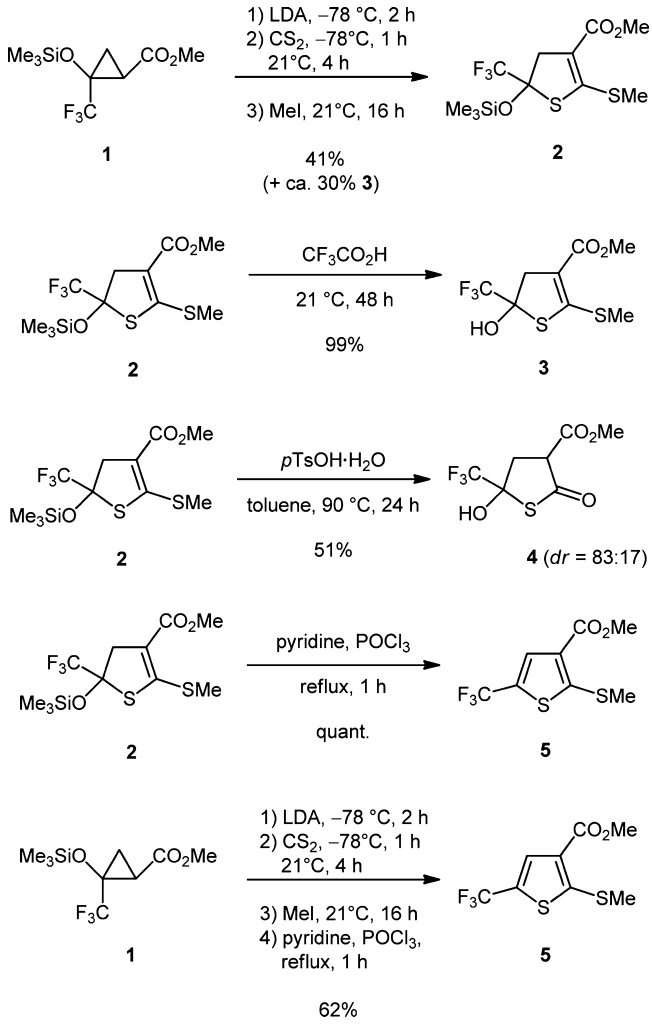
unexpected ring-enlargement of cyclopropane intermediates **A**; this anionic [1,3] sigmatropic rearrangement occurred already at −78 °C to provide thia- or azacyclopentene derivatives **B** (Scheme 1). S-Methylation and subsequent acid-mediated elimination of trimethylsilanol afforded the aromatic heterocycles. In this context, a theoretical study of [1,3] sigmatropic rearrangements of vinylcyclopropanes and heteroanalogues was published.[21] In addition, rearrangements of substituted donor−acceptor cyclopropanes forming furan,[22a,b] thiophene,[22c] as well as pyrrole[22d,e] derivatives were reported and the susceptibility of certain donor−acceptor cyclopropanes for rearrangements was studied.[22f] Examples of ring-expansion of donor−acceptor cyclopropanes affording other heterocycles were also reported.[23]

Although perfluoroalkyl- and perfluoroaryl-substituted silyl enol ethers are considerably less nucleophilic,[24a] the corresponding donor−acceptor cyclopropanes were easily accessible by rhodium-catalyzed reactions with methyl diazoacetate.[24b] Their subsequent deprotonation with lithium diisopropylamide also proceeded smoothly, leading, after C-1 alkylation with alkyl halides, to substituted derivatives. The ring-opening of these cyclopropanes, either in situ or directly, afforded valuable γ-oxo esters that were isolated or immediately converted into perfluoroalkylated or perfluoroarylated lactones and pyridazinones in good yields.[24b,c] We envisioned that heterocycles with fluorinated substituents should be accessible by reaction of the corresponding ester enolates with appropriate heterocumulenes, analogously to the transformations depicted in Scheme 1, if the crucial ring-enlargement also proceeds in the presence of the strongly electron-withdrawing perfluorinated moieties. These substituents could also hamper the final elimination of trimethylsilanol, and hence, it was not obvious whether conditions to overcome these issues could be established.

RESULTS AND DISCUSSION

First, we turned our attention to the preparation of thiophene derivatives by deprotonation of 2-trifluoromethyl-substituted siloxycyclopropane **1** and reaction with carbon disulfide. Deprotonation of **1** with lithium diisopropylamide and sequential addition of carbon disulfide and methyl iodide afforded the desired dihydrothiophene **2** in 41% yield (Scheme 2). Along with **2**, the corresponding desilylated thiophene derivative **3** was obtained in approximately 30% yield, but it could not be easily purified. We, therefore, explored conditions to convert dihydrothiophene **2** into desilylated compound **3** or to induce elimination to compound **5**. Treatment of **2** with tetra-*n*-butylammonium fluoride afforded a complex product mixture. However, trifluoroacetic acid smoothly desilylated dihydrothiophene derivative **2** and provided the corresponding 5-hydroxy-substituted compound **3** in excellent yield. On the other hand, under harsh conditions employing *p*-toluenesulfonic acid monohydrate at 90 °C, the thioacetal moiety of **2** was hydrolyzed to give thiolactone **4** in 51% yield as a mixture of diastereomers. Moreover, elimination to thiophene **5** did not occur even if the reaction of **2** with trifluoroacetic acid was performed in refluxing toluene. This process seems to require harsher conditions compared to the examples published before.[19] Gratifyingly, phosphoryl chloride in boiling pyridine[25] enabled the elimination and converted compound **2** into the desired thiophene derivative **5** in quantitative yield. At lower temperatures or with Eaton's reagent (methanesulfonic acid/

Scheme 2. Preparation of Dihydrothiophene 2 and Subsequent Elimination Affording Trifluoromethyl-Substituted Thiophene Derivative 5



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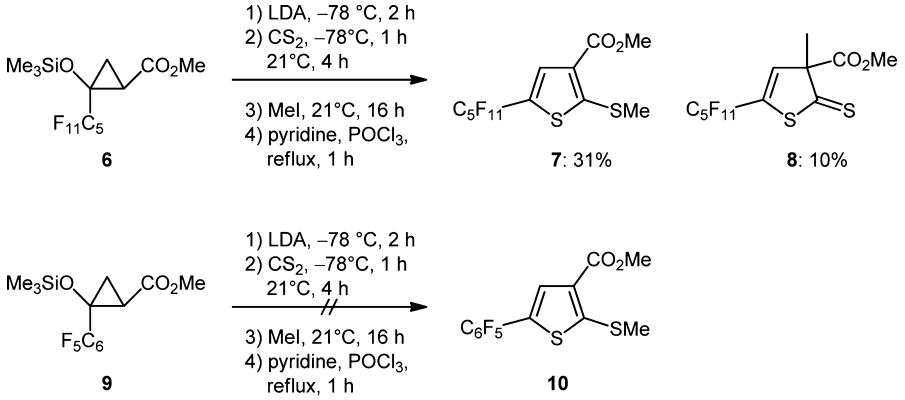
Scheme 3. Influence of Other Perfluorinated Substituents of Siloxycyclopropanes on the Preparation of Thiophene Derivatives



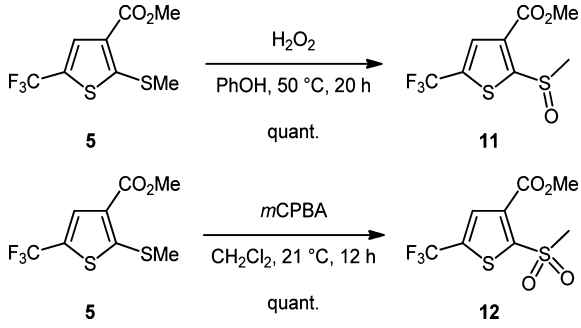
P_2O_5),[26] no dehydration occurred. After having established these conditions, we performed all four steps in a one-pot fashion and obtained thiophene derivative **5** in 62% overall yield.

Since we could show earlier that perfluoropentyl- and perfluorophenyl-substituted cyclopropanecarboxylates could successfully be deprotonated and alkylated,[24c] we were also interested in the preparation of thiophene derivatives with these substituents. When 2-perfluoropentylcyclopropane **6** was subjected to the optimized one-pot procedure, the desired thiophene derivative **7** was isolated in 31% yield. Unexpectedly, the C-alkylated product **8** was also obtained in 10% yield, although analogous compounds were never detected in the reactions of trifluoromethyl-substituted siloxycyclopropane **1**. Surprisingly, a complex product mixture was obtained when 2-perfluorophenylcyclopropane **9** was subjected to the procedure, and the desired thiophene derivative **10** was not isolated (Scheme 3). Different conditions during the deprotonation/addition reaction did not give other results. At the moment, we can only speculate about the moderate regioselectivity of alkylation in the case of **6** and the failure of substrate **9** in providing the expected product.

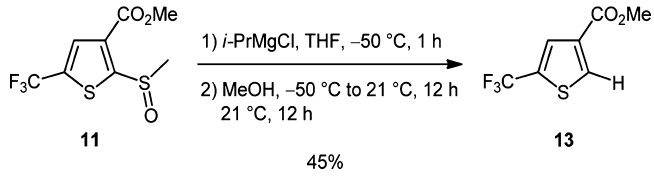
The methylthio group of compounds such as **5** and **7** should allow various transformations leading to new functional groups. Compounds with a sulfinyl moiety are biologically relevant compounds[27] and have also found various applications in organic synthesis.[28] However, selective oxidation of thio ethers to sulfoxides is challenging and frequently overoxidation to sulfones is observed.[29] Recently, Xu et al. reported the mild oxidation of aliphatic and aromatic thio ethers to sulfoxides using hydrogen peroxide in phenol.[30] Applying this method, we achieved selective oxidation of compound **5** to sulfinyl thiophene **11** in quantitative yield (Scheme 4). On the other hand, sulfonyl thiophene **12** was quantitatively generated from **5** by treatment with *m*-chloroperoxybenzoic acid (*m*CBPA). We also note that treatment of thio ether **5** with *N*-bromosuccinimide (NBS) in acetic acid also furnished sulfoxide **11** in high yield.[31]

Sulfoxides undergo facile exchange with Grignard reagents or alkyllithium reagents, and the resulting organometallic compounds readily react with different electrophiles.[32] Treatment of sulfinyl thiophene **11** with a slight excess of isopropylmagnesium chloride for 1 h at −50 °C generated the corresponding metalated thiophene intermediate that was quenched with methanol to afford the desulfinated thiophene **13** in 45% yield (Scheme 5).[33]

Scheme 4. Selective Oxidations of Methylthio-Substituted Thiophene Derivative 5 to the Corresponding Sulfinyl Thiophene 11 and Sulfonyl Thiophene 12



Scheme 5. Magnesation of Thiophene 11 by a Sulfoxide–Magnesium Exchange and Subsequent Protonation



The increased acidity of sulfones compared to sulfoxides allows smooth deprotonation of these compounds with amide bases.[34] Sulfonyl thiophene **12** was successfully deprotonated by 2 equiv of lithium diisopropylamide, and ring closure with the adjacent ester group afforded thienothiophene derivative **14** in 99% yield (Scheme 6). Because of the higher acidity of product **14** compared to that of precursor **12**, 2 equiv of base was required for complete transformation. To the best of our knowledge, this procedure represents a novel access to this scarcely explored compound class.[35,36] A first attempt to introduce an allyl substituent by addition of allyl bromide to the intermediate carbanion was not successful and gave a complex product mixture.

Thio ether moieties can act as leaving groups in transition-metal-catalyzed C–C coupling reactions. First reports by Takei et al. and Wenkert et al. involved a low-valent nickel catalyst and Grignard reagents that were later substituted by alkylzinc reagents.[37] Iron- and palladium-catalyzed versions have also been reported.[38] Liebeskind et al. and Guillaumet et al. reported efficient palladium-catalyzed copper(I)-promoted cross-couplings of functionalized heteroaromatic thio ethers with boronic acids and organostannanes.[39] We first attempted

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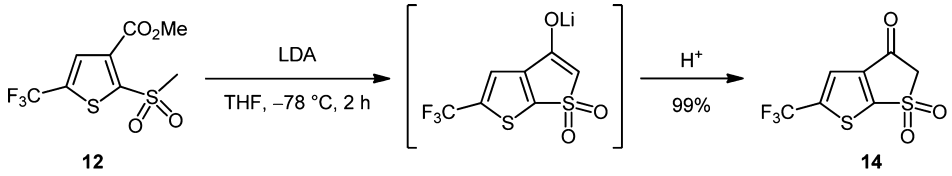
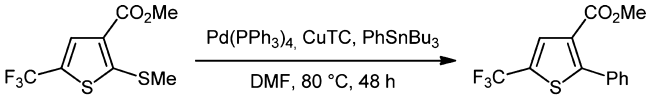
Scheme 6. Preparation of a Thienothiophene Derivative 14 by Deprotonation and Cyclization of Sulfonyl Thiophene 12



12 14

the Suzuki-type coupling of thiophene **5** with phenylboronic acid under the reported conditions (cat. $Pd(dba)_2$, trifurylphosphane, copper(I) 2-thiophenecarboxylate (CuTC), THF, 50 °C, 18 h), but the reaction was very sluggish and the desired coupling product **15** was isolated in only 10% yield.[40] We, therefore, turned our attention to a Stille coupling with phenyltributylstannane as the reaction partner. Gratifyingly, under these conditions, **5** was converted into **15** in 81% yield (Scheme 7); however, to achieve full conversion, the stannane

Scheme 7. Copper(I)-Mediated Stille-type Cross-Coupling of Thio Ether 5 with Phenyltributyltin Leading to Thiophene Derivative 15

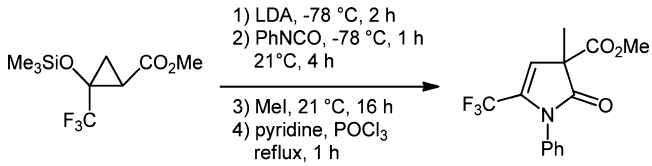


5 15

and the catalysts had to be added in two portions to the reaction mixture (for details, see the Experimental Section). The transformation was not accurately reproducible with yields ranging between 40% and 80%. The efficacy of the cross-coupling of **5** seems to be strongly dependent on the exact reaction conditions and the addition of reagents.[41,42] This example demonstrates that coupling reactions of thiophenes such as **5** should provide access to a variety of new compounds.[43]

Consequently, we were also interested in the analogous reactions of trifluoromethyl-substituted siloxycyclopropane **1** with other heterocumulenes in order to generate different heterocycles. Pyrrole derivatives can be obtained by Lewis acid promoted [3 + 2] cycloadditions of donor–acceptor cyclopropanes with nitriles.[18] We, therefore, investigated the reaction of cyclopropane **1** and benzonitrile under different reaction conditions, employing trimethylsilyl triflate or tin tetrachloride as Lewis acids. However, either complex product mixtures were obtained or the corresponding γ-oxo ester resulting from simple acid-induced ring-opening of **1** was isolated. Thus, we employed the route described in Scheme 1 and investigated the additions of enolates derived from cyclopropane **1** to nitrogen-containing heterocumulenes. In the reaction of deprotonated **1** with dicyclohexyl carbodiimide, followed by addition of methyl iodide, no pyrrole derivative was identified, and the analogous reaction employing ethyl isocyanate afforded a complex product mixture.[44] Gratifyingly, deprotonation of **1**, followed by addition of phenyl isocyanate and methyl iodide, selectively afforded the C-methylated γ-lactam derivative **16** in 50% yield (Scheme 8). The expected O-methylated compound could not be detected; methylation of the anionic intermediate derived from **1** and the isocyanate with methyl triflate did not influence the regioselectivity and afforded **16** in 25% yield.

Scheme 8. Synthesis of Trifluoromethyl-Substituted γ-Lactam 16



1 50% 16

Whereas the experiments with the two isocyanates indicate that the scope of this reaction is possibly limited, isothiocyanates behaved reliably as already shown in our studies with siloxycyclopropanes without perfluorinated substituents.[20] Deprotonation of compound **1** and successive treatment with phenyl isothiocyanate, methyl iodide, and pyridine/phosphoryl chloride afforded the desired pyrrole derivative **17a** in very good yield of 85% (Scheme 9). We investigated the substrate scope and performed the reactions with 3,5-bis(trifluoromethyl)phenyl and 4-methoxyphenyl isothiocyanate. The corresponding pyrroles **17b** and **17c** were isolated in 45% and 44% yield, respectively. It is not clear whether the electronic nature of the aryl substituents really influences the efficacies of the transformation. Interestingly, ethyl isothiocyanate provided a 87:13 mixture of the desired S-methylated pyrrole derivative **17d** and the C-alkylated thiolactam **18** in 74% yield. Cyclopropyl isothiocyanate afforded pyrrole **17e** in 63% yield, but with *t*-butyl isothiocyanate as electrophile, the expected pyrrole **17f** was not formed, possibly due to the steric bulk of the *t*-butyl group.

As observed with the thiophene derivatives, the thio ether moiety of pyrrole **17a** was quantitatively oxidized with hydrogen peroxide to give the corresponding sulfinyl pyrrole **19** or with *m*-chloroperoxybenzoic acid the sulfonyl pyrrole **20** (Scheme 10).[45]

We also investigated the metalation of pyrrole **19** by sulfoxide–magnesium exchange. Thus, treatment of sulfinyl pyrrole **19** with isopropylmagnesium chloride and protonation with methanol afforded desulfinated pyrrole **21** in 54% yield (Scheme 11).

Sulfonyl pyrrole **20** was successfully deprotonated by 2 equiv of lithium diisopropylamide, and ring closure with the adjacent ester group afforded thienopyrrole derivative **22** in very good yield (Scheme 12). To the best of our knowledge, there is only one literature report for the preparation of compounds with a similar SO_2 moiety, which provide access to unique functional materials.[46]

SUMMARY

One-pot procedures for the preparation of perfluoroalkyl-substituted thiophenes and pyrroles from the corresponding siloxycyclopropanes were established. Like their nonfluorinated analogues, ester enolates of 2-perfluoroalkyl-substituted cyclopropanes **1** and **6** readily added to carbon disulfide and the

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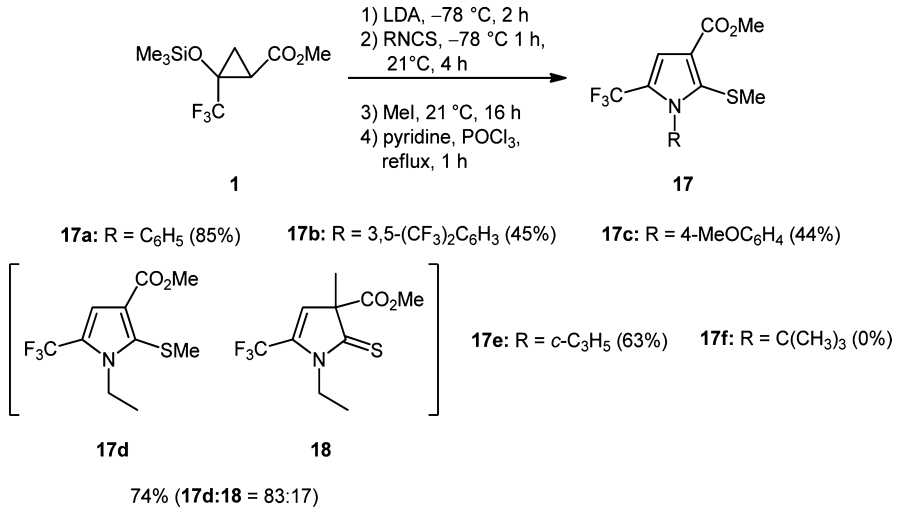
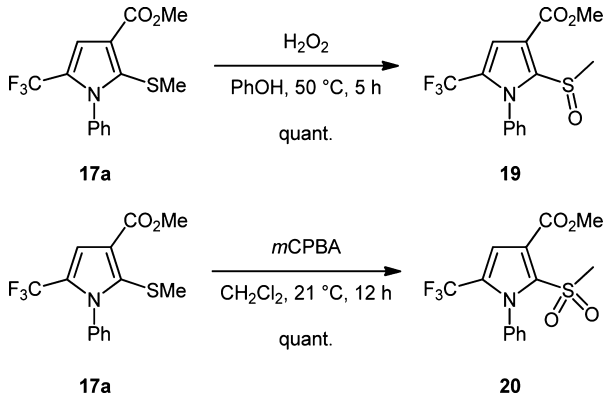
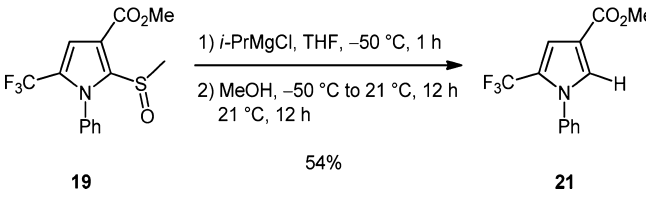
Scheme 9. Synthesis of Trifluoromethyl-Substituted Pyrrole Derivatives 17 and 18 by Variation of the Isothiocyanate



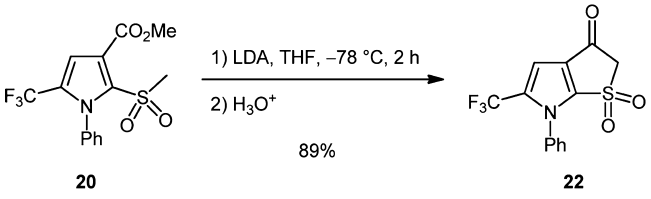
Scheme 10. Selective Oxidations of Trifluoromethyl-Substituted Pyrrole Derivative 17a to the Corresponding Sulfinyl Pyrrole 19 and Sulfonyl Pyrrole 20



Scheme 11. Conversion of Compound 19 into Pyrrole 21 by Sulfoxide–Magnesium Exchange and Subsequent Protonation



Scheme 12. Preparation of a Thienopyrrole Derivative 22 by Deprotonation of 20 and Subsequent Cyclization



resulting anionic intermediates underwent ring-expansion to afford the corresponding dihydrothiophenes. Because of the strong electron-withdrawing effect of the perfluoroalkyl moieties, dehydration of these intermediates occurred only under forcing conditions. Nevertheless, thiophene derivatives **5** and **7** were obtained in good overall yields, whereas the perfluorophenyl-substituted cyclopropane **9** did not afford the corresponding thiophene. Aryl and alkyl isothiocyanates also proved to be suitable electrophiles, which efficiently afforded 5-trifluoromethylpyrroles **17a–17e** with different substituents at the nitrogen atom. In exceptional cases, C-methylated instead of S-methylated isomers were obtained. The reaction of the enolate of **1** with phenyl isocyanate/methyl iodide afforded solely the C-methylation product **16**.

In explorative fashion, we investigated possible transformations of the prepared methylthio-substituted 5-trifluoromethylthiophene and -pyrrole derivatives. Oxidations of the methylthio moiety selectively produced sulfoxides **11** and **19** or sulfones **12** and **20** in excellent yields. Sulfoxide–magnesium exchange reactions furnished desulfinated products **13** and **21**. The sulfones could smoothly be cyclized to obtain thienothiophene **14** and thienopyrrole **22**, both belonging to scarcely explored classes of compounds. Trifluoromethyl-substituted thiophene derivative **5** was also coupled with phenyltributylstannane in a copper(I)-promoted Stille-type reaction. All of these transformations prove that compounds such as **5** and **17** allow the preparation of quite a number of different perfluoroalkyl-substituted heterocycles. In our approach, simple commercially available fluorinated compounds are the precursors.[47] This method nicely complements the common strategy for preparing perfluoroalkyl-substituted heterocycles by the late stage introduction of the appropriate fluorinated group, frequently by use of organometallic species.[48]

EXPERIMENTAL SECTION

General. Compounds **1**, **6**, and **9** were prepared according to literature procedures.[24b] Diisopropylamine was stored over solid NaOH for several days before being used; all other reagents were purchased and used without further purification. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon, and solvents were purified with an MB SPS-800-dry solvent system. Melting points were determined on a melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F [frequency calibrated lock with ±1 ppm deviation] NMR spectra were recorded on 250, 400, 500, and 700 MHz instruments in $CDCl_3$ solutions, and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane or the internal (NMR) solvent signals. $^{13}C\{^{19}F\}$ NMR spectra were recorded to enable correct assignment. The high-resolution mass

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spectra were obtained with an ESI-TOF spectrometer. Silica gel (0.040−0.063 mm) was used for column chromatography. IR spectra were recorded on an FT-IR spectrometer.

Methyl 2-(Methylthio)-5-(trifluoromethyl)-5-(trimethylsiloxy)-4,5-dihydrothiophene-3-carboxylate (2). A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 470 μL, 1.17 mmol) was added at −78 °C to a solution of diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), and the resulting mixture was stirred for 20 min. A solution of cyclopropane **1** (200 mg, 0.780 mmol) in THF (1 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. Carbon disulfide (149 mg, 1.95 mmol) was added, and stirring was continued for 1 h at −78 °C and for 4 h at 21 °C. After addition of methyl iodide (277 mg, 1.95 mmol), the mixture was stirred at 21 °C for 16 h, then diluted with Et_2O (100 mL) and sat. aqueous NH_4Cl solution (50 mL), and the phases were separated. The organic layer was washed with brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10−100% AcOEt in hexanes) to afford **2** (111 mg, 41%) as a yellow oil and an impure sample of **3** (75 mg, ∼30%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.56, 3.26 (2 d, J = 17.3 Hz each, 2H), 2.47 (s, 3H), 0.20 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 154.6, 123.7 (q, J_{CF} = 283 Hz), 112.6, 93.3 (q, J_{CF} = 31.9 Hz), 51.5, 47.2, 17.2, 1.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.0 (s) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{11}H_{17}F_3NaO_3S_2Si$ 369.0233; found 369.0262; IR (neat) ν 3050−2805 (C−H), 1700 (C═O), 1540, 1435 (C═C), 1315, 1250, 1175, 1120 (C−F) cm^{-1}. Anal. Calcd for $C_{11}H_{17}F_3O_3S_2Si$: C, 38.13; H, 4.95; S, 18.51. Found: C, 38.08; H, 5.03; S, 18.59.

Methyl 5-Hydroxy-2-(methylthio)-5-(trifluoromethyl)-4,5-dihydrothiophene-3-carboxylate (3). Thiophene derivative **2** (10 mg, 0.029 mmol) and trifluoroacetic acid (30 mg, 0.260 mmol) were stirred for 48 h at 21 °C. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (2 × 20 mL). The organic layer was washed with brine (20 mL), dried with Na_2SO_4, and concentrated under reduced pressure to afford **3** (7.8 mg, 99%) as a yellow solid. mp 105−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.57, 3.34 (2 d, J = 17.2 Hz each, 2H), 2.47 (s, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.0 (s) ppm.

Methyl 5-Hydroxy-2-oxo-5-(trifluoromethyl)tetrahydrothiophene-3-carboxylate (4). Thiophene derivative **2** (92 mg, 0.266 mmol) and *p*-toluenesulfonic acid monohydrate (56 mg, 0.292 mmol) were stirred in toluene (5 mL) for 24 h at 90 °C. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (2 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 20% AcOEt in hexanes) to afford **4** (33 mg, 51%) as a yellow oil. *d.r.* = 83:17; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_7H_7F_3NaO_4S$ 266.9909; found 266.9903; IR (neat) ν 3650−3110 (O−H), 2990−2830 (C−H), 1745, 1720 (C═O), 1285, 1180, 1120 (C−F) cm^{-1}.

Spectroscopic Data of the Major Diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 3.97 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 2.81 (dd, J = 8.0, 14.4 Hz, 1H), 2.67 (d, J = 14.4 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 170.8, 123.4 (q, J_{CF} = 283 Hz), 94.4 (q, J_{CF} = 32.8 Hz), 58.8, 54.7 (q, J_{CF} = 2.0 Hz), 36.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.3 (s) ppm.

Spectroscopic Data of the Minor Diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 4.16 (dd, J = 7.0, 12.4 Hz, 1H), 3.82 (s, 3H), 2.91 (dd, J = 12.4, 13.3 Hz, 1H), 2.68 (dd, J = 7.0, 13.3 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 166.9, 123.5 (q, J_{CF} = 282 Hz), 90.3 (q, J_{CF} = 33.3 Hz), 56.5, 53.4 (q, J_{CF} = 1.4 Hz), 36.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.1 (s) ppm.

Methyl 2-(Methylthio)-5-(trifluoromethyl)thiophene-3-carboxylate (5). *From Thiophene 2.* Thiophene derivative **2** (50 mg, 0.144 mmol) was dissolved in pyridine (3 mL), $POCl_3$ (165 mg, 1.07 mmol) was added, and the solution was heated to reflux for 1 h. The heating bath was replaced by an ice bath, and after dilution with Et_2O (20 mL), water (1 mL) was added carefully by syringe to quench the excess of $POCl_3$. The mixture was further diluted with Et_2O (50 mL) and washed with aqueous 1 M HCl (50 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to afford **5** (37 mg, quant.) as a yellow solid. mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (q, J_{HF} = 1.2 Hz, 1H), 3.88 (s, 3H), 2.62 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.0, 156.9, 131.0 (q, J_{CF} = 3.9 Hz), 126.2 (q, J_{CF} = 39.5 Hz), 125.1, 121.9 (q, J_{CF} = 269 Hz), 52.0, 18.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.8 (d, J_{FH} = 1.2 Hz) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_8H_7F_3NaO_2S_2$ 278.9732; found 278.9722; IR (neat) ν 3180−2835 (═C−H, C−H), 1710 (C═O), 1550, 1450, 1425 (C═C), 1295, 1240, 1195, 1150, 1120 (C−F) cm^{-1}. Anal. Calcd for $C_8H_7F_3O_2S_2$: C, 37.49; H, 2.75; S, 25.02. Found: C, 37.50; H, 2.79; S, 25.09.

From Cyclopropane 1. A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 230 μL, 0.585 mmol) was added at −78 °C to a solution of diisopropylamine (59 mg, 0.585 mmol) in THF (590 μL), and the resulting mixture was stirred for 20 min. A solution of cyclopropane **1** (100 mg, 0.390 mmol) in THF (1 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. Carbon disulfide (74 mg, 0.98 mmol) was added, and stirring was continued for 1 h at −78 °C and for 4 h at 21 °C. After addition of methyl iodide (138 mg, 0.975 mmol), the mixture was stirred at 21 °C for 16 h. The mixture was diluted with both Et_2O (100 mL) and sat. aqueous NH_4Cl solution (100 mL), and the phases were separated. The organic layer was washed with brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine (3 mL), $POCl_3$ (420 mg, 2.70 mmol) was added, and the solution was heated to reflux for 1 h. The heating bath was replaced by an ice bath, and after dilution with Et_2O (10 mL), water (1 mL) was added carefully via syringe to quench the excess of $POCl_3$. The reaction mixture was further diluted with Et_2O (100 mL), and the soluble parts were decanted from the remaining black slurry. This ether solution was washed with aqueous 1 M HCl (100 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% AcOEt in hexanes) to afford **5** (62 mg, 62%) as a pale yellow solid. Larger scale experiments with 1−2 g of cyclopropane **1** afforded **5** in yields ranging between 55% and 60%.

Methyl 2-(Methylthio)-5-(perfluoropentyl)thiophene-3-carboxylate (7) and Methyl 3-Methyl-5-(perfluoropentyl)-2-thioxo-2,3-dihydrothiophene-3-carboxylate (8). A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 460 μL, 1.15 mmol) was added at −78 °C to a solution of diisopropylamine (116 mg, 1.15 mmol) in THF (1.20 mL), and the resulting mixture was stirred for 20 min. A solution of cyclopropane **6** (350 mg, 0.77 mmol) in THF (2 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. Then, carbon disulfide (88 mg, 1.15 mmol) was added, and stirring was continued for 1 h at −78 °C and for 4 h at 21 °C. After addition of methyl iodide (272 mg, 1.92 mmol), the mixture was stirred at 21 °C for 16 h. The mixture was diluted with both Et_2O (100 mL) and sat. aqueous NH_4Cl solution (100 mL), and the phases were separated. The organic layer was washed with brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine (5 mL), $POCl_3$ (823 mg, 5.37 mmol) was added, and the solution was heated to reflux for 1 h. The heating bath was replaced by an ice bath, and after dilution with Et_2O (15 mL), water (2 mL) was added carefully via syringe to quench the excess of $POCl_3$. The reaction mixture was further diluted with Et_2O (150 mL), and the soluble parts were decanted from the remaining black slurry. This ether solution was washed with aqueous 1 M HCl (150 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 7% AcOEt in hexanes) to afford **7** (109 mg, 31%) as a brown solid and **8** (32 mg, 10%) as a brown oil.

Analytical Data of 7. mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 3.87 (s, 3H), 2.62 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 158.0 (t, J_{CF} = 1.3 Hz), 132.7 (t, J_{CF} = 6.0 Hz), 125.6, 124.2 (t, J_{CF} = 29.9 Hz), 117.3 (tq, J_{CF} = 33.1 Hz, 289 Hz), 114.3, 110.8, 110.6, 108.6 (4 m_c), 52.0, 18.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.7 (t, J = 9.7 Hz, 3F), −101.8 (t, J = 13.9 Hz, 2F), −121.7, −122.2, −126.2 (3 m_c, 6F) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{12}H_7F_{11}NaO_2S_2$ 478.9604; found 478.9625; IR (neat)

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ν 3185−2840 (=C−H, C−H), 1700 (C=O), 1540, 1445, 1420 (C=C), 1230, 1190, 1140 (C−F) cm^{-1}. Anal. Calcd for $C_{12}H_7F_{11}O_2S_2$: C, 31.59; H, 1.55; S, 14.05. Found: C, 31.89; H, 1.61; S, 13.74.

Analytical Data of ***8***. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J_{HF} = 1.0 Hz, 1H); 3.86 (s, 3H); 2.62 (s, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.7, 160.9, 140.8 (t, J_{CF} = 34.6 Hz), 116.3 (t, J_{CF} = 3.5 Hz), 117.4, 114.0, 111.0, 110.7, 110.6, 108.6 (5 m_c), 52.0, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.7 (t, J = 8.6 Hz, 3F), −111.4 (t, J = 11.2 Hz, 2F), −122.7, −126.1 (2 m_c) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{12}H_7F_{11}NaO_2S_2$ 478.9604; found 478.9623; IR (neat) ν 3120−2800 (=C−H, C−H), 1720 (C=O), 1600, 1515 (C=C), 1230, 1200, 1140, 1105 (C−F) cm^{-1}.

Methyl 2-(Methylsulfinyl)-5-(trifluoromethyl)thiophene-3-carboxylate (11). Thiophene derivative **5** (46 mg, 0.180 mmol), phenol (507 mg, 5.39 mmol), and hydrogen peroxide (30% in water, 24 mg, 0.72 mmol) were stirred at 50 °C for 20 h. The mixture was diluted with AcOEt (80 mL) and washed with sat. aqueous Na_2SO_3 solution (2 × 50 mL). The organic layer was washed with 10% aqueous NaOH solution (2 × 50 mL) and brine (50 mL). Drying with Na_2SO_4 and removal of the solvent afforded **11** (49 mg, quant.) as a pale yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m_c, 1H), 3.91 (s, 3H), 3.03 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 161.6, 134.5 (q, J_{CF} = 39.5 Hz), 130.7 (q, J_{CF} = 3.7 Hz), 129.1, 121.5 (q, J_{CF} = 270 Hz), 52.9, 44.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.4 (s) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_8H_7F_3NaO_3S_2$ 294.9681; found 294.9679; IR (neat) ν 3160−2785 (=C−H, C−H), 1710 (C=O), 1550, 1465 (C=C), 1290, 1240, 1125, 1060 (C−F, S=O) cm^{-1}.

Methyl 2-(Methylsulfonyl)-5-(trifluoromethyl)thiophene-3-carboxylate (12). To a solution of thiophene derivative **5** (50 mg, 0.195 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C *m*CPBA (144 mg, 0.585 mmol), and the resulting suspension was stirred at 21 °C for 12 h. The mixture was diluted with CH_2Cl_2 (80 mL) and washed with sat. aqueous $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 25% AcOEt in hexanes) to afford **12** (56 mg, quant.) as a colorless solid. mp 68−70 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (q, J_{HF} = 0.9 Hz, 1H), 3.95 (s, 3H), 3.53 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 151.0 (q, J_{CF} = 1.2 Hz), 135.9 (q, J_{CF} = 39.9 Hz), 133.7, 131.9 (q, J_{CF} = 3.6 Hz), 121.1 (q, J_{CF} = 271 Hz), 53.3, 44.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.5 (s) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_8H_7F_3NaO_4S_2$ 310.9630; found 310.9616; IR (neat) ν 3075−2760 (=C−H, C−H), 1730 (C=O), 1555, 1465, 1370 (C=C), 1300, 1245, 1125, 1015 (C−F, SO_2) cm^{-1}.

Methyl 5-(Trifluoromethyl)thiophene-3-carboxylate (13). Isopropylmagnesium chloride (2.0 M in THF, 110 μL, 0.220 mmol) was added dropwise at −50 °C to a stirring solution of sulfinyl thiophene **11** (20 mg, 0.073 mmol) in THF (2 mL). The resulting solution was stirred for 1 h, and then methanol (50 μL, 1.24 mmol) was added. The reaction mixture was warmed to 21 °C within 12 h and stirred for an additional 12 h. This mixture was diluted with Et_2O (50 mL) and washed with water (50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 10% AcOEt in hexanes) to afford **13** (7 mg, 45%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 1.4 Hz, 1H), 7.85 (m_c, 1H), 3.88 (s, 3H) ppm. The NMR data are in agreement with literature data.[49]

5-(Trifluoromethyl)thieno[2,3-*b*]thiophen-3(2*H*)-one 1,1-Dioxide (14). A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 170 μL, 0.434 mmol) was added at −78 °C to a solution of diisopropylamine (44 mg, 0.434 mmol) in THF (440 μL), and the resulting mixture was stirred for 20 min. A solution of sulfonyl thiophene **12** (50 mg, 0.173 mmol) in THF (2 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. Upon addition of **12**, the reaction mixture turned yellow and eventually wine red. The reaction mixture was diluted with AcOEt (100 mL) and sat. aqueous NH_4Cl solution (50 mL), and the phases were separated. The organic layer was washed with brine (30 mL) and dried with Na_2SO_4. Removal of all volatile components *in vacuo* afforded **14** (44 mg, 99%) as a yellow solid. mp 140−142 °C; ^1H NMR (400 MHz, $CDCl_3$:CD_2Cl_2 = 10:1) δ 7.72 (q, J_{HF} = 1.1 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$:CD_2Cl_2 = 10:1) δ 179.8, 159.5, 146.8, 143.3 (q, J_{CF} = 40.0 Hz), 122.3 (q, J_{CF} = 3.7 Hz), 121.3 (q, J_{CF} = 272 Hz), 64.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$:CD_2Cl_2 = 10:1) δ −57.1 (s) ppm; HRMS (ESI-TOF) $[M - H]^-$ calcd for $C_7H_2F_3O_3S_2$ 254.9403; found 254.9413; IR (neat) ν 3150−2770 (=C−H, C−H), 1730 (C=O), 1540 (C=C), 1325, 1290, 1210, 1140 (C−F, SO_2) cm^{-1}.

Methyl 2-Phenyl-5-(trifluoromethyl)thiophene-3-carboxylate (15). Thiophene derivative **5** (50 mg, 0.195 mmol), $Pd(PPh_3)_4$ (11 mg, 9.76 μmol), and copper(I) thiophene-2-carboxylate (48 mg, 0.254 mmol) were placed in a flask, and after flushing with argon, degassed DMF (5 mL) and tributylphenyltin (86 mg, 0.234 mmol) were added. The mixture was stirred at 80 °C for 8 h. Then, another portion of tributylphenyltin (86 mg, 0.234 mmol) was added, and stirring was continued for 14 h. Then, $Pd(PPh_3)_4$ (11 mg, 9.76 μmol) was added, and after an additional 14 h, copper(I) thiophene-2-carboxylate (48 mg, 0.254 mmol) was added. The mixture was then stirred at 21 °C for 12 h. The reaction mixture was diluted with AcOEt (80 mL) and washed with sat. aqueous $NaHCO_3$ (80 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 5% AcOEt in hexanes) to afford **15** (45 mg, 81%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (q, J_{HF} = 1.2 Hz, 1H), 7.54−7.39 (m, 5H), 3.76 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 154.4, 131.8, 131.3 (q, J_{CF} = 3.9 Hz), 129.9, 129.7, 128.4, 129.6 (q, J_{CF} = 39.6 Hz), 127.6, 122.0 (q, J_{CF} = 269 Hz), 52.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.9 (s) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_9F_3NaO_2S$ 309.0168; found 309.0194; IR (neat) ν 3160−2765 (=C−H, C−H), 1730 (C=O), 1560, 1470, 1400 (C=C), 1295, 1260, 1210, 1125 (C−F) cm^{-1}.

Methyl 3-Methyl-2-oxo-1-phenyl-5-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (16). A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 470 μL, 1.17 mmol) was added at −78 °C to a solution of diisopropylamine (120 mg, 1.17 mmol) in THF (1.20 mL), and the resulting mixture was stirred for 20 min. A solution of cyclopropane **1** (200 mg, 0.781 mmol) in THF (1 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. Then, phenyl isocyanate (140 mg, 1.17 mmol) was added, and stirring was continued for 1 h at −78 °C and for 4 h at 21 °C. After addition of methyl iodide (277 mg, 1.95 mmol), the mixture was stirred at 21 °C for 16 h. The mixture was diluted with both Et_2O (100 mL) and sat. aqueous NH_4Cl solution (100 mL), and the phases were separated. The organic layer was washed with brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine (4 mL), $POCl_3$ (838 mg, 5.47 mmol) was added, and the solution was heated to reflux for 1 h. The heating bath was replaced by an ice bath, and after dilution with Et_2O (10 mL), water (1 mL) was added carefully via syringe to quench the excess of $POCl_3$. The reaction mixture was further diluted with Et_2O (100 mL), and the soluble parts were decanted from the remaining black slurry. This ether solution was washed with aqueous 1 M HCl (100 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% AcOEt in hexanes) to afford **16** (116 mg, 50%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.19 (m, 5H), 6.00 (q, J_{HF} = 1.5 Hz, 1H), 3.79 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (q, J_{CF} = 1.0 Hz), 168.4 (q, J_{CF} = 1.2 Hz), 136.1 (q, J_{CF} = 37.5 Hz), 133.7, 129.5, 129.4, 128.4, 118.9 (q, J_{CF} = 271 Hz), 114.1 (q, J_{CF} = 5.0 Hz), 56.2, 53.5, 19.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.4 (s) ppm; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{12}F_3NNaO_3$ 322.0661; found 322.0669; IR (neat) ν 3190−2750 (=C−H, C−H), 1750, 1730 (C=O), 1485, 1400 (C=C), 1240, 1175, 1135, 1110 (C−F) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_3$: C, 56.19; H, 4.04; N, 4.68. Found: C, 56.18; H, 4.15; N, 4.73.

General Procedure for the One-Pot Synthesis of Pyrroles 17a−17e and 18. A 1 M LDA solution was freshly prepared: *n*-BuLi

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(2.5 M in hexanes, 1.5 equiv) was added at −78 °C to a solution of diisopropylamine (1.5 equiv) in THF, and the resulting mixture was stirred for 20 min. A THF solution of cyclopropane **1** (1.0 equiv) was added, and the reaction mixture was stirred for 2 h at −78 °C. The corresponding isothiocyanate (1.5 equiv) was added, and stirring was continued for 1 h at −78 °C and for 4 h at 21 °C. After addition of methyl iodide (2.5 equiv), the mixture was stirred at 21 °C for 16 h. The mixture was diluted with both Et_2O and sat. aqueous NH_4Cl solution, and the phases were separated. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in pyridine, $POCl_3$ (7.0 equiv) was added, and the solution was heated to reflux for 1 h. The heating bath was replaced by an ice bath, and after dilution with Et_2O, water was added carefully by syringe to quench the excess of $POCl_3$. The reaction mixture was further diluted with Et_2O, and the soluble parts were decanted from the remaining black slurry. This ether solution was washed with aqueous 1 M HCl and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the pure product.

Methyl 2-(Methylthio)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (17a). According to the general procedure, *n*-BuLi (470 μL, 1.17 mmol) and diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), cyclopropane **1** (199 mg, 0.778 mmol), phenyl isothiocyanate (158 mg, 1.17 mmol), methyl iodide (276 mg, 1.94 mmol), pyridine (3 mL), and $POCl_3$ (835 mg, 5.44 mmol) afforded **17a** (208 mg, 85%) as an orange solid. mp 78−80 °C; eluent 15% AcOEt in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.45 (m, 3H), 7.27, 7.25 (2 m$_o$, 2H), 7.18 (q, J_{HF} = 0.6 Hz, 1H), 3.89 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 136.5 (q, J_{CF} = 1.9 Hz), 136.3, 129.8, 128.9, 128.7, 124.4 (q, J_{CF} = 38.8 Hz), 120.1 (q, J_{CF} = 268 Hz), 118.5, 114.1 (q, J_{CF} = 3.5 Hz), 51.6, 19.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.9 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{12}F_3NNaO_2S$ 338.0433; found 338.0438; IR (neat) ν 3190−2775 (=C−H, C−H), 1715 (C=O), 1560, 1500, 1475, 1420 (C=C), 1255, 1220, 1150, 1115, 1055 (C−F) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_2S$: C, 53.33; H, 3.84; N, 4.44; S, 10.17. Found: C, 53.33; H, 3.86; N, 4.43; S, 10.15.

Methyl 1-[3,5-Bis(trifluoromethyl)phenyl]-2-(methylthio)-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (17b). According to the general procedure, *n*-BuLi (470 μL, 1.17 mmol) and diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), cyclopropane **1** (200 mg, 0.781 mmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (317 mg, 1.17 mmol), methyl iodide (277 mg, 1.95 mmol), pyridine (3 mL), and $POCl_3$ (838 mg, 5.47 mmol) afforded **17b** (158 mg, 45%) as an orange oil; eluent 15% AcOEt in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06, 7.75 (2 s, 3H), 7.24 (q, J_{HF} = 0.7 Hz, 1H), 3.91 (s, 3H), 2.32 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 137.8, 136.7 (q, J_{CF} = 2.0 Hz), 132.9 (q, J_{CF} = 34.5 Hz), 129.4 (q, J_{CF} = 2.8 Hz), 124.5 (q, J_{CF} = 39.2 Hz), 123.9, 123.8 (2 q, J_{CF} = 3.7 Hz each), 122.9 (q, J_{CF} = 272 Hz), 119.86 (q, J_{CF} = 269 Hz), 119.86, 115.1 (q, J_{CF} = 3.5 Hz), 51.8, 19.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.6 (s, 3F), −62.8 (s, 6F) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{16}H_{10}F_9NNaO_2S$ 474.0181; found 474.0192; IR (neat) ν 3150−2790 (=C−H, C−H), 1725 (C=O), 1565, 1470 (C=C), 1280, 1250, 1175, 1120, 1060 (C−F) cm^{-1}. Anal. Calcd for $C_{16}H_{10}F_9NO_2S$: C, 42.58; H, 2.23; N, 3.10; S, 7.10. Found: C, 42.22; H, 2.30; N, 3.45; S, 7.01.

Methyl 1-(4-Methoxyphenyl)-2-(methylthio)-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (17c). According to the general procedure, *n*-BuLi (470 μL, 1.17 mmol) and diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), cyclopropane **1** (200 mg, 0.781 mmol), 4-methoxyphenyl isothiocyanate (194 mg, 1.17 mmol), methyl iodide (277 mg, 1.95 mmol), pyridine (3 mL), and $POCl_3$ (838 mg, 5.47 mmol) afforded **17c** (119 mg, 44%) as a yellow oil; eluent 5% AcOEt in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−6.96 (m, 5H), 3.883, 3.879 (2 s, 6H), 2.28 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 160.4, 136.8 (q, J_{CF} = 2.0 Hz), 129.7, 128.9, 124.6 (q, J_{CF} = 38.5 Hz), 120.1 (q, J_{CF} = 268 Hz), 118.3, 114.04, 113.95 (q, J_{CF} = 3.6 Hz), 55.5, 51.6, 19.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.1 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{15}H_{14}F_3NNaO_3S$ 368.0539; found 368.0533; IR (neat) ν 3215−2775 (=C−H, C−H), 1720 (C=O), 1560, 1475 (C=C), 1255, 1220, 1150, 1115, 1055 (C−F) cm^{-1}. Anal. Calcd for $C_{15}H_{14}F_3NO_3S$: C, 52.17; H, 4.09; N, 4.06; S, 9.29. Found: C, 52.44; H, 3.92; N, 4.12; S, 8.90.

Methyl 1-Ethyl-2-(methylthio)-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (17d) and Methyl 1-Ethyl-3-methyl-2-thioxo-5-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (18). According to the general procedure, *n*-BuLi (470 μL, 1.17 mmol) and diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), cyclopropane **1** (200 mg, 0.781 mmol), ethyl isothiocyanate (102 mg, 1.17 mmol), methyl iodide (277 mg, 1.95 mmol), pyridine (3 mL), and $POCl_3$ (838 mg, 5.47 mmol) afforded a mixture of **17d** and **18** (155 mg, 74%, **17d**:**18** = 83:17); eluent 5% AcOEt in hexanes; separation of the mixture by HPLC (silica gel, 3% AcOEt in hexanes) afforded **17d** (95 mg, 45%) and **18** (17 mg, 8%), both as yellow oils.

*Analytical Data of **17d**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (q, J_{HF} = 0.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.47 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 134.4 (q, J_{CF} = 2.0 Hz), 122.2 (q, J_{CF} = 38.8 Hz), 120.6 (q, J_{CF} = 267 Hz), 114.1 (q, J_{CF} = 3.8 Hz), 51.4, 41.2 (q, J_{CF} = 1.5 Hz), 19.7, 16.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.3 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{10}H_{12}F_3NNaO_2S$ 290.0433; found 290.0444; IR (neat) ν 3100−2800 (=C−H, C−H), 1720 (C=O), 1560, 1480 (C=C), 1240, 1210, 1110, 1060 (C−F) cm^{-1}. Anal. Calcd for $C_{10}H_{12}F_3NO_2S$: C, 44.94; H, 4.53; N, 5.24; S, 12.00. Found: C, 44.91; H, 4.45; N, 5.53; S, 11.87.

*Analytical Data of **18**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (q, J_{HF} = 1.5 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 1.59 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 167.7 (q, J_{CF} = 1.0 Hz), 136.8 (q, J_{CF} = 37.9 Hz), 122.4 (q, J_{CF} = 4.9 Hz), 119.0 (q, J_{CF} = 270 Hz), 67.2, 53.6, 41.5 (q, J_{CF} = 1.7 Hz), 23.2 (q, J_{CF} = 0.8 Hz), 11.6 (q, J_{CF} = 1.2 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.7 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{10}H_{12}F_3NNaO_2S$ 290.0433; found 290.0440; IR (neat) ν 3180−2760 (=C−H, C−H), 1750 (C=O), 1450 (C=C), 1230, 1185, 1130, 1055 (C−F) cm^{-1}.

Methyl 1-Cyclopropyl-2-(methylthio)-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (17e). According to the general procedure, *n*-BuLi (470 μL, 1.17 mmol) and diisopropylamine (118 mg, 1.17 mmol) in THF (1.20 mL), cyclopropane **1** (199 mg, 0.778 mmol), cyclopropyl isothiocyanate (116 mg, 1.17 mmol), methyl iodide (277 mg, 1.95 mmol), pyridine (3 mL), and $POCl_3$ (838 mg, 5.47 mmol) afforded **17e** (138 mg, 63%) as a yellow oil; eluent 15% AcOEt in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (q, J_{HF} = 0.8 Hz, 1H), 3.82 (s, 3H), 3.14 (tt, J = 4.6, 6.8 Hz, 1H), 2.48 (s, 3H), 1.26−1.15 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 137.9 (q, J_{CF} = 2.0 Hz), 124.6 (q, J_{CF} = 32.6 Hz), 121.2 (q, J_{CF} = 268 Hz), 117.7, 114.6 (q, J_{CF} = 4.2 Hz), 51.4, 28.7, 19.3, 8.9 (q, J_{CF} = 2.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.8 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{11}H_{12}F_3NNaO_2S$ 302.0433; found 302.0432; IR (neat) ν 3200−2785 (=C−H, C−H), 1720 (C=O), 1560, 1475 (C=C), 1255, 1220, 1190, 1160, 1150, 1115, 1060 (C−F) cm^{-1}. Anal. Calcd for $C_{11}H_{12}F_3NO_2S$: C, 47.31; H, 4.33; N, 5.02; S, 11.48. Found: C, 47.26; H, 4.29; N, 5.17; S, 11.53.

Methyl 2-(Methylsulfinyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (19). Pyrrole derivative **17a** (20 mg, 0.064 mmol), phenol (179 mg, 1.90 mmol), and hydrogen peroxide (30% in water, 29 mg, 0.254 mmol) were stirred at 50 °C for 5 h. The mixture was diluted with AcOEt (80 mL) and was washed with sat. aqueous Na_2SO_3 solution (2 × 50 mL). The organic layer was washed with 10% aqueous NaOH solution (2 × 50 mL) and brine (50 mL). Drying with Na_2SO_4, removal of the solvent, and filtration (silica gel, 30% then 50% AcOEt in hexanes) afforded **19** (21 mg, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.30 (m, 5H), 7.17 (s, 1H), 3.89 (s, 3H), 3.01 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 140.8 (q, J_{CF} = 1.4 Hz), 135.0, 130.5, 129.0, 128.9, 128.8, 128.1, 126.7 (q, J_{CF} = 38.7 Hz), 119.8 (q, J_{CF} = 269 Hz), 117.1, 114.0 (q, J_{CF} = 3.3 Hz), 52.2, 44.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$)

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δ −57.8 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{12}F_3NNaO_3S$ 354.0382; found 354.0402; IR (neat) ν 3220−2760 (=C−H, C−H), 1715 (C=O), 1560, 1485, 1420 (C=C), 1225, 1125, 1045 (C−F, S=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_3S$: C, 50.75; H, 3.65; N, 4.23; S, 9.68. Found: C, 50.78; H, 3.78; N, 4.02; S, 11.51.

Methyl 2-(Methylsulfonyl)-1-phenyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (20). To a solution of pyrrole derivative **17a** (50 mg, 0.159 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C *m*CPBA (117 mg, 0.476 mmol), and the resulting suspension was stirred at 21 °C for 12 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aqueous $NaHCO_3$ solution (3 × 50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 30% AcOEt in hexanes) to afford **20** (55 mg, quant.) as a colorless solid. mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.30 (2 m, 5H), 7.13 (s, 1H), 3.91 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 134.7 (q, J_{CF} = 1.6 Hz), 135.3, 130.4, 128.8, 128.2, 127.1 (q, J_{CF} = 38.9 Hz), 121.0, 119.4 (q, J_{CF} = 269 Hz), 113.5 (q, J_{CF} = 3.3 Hz), 52.7, 45.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{12}F_3NNaO_4S$ 370.0331; found 370.0351; IR (neat) ν 3160−2775 (=C−H, C−H), 1730 (C=O), 1560, 1490, 1430, 1365 (C=C), 1320, 1235, 1125, 1055 (C−F, SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_4S$: C, 48.41; H, 3.48; N, 4.03; S, 9.23. Found: C, 48.43; H, 3.64; N, 3.75; S, 9.77.

Methyl 1-Phenyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (21). Isopropylmagnesium chloride (2.0 M in THF, 230 μL, 0.453 mmol) was added dropwise at −50 °C to a stirring solution of sulfinyl pyrrole **19** (50 mg, 0.151 mmol) in THF (2 mL). The resulting solution was stirred for 1 h, and then methanol (50 μL, 1.24 mmol) was added. The reaction mixture was slowly warmed to 21 °C and stirred for an additional 12 h. This mixture was diluted with Et_2O (50 mL) and washed with water (50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 10% AcOEt in hexanes) and subsequent HPLC (silica gel, 4% AcOEt in hexanes) to afford **21** (22 mg, 54%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.34 (m, 6H), 7.14 (s, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 138.2, 131.3 (q, J_{CF} = 1.8 Hz), 129.5, 129.4, 126.5, 123.6 (q, J_{CF} = 39.0 Hz), 120.5 (q, J_{CF} = 268 Hz), 116.0, 113.7 (q, J_{CF} = 3.5 Hz), 51.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.9 (s) ppm; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{13}H_{10}F_3NaNO_2$ 292.0556; found 292.0578; IR (neat) ν 3175−2805 (=C−H, C−H), 1720 (C=O), 1570, 1500, (C=C), 1270, 1235, 1120, (C−F) cm^{-1}.[50]

6-Phenyl-5-(trifluoromethyl)-2*H*-thieno[2,3-*b*]pyrrol-3(6*H*)-one 1,1-Dioxide (22). A 1 M LDA solution was freshly prepared: *n*-BuLi (2.5 M in hexanes, 100 μL, 0.250 mmol) was added at −78 °C to a solution of diisopropylamine (26 mg, 0.259 mmol) in THF (260 μL), and the resulting mixture was stirred for 20 min. A solution of sulfonyl thiophene **12** (36 mg, 0.104 mmol) in THF (2 mL) was added, and the reaction mixture was stirred for 2 h at −78 °C. The yellow reaction mixture was diluted with AcOEt (60 mL) and sat. aqueous NH_4Cl solution (20 mL), and the phases were separated. The organic layer was washed with brine (20 mL) and dried with Na_2SO_4. Removal of all volatile components *in vacuo* afforded **22** (29 mg, 89%) as a orange solid. mp 135−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m_c, 5H), 7.03 (s, 1H), 4.33 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 148.7 (q, J_{CF} = 1.3 Hz), 134.2, 133.2 (q, J_{CF} = 40.0 Hz), 131.2, 130.0, 128.7, 126.5 (q, J_{CF} = 1.1 Hz), 119.1 (q, J_{CF} = 270 Hz), 106.5 (q, J_{CF} = 3.6 Hz), 65.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.3 (s) ppm; HRMS (ESI-TOF) [M − H]$^-$ calcd for $C_{13}H_7F_3NO_3S$ 314.0104; found 314.0103; IR (neat) ν 3160−2800 (=C−H, C−H), 1725 (C=O), 1545, 1500 (C=C), 1330, 1200, 1180, 1135 (C−F, SO_2) cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H-, ^{13}C-, and ^{19} F-NMR spectra for compounds **2**−**5**, **7**, **8**, **11**, **12**, and **14**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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