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Thiophilic nucleophilic trifluoromethylation of α-substituted dithioesters. Access to *S*-trifluoromethyl ketene dithioacetals and their reactivity with electrophilic species

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ABSTRACT

The nucleophilic trifluoromethylation of dithioesters bearing a nucleofugal group in α-position, using CF_3TMS under fluoride activation, afforded unprecedented *S*-CF_3 ketene dithioacetals via a domino process thiophilic trifluoromethylation–β-elimination. The best results were obtained with non-enolisable α-carbamoyloxydithioesters. The higher homologues *S*-C_2F_5 ketene dithioacetals were prepared by a similar way. These new dithioacetals react with methylating reagents quantitatively and chemoselectively at sulfur to give stable dimethylsulfonium type salts. They react more classically with triflic acid, protonation taking place at the β-carbon to give a dithiolium salt, characterized in solution but non-isolable.

Research topic

Fluorine Chemistry at the university of Reims

The group from Reims became involved in fluorine chemistry around 1985. Our interest was focused on methodologies in organofluorine chemistry, sometimes turned towards specific applications in the framework of cooperation with industrial companies (building blocks (BB) of pharmaceutical interest, surfactants). The main research topics have been:

- *Fluorine associated with other heteroelements*
  (i) F & Si. Taking advantage of the high reciprocal affinity of these two elements to develop new multistep one pot transformations, in particular from reaction of acylsilanes and organometallic reagents (R_FLi, R_FMgI, R_FSiMe_3). Key BBs in this field: perfluoroenoxysilanes, which are both nucleophilic and electrophilic. Applications: *gem*-difluoro terpenes, difluoro-*C*-glycosides, *vic*-F,R_F-heterocycles, difluoromethyl derivatives.
  (ii) F & S. Taking advantage of the versatility of sulfur (various oxidation states, low polarizability…). Key BBs in this field: perfluoroketene dithioacetals and perfluorodithiocarboxylic acid derivatives. Main applications: synthesis of a wide variety of trifluoromethylated heterocycles via γ-keto-α-R_F-thiolesters, α-R_F-succinic derivatives…

- *Perfluoroalkylation*
  Radical and nucleophilic *F*-alkylation using R_FI and R_FTMS were used for well defined applications: synthesis of highly fluorinated compounds, of *C*-trifluoromethylated sugars or more generally of multifunctionalized fluorinated derivatives.

- *Quaternary CF_3-containing BBs*
  (i) Synthesis of enantiopure trifluoromethylated BBs from tartaric acid based substrates.
  (ii) Development of new CF_3-cyclopentane difunctionalized BBs.

1. Introduction

Due to the high polarizability of sulfur, sulfur containing organic compounds exhibit a versatile chemistry. Thus both carbophilic and thiophilic addition can be observed on thiocarbo-

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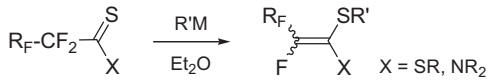


Scheme 1. *S*-alkylation of perfluorodithioacid derivatives.

nyl compounds as well as on dithiocarboxylic derivatives [1]. The strong withdrawing character of fluorine allows perfluorothiocarboxylic derivatives to react selectively with organometallics at sulfur, with subsequent fluoride β-elimination. We have thus developed a closely related chemistry of perfluoroketene dithioacetals and perfluorodithioesters or, more generally, perfluorothiocarboxylic derivatives (Scheme 1) [2]. These studies were focused on the addition of non-fluorinated reagents on fluorinated substrates [3]. More recently we reported that nucleophilic trifluoromethylation of perfluorodithioesters occurs also at sulfur as the first step of a domino process where the corresponding *S*-CF_3 perfluoroketene dithioacetal is the first intermediate [4].

To complete these studies we have investigated the behavior of non-fluorinated substrates bearing in α-position a nucleofugal group under nucleophilic trifluoromethylation conditions with the expectation that a similar sequence *S*-addition–β-elimination would give an unprecedented *S*-CF_3 ketene dithioacetal (Scheme 2). The properties of such a new intermediate of course would deserve to be explored. We report herein the results of this study.

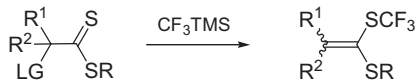
2. Results and discussion

2.1. Preconditions

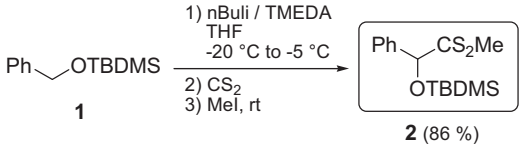
Regarding the model substrates for this study, we have chosen α-phenyl dithioacetic esters type derivatives, considering that a phenyl substituent would stabilize the postulated ketene dithioacetal and possible further intermediates for reactivity study. Trifluoromethyl(trimethyl)silane (TFMTMS), already assessed as a thiophilic reagent on perfluorodithioesters [4] and widely used in this laboratory, was systematically used for nucleophilic trifluoromethylation experiments. Extension to pentafluoroethyl(trimethyl)silane (PFETMS) was also considered. The leaving group should have the property to favor the chain transfer in a reaction performed under nucleophilic initiation.

2.2. Synthesis of substrates

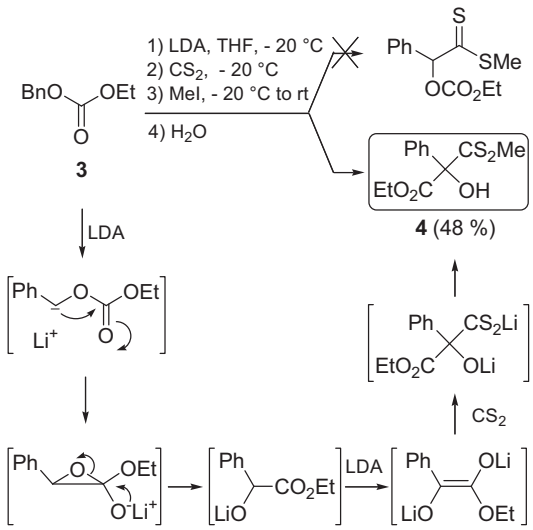
In a first approach, α-*t*-butyl(dimethyl)silyl (TBDMS) dithioester **2** was prepared from silyl ether **1**, with a good yield of 86% (Scheme 3).[3] Ethoxycarbonyloxyl group was a second possible leaving group, since the corresponding ethoxide resulting from its decarboxylation would constitute an excellent transfer reagent to activate TFMTMS. The corresponding carbonate **3** was submitted



Scheme 2. Purpose: *S*-trifluoromethylation of α-substituted dithioesters.



Scheme 3. Synthesis of α-*t*-butyl(dimethyl)silyloxy dithioester **2**.



Scheme 4. Synthesis of dithioester **4** via a rearrangement of a lithiated carbonate.

to a similar reaction sequence, giving the unexpected rearranged dithioester **4**, the structure of which was confirmed by X-Ray diffraction analysis [6] (Scheme 4 and Fig. 1).

Compound **4** is the result of a Chan type rearrangement [7] occurring at the intermediate carbanion stage, followed by a second deprotonation prior to reaction with carbon disulfide (Scheme 4). Such a rearrangement, discovered with acyloxyacetates, was reported later from carbonate derivatives [8]. This transformation required two equivalents of LDA, which is consistent with such a mechanism. The selectivity in the final methylation at sulfur is coherent in terms of HSAB correlation.

To avoid this rearrangement, we decided to synthesize a carbamate derivative (Scheme 5). Starting from benzylcarbamate **5**, the desired carbamate **6** was obtained in a poor yield using LDA as a base. Changing LDA for *sec*-butyl lithium/TMEDA [9] afforded, from a complex reaction mixture, the dithioketene **7**, indicating that the deprotonation and further transformation of **6** is the limiting factor of this synthesis. To circumvent this side reaction, we turned to α-alkyl substituted compounds. 1-Phenylethyl and 1-phenylpropyl dimethylcarbamates **8a**,**b** were easily prepared. They were deprotonated according to conditions previously described [10] and converted in high yields into the desired dithioesters **9a**,**b** (Scheme 6). The latter were obtained in high purity after the simple filtration of their dichloromethane solution through a pad of silicagel and solvent removal.

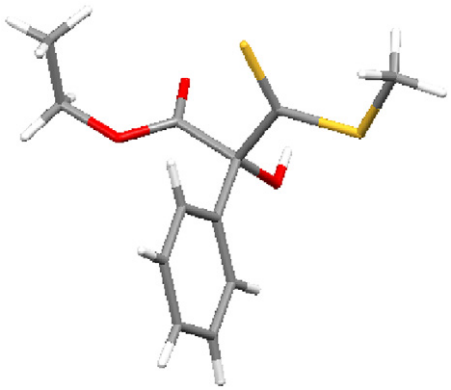
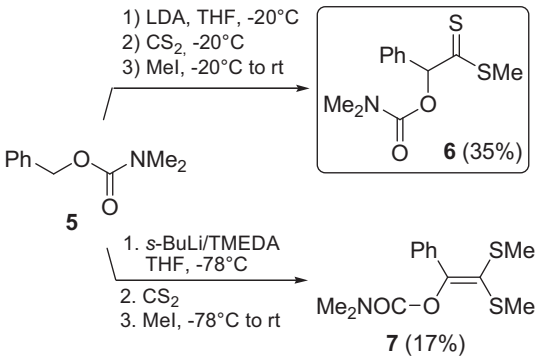
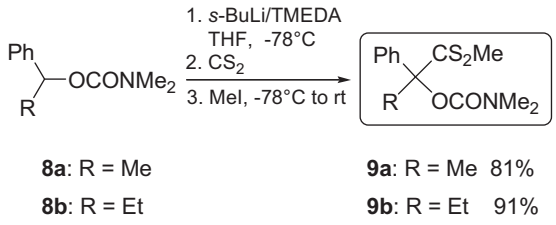


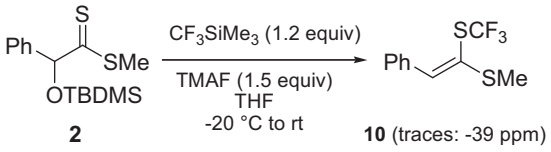
Fig. 1. Structure of **4** from X-ray analysis.



Scheme 5. Synthesis of α-carbamoyloxy dithioester **6**.



Scheme 6. Synthesis of α-alkyl-α-carbamoyloxy dithioesters **9**.



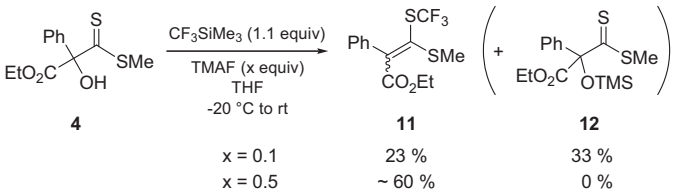
Scheme 7. Reaction of α-*t*-butyl(dimethyl)silyl dithioester **2** with CF_3TMS.

2.3. S-perfluoroalkylation of dithioesters

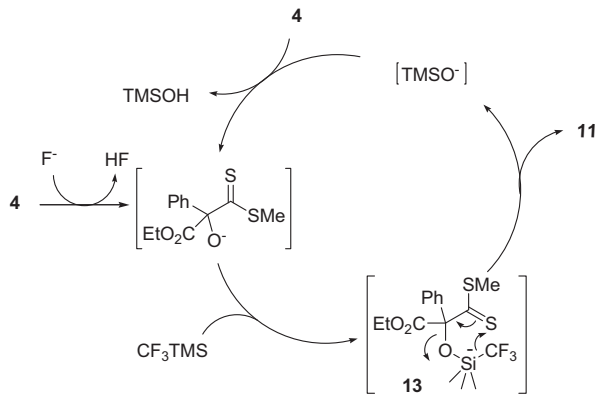
We have now a variety of dithioesters bearing a leaving group in α position to submit them to nucleophilic trifluoromethylation (pefluoroalkylation) conditions. As mentioned above, TFMTMS was a reagent of choice for such a purpose, as was pentafluoroethyl(-trimethyl)silane (PFETMS) for an extension to the higher homologue.

The α-OTBDMS dithioester **2** was treated in THF with TFMTMS and tetramethylammonium fluoride (TMAF) as initiator. No reaction was observed when using a catalytic amount (0.1 equiv.) of TMAF. With an excess of TMAF (1.5 equiv.), a complex reaction took place with total conversion of **2**. A weak signal at −39 ppm in the ^{19}F NMR spectrum of the complex crude mixture indicates the presence of an *S*-CF_3 moiety, thus probably of traces of the expected ketene dithioacetal **10** (Scheme 7). We assume that TMAF acts also as a base which can deprotonate the substrate and lead to its degradation.

The reaction of the dithiomalonic derivative **4** under the same conditions is more interesting (Scheme 8). The results also depend



Scheme 8. Reaction of α-hydroxy dithioester **4** with CF_3TMS.

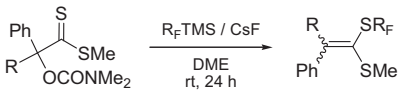


Scheme 9. Proposed chain mechanism for *S*-trifluoromethylation of **4**.

on the stoichiometry of TMAF, but a catalytic amount of TMAF (0.1 equiv.) is enough for a complete conversion of the substrate, giving the expected ketene dithioacetal **11** (two diastereomers) and the compound **12** which corresponds to the silyl ether of the substrate. The selectivity towards **11** was improved when the reaction was activated with 0.5 equiv. of TMAF, but it could not be separated from an unidentified trifluromethylated by-product exhibiting a CF_3 signal at −60.8 ppm. The transformation corresponds formally to an hydroxide β-elimination subsequent to the thiophilic trifluoromethylation, but the initiation of the reaction proceeds probably by a prior deprotonation of **4**, the resulting alkoxide being the actual anionic activator of TFMTMS. The TFM transfer possibly occurs via an intramolecular way through intermediate **13** (Scheme 9).

As observed for their preparation, the reactivity of carbamate derivatives depends on the degree of substitution of the α carbon. Reaction of **6** with TFMTMS led to partial conversion and a complex mixture, using either TMAF or CsF as initiator, and THF or dimethoxyethane (DME) as solvent. At the best, a small signal at −39 ppm disclosed the possible presence of traces of the *S*-CF_3 ketene dithioacetal when the reaction was performed at −20 °C. In contrast clean and total conversion of compounds **9** containing a quaternary α carbon was observed under CsF activation in DME, and the corresponding ketene dithioacetals **14** were isolated in high yields (Scheme 10). The efficiency of the reaction prompted us to extend it to PFETMS reagent. Indeed the *S*-C_2F_5 ketene dithioacetals **15** were isolated in high yields (Scheme 10).

Compounds **14** and **15** were isolated as a mixture of diastereomers which, in spite of their very low polarity, could be separated by flash chromatography using petroleum ether as eluent. *E* configuration was assigned to the major isomer of **15a** by NOESY analysis (Fig. 2). The ^1H NMR spectrum of this major isomer exhibits SMe protons at higher field (2.2 vs 2.4 ppm), which allows to determine the *E*/*Z* ratio for the set of analogues.



R_F	R	Product	%Yied (E/Z)
CF_3	Me	**14a**	79 (82/18)
CF_3	Et	**14b**	91 (87/13)
C_2F_5	Me	**15a**	83 (86/14)
C_2F_5	Et	**15b**	90 (88/12)

Scheme 10. Reaction of α-carbamoyloxy dithioesters **9** with CF_3TMS or C_2F_5TMS.

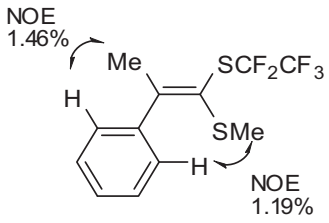


Fig. 2. NOE measurement on compound **15a** (major isomer).

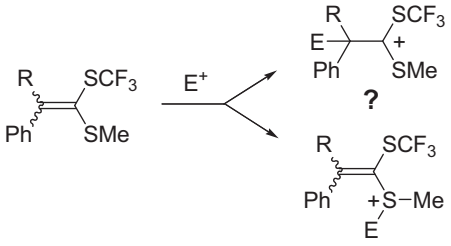


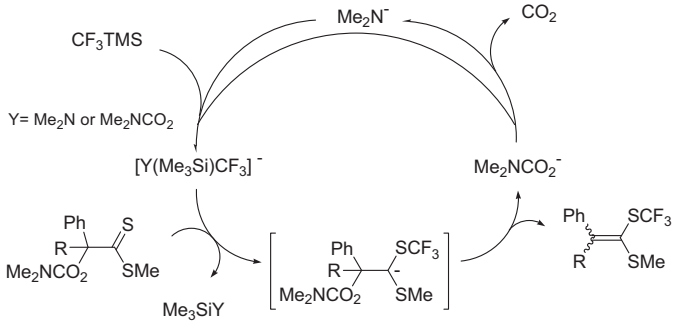
Fig. 3. Possible reactions of *S*-CF_3 ketene dithioacetals with electrophiles.

This reaction worked effectively with less than 20 mol% of CsF, confirming the role of the latter as initiator of a chain reaction where the carbamoyloxy group proved to be an excellent chain transfer agent. However, it is difficult to discriminate the actual chain transfer agent between the carbamoyloxy group itself or the dimethylamide moiety resulting from decarboxylation (Scheme 11).

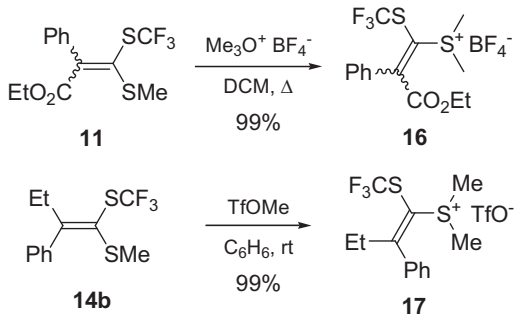
2.4. Reaction of S-CF_3 ketene dithioacetals with some electrophiles

This new type of ketene dithioacetal bearing an *S*-CF_3 moiety seemed to us of great interest, in particular regarding their nucleophilic behavior towards protonation or reaction with carbon electrophiles (Fig. 3). The presence of the TFM group on sulfur might change significantly the chemoselectivity. Indeed, the usual electrophilic attack on β carbon favored by sulfur stabilizing the resulting carbocation might be prevented by the presence of the strong withdrawing character of TFM. On the other hand reaction at β carbon would give a dithiolium salt which could be a source of electrophilic TFM, thus would represent a new system to reverse the polarity of TFMTMS [11].

Treatment of the dithioacetal **11** with triflic acid led to an intractable mixture. Compound **11** did not react with dimethylsulfate, but gave stable salt when treated in dichloromethane with trimethyloxonium tetrafluoroborate. Methylation occurred exclusively at sulfur to give quantitatively the dimethylsulfonium salt derivative **16** (Scheme 12). A similar reaction took place when



Scheme 11. Proposed chain mechanism for *S*-trifluoromethylation of α-carbamoyloxydithioesters.



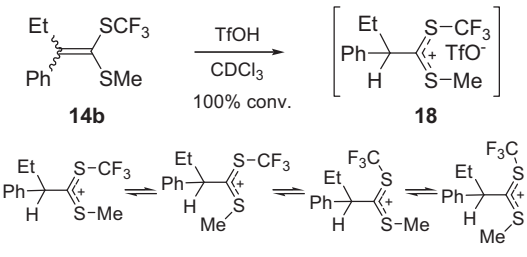
Scheme 12. Methylation of ketene dithioacetal **11** and **14b**.

compound **11** was treated with methyl triflate. The salt **16** proved to be stable and no rearrangement was observed even after heating in acetonitrile. Similarly, compound (*E*)-**14b** was converted quantitatively into the corresponding dimethylsulfonium salt **17** on reaction with methyl triflate (Scheme 12). Thus the reaction is totally chemoselective, *S*-methylation being preferred to β-*C*-methylation. As for the exclusive formation of the dimethylsulfonium salts, this selectivity is less surprising because of the weak nucleophilicity of the *S*-CF_3 moiety.

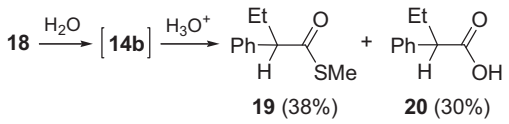
In contrast to methylation reaction, reaction of **14b** with triflic acid led to the β-protonated salt **18** (Scheme 13). This salt is stable enough in DCM or chloroform solution but could not be isolated. Its structure was confirmed by NMR analysis. After the addition of 3 equivalents of triflic acid to a $CDCl_3$ solution of **14b**, the signals of the starting compound disappeared and a double set of new signals was observed. The NMR spectra exhibit the same set of signals for reaction of the pure isomer (*E*)-**14b** or of the mixture of stereoisomers. The ^{19}F NMR spectrum displays two singlets of *S*-CF_3 groups at −35.7 and −40.0 ppm in a 55:45 ratio. This ratio is confirmed in the ^1H NMR spectrum for (i) signals corresponding to the quaternary proton, which appeared as two doublets of doublets in the 4.9 ppm region (coupling with non-equivalent CH_2 protons); (ii) for SMe (two singlets at 3.5 and 3.3 ppm). The cationic character of the dithiolium moiety is confirmed by a signal at 247 ppm in the ^{13}C NMR spectrum. The double set of signals observed may be explained by a geometric type isomerism, with two major configurations among the four ones presented in Scheme 13.

Compound **14b** was recovered after treatment with trifluoroacetic acid. The same is true of its treatment with trifluoroacetic anhydride and triflic anhydride. This inertness could be actually due to an equilibrium in favor of the reversed reaction.

The salt **18** can be considered itself as a super acid as it gave back its proton to compounds as weakly basic as phenol, tolylmercaptan, triphenylphosphine or ethyl acetoacetate. The ketene dithioacetal **14b** was recovered, as a 1:1 mixture of *E*,*Z*-isomers, on the addition of any of these compounds to a chloroform solution of **18**. The addition of water to **18** affords the thiol ester **19** and the corresponding acid **20**, the expected products of acid



Scheme 13. Reaction of the ketene dithioacetal **14b** with triflic acid.



Scheme 14. Hydrolysis of ketene dithioacetal **14b**.

hydrolysis of the ketene dithioacetal **14b** resulting from proton transfer to water (Scheme 14).

3. Conclusion

We have described the reactions of α-substituted dithioesters with TFMTMS under fluoride activation. A domino process thiophilic trifluoromethylation–β-elimination afforded new *S*-CF_3 ketene dithioacetals via a chain mechanism. The best results were obtained with a carbamoyloxy leaving group and substrates non-bearing hydrogen in α-position. The transformation worked with PFETMS as well. These dithioacetals react quantitatively with methylating reagents exclusively at sulfur to give stable dimethylsulfonium type salts. Their chemoselectivity is more classical with triflic acid, protonation taking place at β-carbon to give a dithiolium salt, well characterized in solution but non-isolable.

4. Experimental

4.1. General remarks

THF was distilled from sodium-benzophenone. CH_2Cl_2 was dried with $CaCl_2$ and distilled over CaH_2. Tetramethylethylenediamine (TMEDA) was freshly distilled prior used. Dried TMAF was prepared by the dehydration of TMAF·$4H_2O$ [12]. Silicagel (Macherey-Nagel GmbH & Co KG – 40–63 μm, ASTM for column chromatography) was used for flash chromatography. Preparative centrifugal thin-layer chromatography was carried out on rotors coated with silica gel 60 PF_{254} containing gypsum, the layer thickness was 1 mm. NMR spectra were recorded, at frequencies of 250 MHz for ^1H, 235.3 MHz for ^{19}F and 62.9 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. In the ^{13}C NMR data, reported signal multiplicities are related to C–F coupling. The following abbreviations are used to indicate the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet). Elemental analyses were performed on a Perkin-Elmer CHN 2400 apparatus and analyses fell within ±0.4% of the calculated values. HRMS were recorded on a Micromass ESI-Q-TOF mass spectrometer using an electrospray source in positive mode (ESI^+). GC–MS data were obtained on a Trace MS Thermoquest apparatus at 70 eV in the electron impact mode.

4.2. Precursors of starting dithioesters

Benzyloxy(*t*-butyl)dimethylsilane **1** was prepared according to the literature [13]. The carbonate **3** was prepared according to a reported procedure [14]. The carbamates **5**, **8a** and **8b** were prepared by treatment of the corresponding benzyl alcohol with dimethylcarbamoyl chloride in pyridine according to a reported procedure [9]. Compounds **5** [9] and **8a** [15] were already described.

4.2.1. 1-Phenylpropyl dimethylcarbamate (8b)

Yield: 92%. Oil, bp 85 °C (2 mbar). ^1H NMR ($CDCl_3$): δ 7.29 (5H, m, Ph), 5.58 (1H, t, *J* = 6.5 Hz, CH–O), 2.97 (3H, br s, NCH_3), 2.89 (3H, br s, NCH_3), 1.87 (2H, m, $C\underline{H}_2CH_3$), 0.89 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$). GC–MS 70 eV, *m*/*z* (rel. int.): 207 [M^+] (1), 118 [M−Me_2NCO_2H] (74), 117 (100), 115 (50), 91 (60).

4.3. Methyl 2-t-butyl(dimethylsilyl)-2-phenyethaneldithioate (2)

To a solution of silylether **1** (1 g, 4.5 mmol) in THF (15 mL) were added successively, at −20 °C and under Ar, TMEDA (2.04 mL, 13.5 mmol, 3 equiv.) and *n*-BuLi (1.8 M in hexanes, 7.5 mL, 13.5 mmol, 3 equiv.). After 4 h of stirring from −20 °C to −5 °C, CS_2 (1.35 mL, 22.5 mmol, 5 equiv.) was added. After 1 h 45 min of stirring from −5 °C to 0 °C, MeI (1.4 mL, 22.5 mmol, 5 equiv.) was added and the stirring was continued for 15 h at rt. The reaction was then diluted with ether and quenched with sat. aq. NH_4Cl. The ethereal layer was extracted, washed successively with H_2O and brine, dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (PE) to afford **2** (1.2 g, 86%) as a solid. ^1H NMR ($CDCl_3$): δ 7.35–7.10 (5H, m, Ph), 6.65 (1H, s, CH-CS_2), 2.58 (3H, s, SCH_3), 0.94 (9H, s, $C(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), −0.11 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 216.1 (CS_2), 139.4 (C *ipso*), 128.4 (2 CH arom), 126.5 (CH *para*), 126.2 (2 CH arom), 79.7 (CH–O), 26.9 ($C(\underline{C}H_3)_3$), 19.3 (SCH_3), 17.1 ($\underline{C}(CH_3)_3$), −7.1 ($SiCH_3$), −8.4 ($SiCH_3$). Anal. calcd for $C_{15}H_{25}OS_2Si$: C, 57.64; H, 7.74. Found: C, 57.72; H, 7.73.

4.4. Methyl 2-hydroxy-2-ethoxycarbonyl-2-phenylethanedithioate (4)

To a solution of diisopropylamine (2.34 mL, 16.66 mmol, 2 equiv.) in THF (30 mL) was added dropwise, at −20 °C and under Ar, *n*-BuLi (2.5 M in hexanes, 6.7 mL, 16.66 mmol, 2 equiv.). After 20 min of stirring at this temperature, the carbonate **3** (1.5 g, 8.33 mmol) was added to the reaction mixture followed by CS_2 (1 mL, 3.18 mmol, 1.1 equiv.) after 20 min of supplementary stirring. After 1 h of supplementary stirring from −20 °C to −5 °C, MeI (1.04 mL, 16.66 mmol, 2 equiv.) was added and the stirring was continued for 4 h at rt. The reaction was diluted with ether and quenched with HCl 1 N. The ethereal layer was extracted, was washed successively with H_2O, sat. aq. $NaHCO_3$ and brine, was dried on $MgSO_4$ and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (PE:EtOAc 95:5) to afford an orange solid **4** (1.07 g, 48%). A single crystal was obtained from ether for X-ray analysis. ^1H NMR ($CDCl_3$): δ 7.73 (2H, m, Ph), 7.38 (3H, m, Ph), 5.12 (1H, s, OH), 4.32 (2H, m, $C\underline{H}_2CH_3$), 2.61 (3H, m, SCH_3), 1.31 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 238.5 (CS_2), 170.5 (CO), 137.6 (C *ipso*), 128.8 (CH *para*), 127.9 (2 CH arom), 127.4 (2 CH arom), 88.3 (C–OH), 63.2 (CH_2O), 20.7 (SCH_3), 13.9 ($CH_2\underline{C}H_3$). ESMS *m*/*z* 293.01 [M+Na]$^+$.

4.5. Methyl 2-(dimethylcarbamoyloxy)-2-phenylethanedithioate (6)

To a solution of diisopropylamine (446 μL, 3.18 mmol, 1.1 equiv.) in THF (7 mL) was added at −20 °C and under Ar, *n*-BuLi (2.34 M in hexanes, 1.36 mL, 3.18 mmol, 1.1 equiv.). After 20 min of stirring at this temperature, the carbamate **5** (600 mg, 2.89 mmol) in solution of THF (3 mL) was added to the reaction mixture followed by CS_2 (191 μL, 3.18 mmol, 1.1 equiv.) after 30 min of supplementary stirring. After 1 h of supplementary, MeI (270 μL, 4.33 mmol, 1.5 equiv.) was added and the stirring was continued for 1 h at rt. The reaction was diluted with ether and quenched with HCl 1 N. The ethereal layer was extracted, was washed with sat. aq. $NaHCO_3$ and brine, was dried on $MgSO_4$ and the solvent was evaporated. The residue was purified by

[3] We have also prepared silyl ethers with different substitution pattern on silicon but their metallation was more problematic: desilylation for TMS derivative; low reactivity for TIPS derivative.

chromatography on SiO_2 (PE:EtOAc 80:20) to afford **6** (300 mg, 35%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, m, Ph), 7.41 (3H, m, Ph), 6.92 (1H, s, CH–O), 3.33 (4H, m, 2 C$\underline{H}_2$CH$_3$), 2.58 (3H, s, SCH$_3$), 1.11 (3H, t, J = 7.0 Hz, CH$_2$C$\underline{H}_3$), 1.08 (3H, t, J = 7.0 Hz, CH$_2$–C$\underline{H}_3$).

4.6. Methyl 2-(dimethylcarbamoyloxy)-2-phenylpropanedithioate (9a)

In a three neck flask, under argon, were introduced carbamate **8a** (3.86 g, 0.02 mol), anhydrous THF (150 mL) and TMEDA (2.4 g, 0.021 mol, 1.05 equiv.). After cooling to −78 °C, *s*-BuLi (1.4 M in cyclohexane, 16 mL, 0.022 mol, 1.1 equiv.) was added slowly. The resulting mixture turned to deep yellow and was kept at −78 °C for 5 min. CS_2 (1.4 mL, 0.023 mol, 1.15 equiv.) was added over 1 min, with a color turning to deep red. Finally methyl iodide (1.4 mL, 0.023 mol, 1.15 equiv.) was added, giving an orange mixture. The cooling bath was removed (a precipitate appeared at −25 °C) and the reaction mixture was left under stirring overnight. The mixture was partitioned between water (100 mL) and ether (150 mL). Ethereal solution was washed with water (3× 50 mL), then with brine (2× 75 mL), dried and concentrated, giving an almost pure product (^{1}H NMR) as an orange oil. Final flash chromatography on silicagel (CH_2Cl_2) yielded **9a** (4.6 g, 81%) as a yellow-orange oil (R_f = 0.75).

^{1}H NMR ($CDCl_3$): δ 7.56 (2H, m, Ph), 7.31 (3H, m, Ph), 3.21 (3H, s, CH$_3$N), 2.92 (3H, s, CH$_3$N), 2.55 (3H, s, CH$_3$S), 2.37 (3H, s, CH$_3$). ^{13}C NMR ($CDCl_3$): δ 239.8 (C=S), 153.6 (C=O), 142.6 (CH *ipso*), 128.0 (CH *ortho*), 127.39 (CH *para*), 124.6 (CH *meta*), 92.5 (C *quat.*), 36.3 (CH$_3$N), 36.2 (CH$_3$N), 27.7 (CH$_3$), 19.5 (CH$_3$S). GC–MS 70 eV, *m*/*z* (rel. int.): 236 [M−CH$_3$S] (5), 195 [M−OCONMe$_2$] (50), 147 [M−OCONMe$_2$–CH$_3$S] (92), 103 (100).

4.7. Methyl 2-(dimethylcarbamoyloxy)-2-phenylbutanedithioate (9b)

The same procedure was applied to carbamate **8b** (4.14 g, 0.02 mol) to prepare **9b** (5.44 g (91%); R_f = 0.4 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ 7.55 (2H, m, Ph), 7.30 (3H, m, Ph), 3.25 (3H, s, CH$_3$N), 3.07 (2H, ddq, ^2J = 14.5 Hz, ^3J = 7.5 Hz, CH$_2$), 2.93 (3H, s, CH$_3$N), 2.54 (3H, s, CH$_3$S), 0.78 (3H, t, ^3J = 7.5 Hz, CH$_3$). ^{13}C NMR ($CDCl_3$): δ 239.9 (C=S), 153.4 (C=O), 141.6 (C *ipso*), 128.05 (CH *ortho*), 127.4 (CH *para*), 124.8 (CH *meta*), 95.6 (C *quat.*), 36.4 (2 CH$_3$N), 31.4 (CH$_2$), 19.4 (CH$_3$S), 7.4 (CH$_3$). GC–MS 70 eV, *m*/*z* (rel. int.): 250 [M−CH$_3$S] (3), 209 [M−OCONMe$_2$] (30), 206 [M−CS$_2$Me] (27), 162 [M−OCONMe$_2$–CH$_3$S] (60), 147 (100).

4.8. Trifluoromethylation of dithiomalonic derivative (4)

To a solution of **4** (220 mg, 0.81 mmol) and dried TMAF (8.3 mg, 0.089 mmol, 0.11 equiv.) in THF (6 mL) was added at −20 °C and under Ar CF_3SiMe_3 (198 μL, 1.36 mmol, 1.67 equiv.). The temperature was slowly raised to rt and the reaction mixture was stirred for 18 h 30 min and then quenched with sat. aq. NH_4Cl. The organic layer was extracted with ether, washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by centrifugal thin layer chromatography (PE:EtOAc 98:2) to afford first **12** (R_f = 0.9, 91 mg, 33%), then **11** (R_f = 0.74, 60 mg, 23%), as oils.

A separate experiment carried out from **4** (300 mg, 1.11 mmol) and TMAF (52 mg, 0.55 mmol, 0.5 equiv.), afforded a mixture (254 mg) of the ketene dithioacetal **11** and a trifluoromethylated by-product **x**. The molar ratio **11**/**x** is 84/16 based on CF_3 signals integration.

4.8.1. 1-Methylsulfanyl-1-trifluoromethylsulfanyl-2-ethoxycarbonyl-2-phenylethene (11)

Mixture of 2 diastereomers (77:23 determined by ^{19}F NMR). ^{19}F NMR ($CDCl_3$): δ −40.4 (*minor*), −41.4 (*major*). ^{1}H NMR ($CDCl_3$): δ 7.42–7.22 (5H, m, Ph), 4.28 (2H, q, J = 7.0 Hz, C$\underline{H}_2$–CH$_3$), 2.49 (s, SCH$_3$ *minor*), 2.33 (s, SCH$_3$ *major*), 1.31 (3H, t, J = 7.0 Hz, C$\underline{H}_2$–CH$_3$). ^{13}C NMR ($CDCl_3$): δ 166.7 (CO *minor*), 166.6 (CO *major*), 148.1 (=C *minor*), 148.0 (=C *major*), 135.3 (C *ipso minor*), 134.6 (C *ipso major*), 129.4, 129.0, 128.8, 128.7, 128.6, 128.5 (CH arom), 128.6 (q, CF$_3$, J_{CF} 308 Hz), 127.6 (C= *minor*), 127.2 (C= *major*), 62.4 (O–CH$_2$ *minor*), 62.1 (O–CH$_2$ *major*), 17.8 (SCH$_3$ *minor*), 17.6 (SCH$_3$ *major*), 14.1 (CH$_2$C$\underline{H}_3$ *minor*), 14.0 (CH$_2$C$\underline{H}_3$ *major*). ESMS *m*/*z* 344.9 [M+Na]$^+$.

4.8.2. Methyl 2-ethoxycarbonyl-2-phenyl-2-(trimethylsilyloxy)ethanedithioate (12)

^{1}H NMR ($CDCl_3$): δ 7.70 (2H, m, Ph), 7.34 (3H, m, Ph), 4.25 (2H, m, C$\underline{H}_2$CH$_3$), 2.55 (3H, s, SCH$_3$), 1.30 (3H, t, J = 7.0 Hz, CH$_2$C$\underline{H}_3$), 0.21 (9H, s, Si(CH$_3$)$_3$). ^{13}C NMR ($CDCl_3$): δ 239.5 (CS$_2$), 169.4 (C=O), 140.6 (C *ipso*), 128.2 (CH *para*), 127.6 (2 CH arom), 127.3 (2 CH arom), 92.6 (C–CS$_2$), 62.3 (CH$_2$O), 19.5 (SCH$_3$), 13.9 (CH$_2$C$\underline{H}_3$), 1.69 (Si(CH$_3$)$_3$). Anal. calcd for $C_{15}H_{22}O_3S_2Si$: C, 52.59; H, 6.47. Found: C, 52.72; H, 6.75.

4.9. 1-Methylsulfanyl-2-phenyl-1-(trifluoromethylsulfanyl)propene (14a). Typical procedure

To predried CsF (0.15 mg, 0.89 mmol, 0.18 equiv.) was added a solution of dithioester **9a** (1.4 g, 4.94 mmol) in DME (20 mL) then CF_3TMS (0.75 mL, 5.07 mmol, 1.02 equiv.). The mixture was vigorously stirred at rt for 14 h. The reaction was monitored by GC–MS. The reaction was completed after the introduction of an additional amount of CF_3TMS (0.35 mL, 2.37 mmol, 0.47 equiv.) and 10 h stirring. The volatile products were evaporated, the residue was stirred with petroleum ether (25 mL), filtered and evaporated to give a crude orange oil (^{19}F NMR ratio of stereoisomers: 1:0.22). Chromatography over silicagel (PE) gave successively as pale yellow oil: (*Z*)-**14a**, R_f = 0.45, 0.065 g; a mixture (*Z*,*E*)-**14a**, 0.31 g and (*E*)-**14a**, R_f = 0.35, 0.66 g. Total yield: 79% (see discussion for configuration assignments).

Major *E*-isomer, R_f 0.35 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −41.8 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 7.37 (3H, m, Ph), 7.20 (2H, m, Ph), 2.43 (3H, s, CH$_3$), 2.24 (3H, s, SCH$_3$). ^{13}C NMR ($CDCl_3$): δ 156.3 (q, J_{CF} = 1.4 Hz, =C), 142.3 (C$_{ipso}$), 129.6 (q, J_{CF} = 310.0 Hz, CF$_3$), 128.4 (CH *ortho*), 127.9 (CH *para*), 127.19 (CH *meta*), 119.6 (q, J_{CF} = 1.3 Hz, C=), 26.1 (CH$_3$), 17.8 (SCH$_3$). GC–MS 70 eV, *m*/*z* (rel. int.): 264 [M$^+$] (70), 195 [M−CF$_3$] (25), 163 [M−*S*-CF$_3$] (8), 148 [M−*S*-CF$_3$–CH$_3$] (100), 115 (54), 103 (64).

Minor *Z*-isomer, R_f 0.45 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −41.9 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 3H, Ph), 7.14 (m, 2H, Ph), 2.46 (s, 3H, CH$_3$), 2.43 (s, 3H, SCH$_3$). ^{13}C NMR ($CDCl_3$): δ 156.3 (q, =C, J_{CF} 1.4 Hz), 143.0 (C$_{ipso}$), 129.1 (q, J_{CF} = 310.0 Hz, CF$_3$), 128.3 (CH *ortho*), 127.7 (CH *para*), 127.6 (CH *meta*), 120.0 (q, J_{CF} = 1.3 Hz, C=), 25.8 (CH$_3$), 17.3 (SCH$_3$).

4.10. 1-Methylsulfanyl-2-phenyl-1-(trifluoromethylsulfanyl)but-1-ene (14b)

According to the typical procedure, reaction of dithioester **9b** (1.74 g, 5.85 mmol) with CF_3TMS (1.0 mL + 0.3 mL, 8.8 mmol, 1.5 equiv.) and CsF (0.1 g, 0.6 mmol, 0.1 equiv.) in DME (20 mL) yielded the ketene dithioacetal **14b** (1.4 g, 86%, 1:0.15 mixture of *E*/*Z* isomers) as a pale yellow oil. In a separate experiment, a careful flash chromatography (PE) allowed to isolate pure samples of each of the stereoisomers: (*Z*)-**14b**, R_f = 0.45, 10%; (*E*)-**14b**, R_f = 0.3, 77%.

Major *E*-isomer, R_f 0.3 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −41.9 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 7.37 (3H, m, Ph), 7.15 (2H, m, Ph), 2.86 (2H, q, ^3J = 7.3 Hz, CH$_2$), 2.22 (3H, s, SCH$_3$), 0.91 (3H, t, ^3J = 7.3 Hz, CH$_3$). ^{13}C NMR ($CDCl_3$): δ 161.6 (q, J_{CF} = 1.0 Hz, =C), 140.8 (C *ipso*), 129.4 (q, J_{CF} = 310.5 Hz, CF$_3$), 128.4 (CH *ortho*), 127.9 (CH *para*), 127.8 (CH *meta*), 119.3 (q, J_{CF} = 1.2 Hz, C=), 32.0 (CH$_2$), 17.8 (q, $^5J_{CF}$ = 0.9 Hz,

SCH_3), 12.4 (CH_3). GC–MS 70 eV, *m/z* (rel. int.): 278 [M^+] (100), 263 [$M-CH_3$] (4), 209 [$M-CF_3$] (30), 162 (45), 129 (70), 115 (70), 103 (64).

Minor *Z*-isomer, R_f 0.45 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −41.8 (s, CF_3). ^1H NMR ($CDCl_3$): δ 7.34 (3H, m, Ph), 7.09 (2H, m, Ph), 2.83 (2H, q, ^3J = 7.4 Hz, CH_2), 2.43 (3H, s, SCH_3), 0.98 (3H, t, ^3J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 162.4 (q, J_{CF} = 1.6 Hz, =C), 141.7 (C *ipso*), 129.1 (q, J_{CF} = 311.4 Hz, CF_3), 128.2 (CH *ortho*), 128.1 (CH *para*), 127.6 (CH *meta*), 119.9 (q, J_{CF} = 1.7 Hz, C=), 32.2 (CH_2), 17.4 (SCH_3), 12.4 (CH_3).

4.11. 1-Methylsulfanyl-1-pentafluoroethylsulfanyl-2-phenylpropene (15a)

According to the typical procedure, reaction of dithioester **9a** (1.4 g, 4.94 mmol) with CF_3CF_2TMS (1.0 g + 0.43 g, 7.44 mmol, 1.5 equiv.) and CsF (0.15 g, 0.89 mmol, 0.18 equiv.) in DME (20 mL) yielded **15a** (1.29 g, 83%, 1:0.16 mixture of isomers) as a pale yellow liquid.

Major *E*-isomer, R_f 0.3 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −83.3 (3F, t, $^3J_{FF}$ = 3.5 Hz, CF_3), −91.7 (2F, q, $^3J_{FF}$ = 3.5 Hz, CF_2). ^1H NMR ($CDCl_3$): δ 7.37 (3H, m, Ph), 7.20 (2H, m, Ph), 2.42 (3H, s, CH_3), 2.24 (3H, s, SCH_3). ^{13}C NMR ($CDCl_3$): δ 157.6 (t, J_{CF} = 1.3 Hz, =C), 142.3 (C *ipso*), 128.5 (CH *ortho*), 128.1 (CH *para*), 127.3 (CH *meta*), 120.8 (tq, J_{CF} = 291.5 Hz, J_{CF} = 40.5 Hz, CF_2), 118.2 (t, J_{CF} = 1.7 Hz, C=), 116.5 (qt, J_{CF} = 287.3 Hz, $^3J_{CF}$ = 37.0 Hz, CF_3), 26.3 (CH_3), 18.0 (SCH_3). GC–MS 70 eV, *m/z* (rel. int.): 314 [M^+] (30), 195 [$M-C_2F_5$] (22), 148 [$M-SC_2F_5-SCH_3$] (100), 103 (64).

Minor *Z*-isomer, R_f 0.4 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −83.6 (3F, t, $^3J_{FF}$ = 3.5 Hz, CF_3), −91.8 (2F, q, $^3J_{FF}$ = 3.5 Hz, CF_2). ^1H NMR ($CDCl_3$): δ 7.32 (3H, m, Ph), 7.11 (2H, m, Ph), 2.45 (3H, s, CH_3), 2.43 (3H, s, SCH_3).

4.12. 1-Methylsulfanyl-1-pentafluoroethylsulfanyl-2-phenylbut-1-ene (15b)

According to the typical procedure, reaction of dithioester **9b** (98 mg, 0.33 mmol) with CF_3CF_2TMS (70 mg + 26 mg, 0.5 mmol, 1.5 equiv.) and CsF (0.10 g, 0.06 mmol, 0.18 equiv.) in DME (4 mL) afforded the ketene dithioacetal **15b** (98 mg, 90%, 1:0.13 mixture of *E*/*Z* isomers) as a pale yellow liquid.

Major *E*-isomer, R_f 0.3 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −83.4 (3F, t, CF_3, $^3J_{FF}$ = 3.5 Hz), −91.72 (2F, q, $^3J_{FF}$ = 3.5 Hz, CF_2). ^1H NMR ($CDCl_3$): δ 7.42 (3H, m, Ph), 7.21 (2H, m, Ph), 2.92 (2H, q, ^3J = 7.7 Hz, CH_2), 2.28 (3H, s, SCH_3), 0.97 (3H, t, ^3J = 7.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 162.8 (t, J_{CF} = 1.0 Hz, =C), 140.8 (C *ipso*), 128.4 (CH *ortho*), 128.0 (CH *para*), 127.7 (CH *meta*), 120.6 (tq, J_{CF} = 292.4 Hz, $^3J_{CF}$ = 40.2 Hz, CF_2), 118.8 (qt, J_{CF} = 286.3 Hz, $^3J_{CF}$ = 36.5 Hz, CF_3), 117.8 (t, J_{CF} = 1.6 Hz, C=), 32.1 (CH_2), 17.9 (SCH_3), 12.4 (CH_3). GC–MS 70 eV, *m/z* (rel. int.): 328 [M^+] (65), 281 [$M-CH_3S$] (2), 209 [$M-C_2F_5$] (40), 162 (66), 128 (68), 115 (90), 103 (100).

Minor *Z*-isomer, R_f 0.45 (PE, SiO_2). ^{19}F NMR ($CDCl_3$): δ −83.6 (3F, t, $^3J_{FF}$ = 4.0 Hz, CF_3), −91.7 (2F, q, $^3J_{FF}$ = 4.0 Hz, CF_2). ^1H NMR ($CDCl_3$): δ 7.32 (3H, m, Ph), 7.08 (2H, m, Ph), 2.85 (2H, q, $^3J_{HH}$ = 7.7 Hz, CH_2), 2.44 (3H, s, SCH_3), 0.99 (3H, t, $^3J_{HH}$ = 7.7 Hz, CH_3).

4.13. 2-Ethoxycarbonyl-2-phenyl-1-(trifluoromethylsulfanyl)eth-1-enyl)dimethylsulfonium trifluoromethanesulfonate (16)

A solution of **11** (100 mg, 0.310 mmol) and trimethyloxonium tetrafluoroborate (90 mg, 0.373 mmol, 1.2 equiv.) in CH_2Cl_2 (4 mL) was stirred at reflux for 11 h and then at rt for 13 h. The reaction mixture was concentrated under reduced pressure. The residue was washed with Et_2O to give **16** (140 mg, 100%, 2 diastereomers (^{19}F NMR), 84:16) as a viscous oil. ^{19}F NMR ($CDCl_3$): δ −38.7 (CF_3 *major*), −38.9 (CF_3 *minor*), −147.5 (BF_4 *minor*), −149.9 (BF_4 major). ^1H NMR ($CDCl_3$): δ 7.47–7.38 (5H, m, Ph), 4.38 (2H, q, J = 7.0 Hz, $C\underline{H}_2CH_3$), 3.03 (s, $S(CH_3)_2$ *minor*), 2.90 (s, $S(CH_3)_2$ *major*), 1.25 (3H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$).

4.14. (Z)-dimethyl(2-phenyl-1-(trifluoromethylsulfanyl)but-1-enyl)sulfonium trifluoromethanesulfonate (17)

To a benzene solution (2 mL) of ketene dithioacetal (*E*)-**14b** (54 mg, 0.194 mmol) was added methyltriflate (32 mg, 0.195 mmol, 1 equiv.) and the mixture was stirred at rt for 2 h. Solvent was removed and the oily residue was washed with ether and dried in vacuum to yield the salt **17** (83 mg, 97%). ^{19}F NMR ($CDCl_3$): δ −41.2 (3F, s, *S*-CF_3), −79.4 (3F, s, SO_2CF_3). ^1H NMR (acetone-d_6): δ 7.52 (3H, m, Ph), 7.41 (2H, m, Ph), 3.18 (2H, q, ^3J = 7.5 Hz, CH_2), 3.11 (6H, s, $S(CH_3)_2$), 0.88 (3H, t, J = 7.5 Hz, CH_3). ESMS *m/z* (rel. int.): 293 [M−TfO] (45), 231 [M−TfO−CH_3SCH_3] (74), 103 (100).

4.15. Reaction of compound 14b with triflic acid and hydrolysis

To a solution of ketene dithioacetal **14b** (140 mg, 0.5 mmol) in 0.5 mL of $CDCl_3$ triflic acid (220 mg, 1.47 mmol, 2.94 equiv.) was added under argon at 0 °C. The color of solution turned to dark yellow from pale yellow and NMR spectra were recorded after 5 min of stirring to room temperature. The salt **18** was observed as a 55/45 mixture of diastereomers.

4.15.1. 1-(Methylsulfanyl)-2-phenyl-1-(trifluoromethylsulfanyl)butan-1-ylium trifluoromethanesulfonate (18)

^{19}F NMR ($CDCl_3$): δ −35.7 (s, *S*-CF_3 *major*), −40.1 (s, *S*-CF_3 *minor*), −77.3 (CF_3SO_3H), −78.7 ($CF_3SO_3^-$). ^1H NMR ($CDCl_3$): 7.6–7.3 (5H, m, Ph), 4.92 (dd, ^3J = 8.5 Hz, ^3J = 5.5 Hz, CH *major*), 4.86 (dd, ^3J = 9.0 Hz, ^3J = 5.0 Hz, CH *minor*), 3.50 (s, SCH_3 *minor*), 3.33 (s, SCH_3 *major*), 2.45 and 2.27 (2H, m, CH_2), 1.17 (t, ^3J = 7.0 Hz, CH_3 *major*), 1.11 (t, ^3J = 7.5 Hz, CH_3 *minor*). ^{13}C NMR ($CDCl_3$): δ 247.3 (q, $^4J_{CF}$ = 1.0 Hz, CS_2), 246.3 (q, $^4J_{CF}$ = 1.0 Hz, CS_2), 134–126 (C arom + CF_3), 118.6 (q, CF_3SO_3H), 62.7 (q, $^3J_{CF}$ = 2.5 Hz, CH), 62.7 (q, $^3J_{CF}$ = 1.5 Hz, CH), 32.9 (CH_2), 29.1 (CH_2), 24.8 (SCH_3), 24.1 (SCH_3), 12.4 (CH_3), 11.5 (CH_3). ESMS *m/z* (rel. int.): 279 [M−TfO] (40), 231 [M−TfO−CH_3SH] (20), 177 [M−TfO−CF_3SH] (35), 129 (100).

After recording of spectra the chloroform solution was poured in cold water (1 mL), and the mixture was stirred for 5 min. The organic layer was separated and washed with water (2× 1 mL). After drying over $MgSO_4$ the solvent was evaporated and residue was filtered through a short column of silicagel using CH_2Cl_2 as eluent. Two fractions were collected, containing the thiol ester **19** [16] (40 mg, 38%) ($R_f \sim 1$) and the acid **20** [17] (26 mg, 30%) (R_f = 0.3) as colorless oils.

4.15.2. S-methyl 2-phenylbutanethioate (19)

^1H NMR ($CDCl_3$): 7.32 (5H, m, Ph), 3.65 (1H, t, ^3J = 7.5 Hz, CH), 2.25 (3H, s, SCH_3), 2.16 (1H, m, $C\underline{H}_AH_B$), 1.85 (1H, m, $CH_A\underline{H}_B$), 0.89 (3H, t, ^3J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 201.0 (C=O), 138.6, 128.7, 128.7, 127.1, 126.9 (C arom), 53.4 (CH), 26.6 (CH_2), 12.4 (SCH_3), 11.8 (CH_3). GC–MS 70 eV, *m/z* (rel. int.): 194 [M^+] (3), 147 [$M-SCH_3$] (10), 119 [PhCHEt] (50), 91 (100).

4.15.3. 2-Phenylbutanoic acid (20)

^1H NMR ($CDCl_3$): 7.31 (5H, m, Ph), 6.5 (1H, br s, OH), 3.46 (1H, t, ^3J = 7.5 Hz, CH), 2.07 (1H, m, $C\underline{H}_AH_B$), 1.80 (1H, m, $CH_A\underline{H}_B$), 0.90 (3H, t, ^3J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 179.8 (C=O), 138.6, 128.8, 128.7, 128.2, 128.0 (C arom), 52.2 (CH), 26.4 (CH_2), 12.2 (CH_3). GC–MS 70 eV, *m/z* (rel. int.): 164 [M^+] (15), 119 [M−COOH] (40), 91 (100).

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