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Nucleophilic chain substitution on perfluoroketene dithioacetals by ethyl 2-trimethysilyl acetate. Application to the synthesis of 2-trifluoromethyl succinic acid derivatives☆

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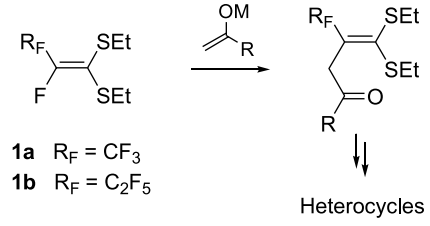
Abstract—A highly efficient substitution of the vinyl fluoride of perfluoroketene dithioacetals was achieved using trimethylsilylacetate to give 2-perfluoroalkyl succinic acid derivatives and 2-trifluoromethyl succinimides. This chain process was initiated by a catalytic amount of fluoride salt, whereas reaction failed with the corresponding lithium enolate.

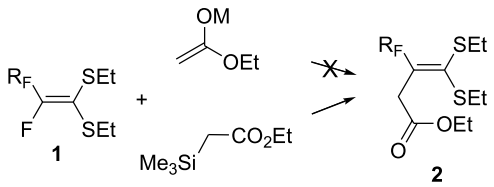
1. Introduction

Within the framework of our studies on new methods for the synthesis of multifunctional organofluorine compounds, we have developed perfluoroketene dithiocetals **1** as versatile building blocks. Compounds **1** are synthetic equivalents of 2-hydroperfluorocarboxylic derivatives.[1] Their umpolung reactivity, associated to the vinyl fluorine substitution, significantly extends their applications. The substitution by alkoxide or simple organometallic reagents has previously been observed for the difluoromethylene analogues.[2] The reaction of **1** with functionalized nucleophiles offers a greater potential because of possible subsequent heterocyclization (Scheme 1). We have reported applications in the synthesis of trifluoromethyl lactones,[3] lactams,[4] pyridazines,[5] furanes and pyrroles.[6] The first step in all these syntheses consists of the reaction of **1** with a ketone enolate.



Scheme 1.

To diversify the synthetic applications of **1**, we wished to extend these reactions to other nucleophilic species, in particular ester enolates. Surprisingly, in contrast to lithium enediolates,[7] various attempts with lithium ethyl acetate enolate (from AcOEt and LDA) failed whatever the reaction conditions (Scheme 2). Instead of the expected product **2**, the only isolated product resulted from the displacement of the vinyl fluoride by the ethoxide group, the latter being produced by a Claisen condensation which eventually occurred after a long reaction time. We wish to describe a chain reaction with ethyl 2-trimethylsilyl acetate which enabled us to overcome this failure and to apply our synthetic method to the synthesis of 2-trifluoromethylsuccinic acid derivatives.



Scheme 2.

2. Results and discussion

Silylated nucleophiles often behave differently than their metallated analogues, due to their stabilized nature. Several

☆ Perfluoroketene dithioacetals. Part 12. For part 11, see Ref. 7

Keywords: Vinyl fluorine substitution; Silyl nucleophile; Succinic acid derivatives; Trifluoromethyl succinimides.
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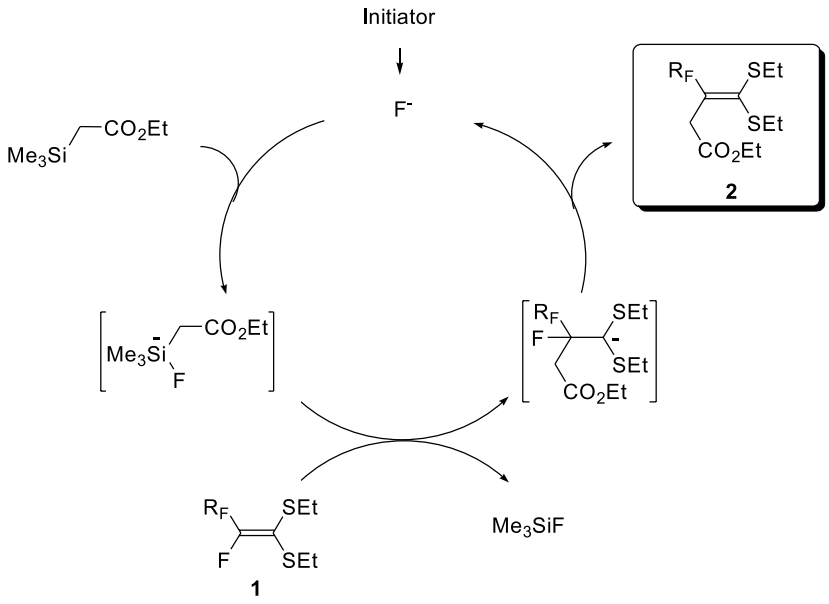


Scheme 3.

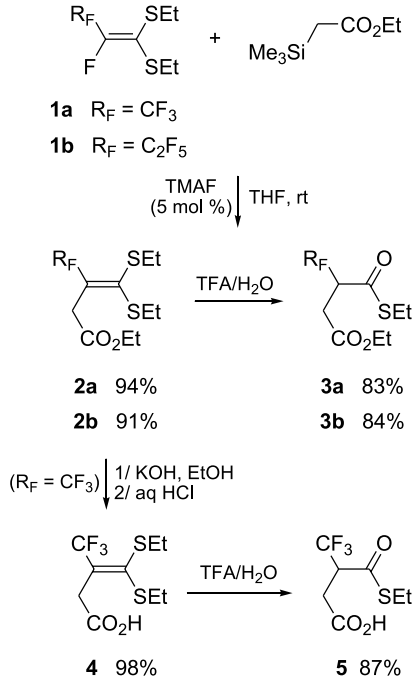
significant examples can be cited: trifluoromethytrimethylsilane is a nucleophilic trifluoromethylating reagent of choice whereas main metal analogues decompose into difluorocarbenes.[8] 2-Trimethylsilyldithiolane acts, under fluoride activation, as an efficient nucleophile whereas the 2-lithio analogue decomposes via ethylene elimination.[9]

A stabilized hypervalent intermediate is the key form of nucleophile donor. If the nucleophilic reaction releases a silicophilic nucleofugal group, the transformation can proceed by a mild chain mechanism. The chain transfer step is often a silicon transfer to an alkoxide, as in the case of nucleophilic additions on carbonyl compounds. Owing to the strength of the Si–F bond, the chain transfer is particularly efficient in reactions involving fluoride elimination, as shown in the conversion of acylsilane into difluoroenol silyl ethers using trifluoromethyl–trimethylsilane.[10] This led us to consider the substitution reaction of the vinyl fluoride of **1** with ethyl 2-trimethylsilyl acetate following the chain reaction depicted in Scheme 3.

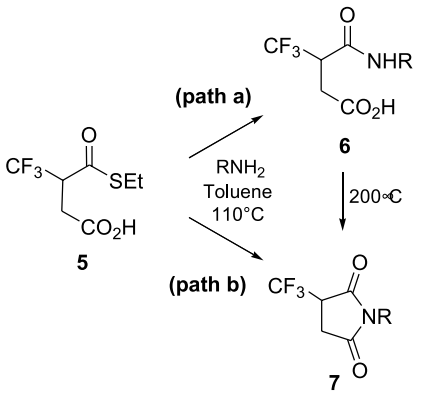
Reaction conditions were optimized regarding the fluoride initiator and the solvent used. With cesium fluoride in DME or the usual tetrabutylammonium fluoride in THF, difficulties were encountered in reaching a total conversion and interesting yields. Tetramethylammonium fluoride (TMAF) in THF proved to be the best initiator. This fluoride salt is easily dehydrated by simple heating under vacuum without the decomposition encountered with TBAF. Unfortunately the very clean reaction observed was initially counterbalanced by an incomplete conversion. As in any chain process, the efficiency of the chain transfer step is crucial in bringing the reaction to completion. Finally, a total conversion with excellent yields of products **2** was achieved using 5% of TMAF in THF, provided that the initiator was added portionwise (see Experimental). The dithioacetal moiety was hydrolyzed under the usual conditions to give the 2-perfluoroalkyl dicarboxylic derivatives **3**, bearing two differentiated carboxyl functions (Scheme 4).

Compound **3a** was initially chosen as a model to explore the reactivity of the dicarboxylic derivatives. A high chemical resistance of the ester moiety was observed in the reaction of **3a** with methylhydrazine which gave the monocondensation product with the thiolester group instead of the expected dihydropyridazinedione. On the other hand, **2a** was easily saponified to give the intermediate ketenedithioacetal **4** in almost quantitative yield. This product was then converted in high yield to the acid thiolester **5** by a stronger acid treatment (Scheme 4). Compound **4** was also prepared in one step by reacting **1a** with the lithium dianion of acetic acid.[7]

In contrast to **3a**, **5** behaved as a bis(electrophilic) species,



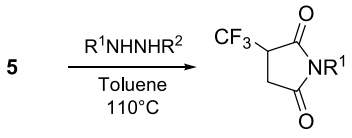
Scheme 4.



R	Path	Product	(%)
Bn	**a**	**7a**	73
nC_5H_{11}	**a**	**7b**	71
*i*Pr	**a**	**7c**	56
$PhCH(CH_3)$	**a**	**7d**	76
Ph	**b**	**7e**	81
pMeOPh	**b**	**7f**	81
2-Pyridyl	**b**	**7g**	31
NH_2	**b**	**7h**	45
NHMe	**b**	**7i**	47

Scheme 5.

giving some unexpected results. Reaction with aliphatic primary amines under standard conditions first gave the opened acid-amide **6a–d** (Scheme 5, path a). Cyclodehydration then gave 2-trifluoromethyl succinimides **7a–d** by heating the corresponding **6a–d** to 200 °C (Scheme 5). The reaction of **5** with aromatic primary amines directly provided the corresponding *N*-aryl succinimides **7e–g** (Scheme 5, path b). Hydrazine and methylhydrazine reacted similarly giving the corresponding *N*-aminosuccinimides **7h**,**7i** in moderate yields. In contrast phenylhydrazine gave **7e**, a condensation product with the loss of one nitrogen. Similar cleavage of the nitrogen–nitrogen bond has already been observed.[11] In the same way, reaction with *N*,*N*′-dimethylhydrazine gave *N*-methyl-2-trifluoromethyl succinimide **7j** (Scheme 6).



R^1	R^2	Product (yield %)
Ph	H	**7e** (38 %)
Me	Me	**7j** (30 %)

Scheme 6.

Succinimides constitute an important class of organic compounds, both as synthetic intermediates and for their biological properties.[12] The introduction of fluorine and in particular of a trifluoromethyl substituent greatly modifies the physico-chemical and biological properties of organic substrates.[13] 2-Trifluoromethyl succinimides, and more generally 2-trifluoromethyl succinic acid derivatives are undoubtedly very interesting building blocks open to a wide range of potential transformations. Several compounds comprising the 2-trifluoromethyl succinic or succinimide framework have been described,[14,15] most of them being obtained from 2-trifluoromethylmaleimide or maleic acid.[15] To our knowledge, there is one report on the direct synthesis of 2-trifluoromethyl succinimides, and this in poor yield.[16] The reaction sequence presented here is thus the first general preparation of *N*-alkyl or *N*-aryl 2-trifluoromethyl succinimides of practical value and transposable to a multigram scale.

3. Conclusions

In summary, we have developed a preparative access to 2-trifluoromethyl and 2-pentafluoroethyl succinic acid derivatives in various forms, particularly in the 2-trifluoromethyl imide series. This is the result of the combination of the starting perfluoroketene dithioacetal functionality and the specific behavior of the silylated precursor of ethyl acetate enolate. Applications in the pentafluoroethyl series are under investigation and will be reported in due course.

4. Experimental

4.1. Materials and general methods

Melting points are uncorrected FT-IR spectra were recorded on a MIDAC Corporation Spectrafile IR apparatus. ^1H, ^{13}C and ^{19}F spectra were recorded on a Bruker AC-250 or AC-500 spectrometer with $CDCl_3$ as the solvent. Tetramethylsilane ($\delta=0.00$ ppm) or $CHCl_3$ ($\delta=7.27$ ppm) were used as internal standards for ^1H, $CDCl_3$ ($\delta=77.23$ ppm) for ^{13}C NMR spectra, and $CFCl_3$ ($\delta=0.0$ ppm) for ^{19}F NMR spectra. GCMS spectra were obtained on Trace MS Thermoquest apparatus (70 eV) in electron impact mode. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micromass in positive ESI mode (CV=30 V). All reactions were monitored by TLC (Merck F 254 silica gel) or by ^{19}F NMR. All anhydrous reactions were carried out under dry argon. THF was dried and distilled from sodium/benzophenone. Ethyl 2-trimethylsilyl acetate was distillated before use. Tetramethylammonium fluoride (TMAF) was dried by heating at 200 °C, under reduced pressure, during 4–5 h. Perfluoroketene dithioacetals **1a**,**b** were prepared according to our reported method.[1] Products were separated by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate.

4.2. Typical procedure for the preparation of compounds (2a,b) (Scheme 4)

To a suspension of TMAF (100 mg, 1.0 mmol, 0.025 equiv) in dry THF (100 mL), under argon atmosphere, was added **1a** (10.1 g, 43.0 mmol, 1 equiv). Ethyl 2-trimethylsilyl acetate (9.4 mL, 51.0 mmol, 1.2 equiv) was then added

dropwise to the resulting suspension. The mixture was stirred at room temperature under argon (4–5 h). Each hour a new portion of TMAF (50 mg, 0.5 mmol) was added until total conversion of the starting dithioacetal **1a** (4–5×). The crude mixture was washed with brine (60 mL). After separation, the aqueous phase was extracted twice with ether (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether–EtOAc (99/1) to give the ketene dithioacetal **2a** (12.2 g, 94%).

4.2.1. Ethyl 4,4-bis(ethylsulfanyl)-3-trifluoromethylbut-3-enoate (2a). Yield: 94%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, $^3J_{H,H}$=7.3 Hz, 3H, SCH_2CH_3), 1.25 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.3 Hz, 3H, SCH_2CH_3), 2.84 (q, $^3J_{H,H}$=7.3 Hz, 2H, SCH_2CH_3), 2.86 (q, $^3J_{H,H}$=7.3 Hz, 2H, SCH_2CH_3), 3.74 (s, 2H, H-2), 4.16 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, OCH_2CH_3), 14.6 and 15.0 (s, 2× SCH_2CH_3), 27.9 and 28.8 (s, 2×SCH_2CH_3), 37.5 (q, $^3J_{C,F}$=2.8 Hz, C-2), 61.2 (s, OCH_2CH_3), 122.7 (q, $^1J_{C,F}$=275.6 Hz, CF_3), 130.2 (q, $^2J_{C,F}$=29.0 Hz, C-3), 146.0 (q, $^3J_{C,F}$=3.1 Hz, C-4), 169.3 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −57.0 (s); IR (film) 2981, 2930, 1740, 1302, 1159, 1132 cm^{-1}; GCMS (EI) *m/e* (%) 302 (M^+), 274, 253, 229, 139 (100), 75. Anal. Calcd for $C_{11}H_{17}F_3O_2S_2$: C, 43.69; H, 5.67. Found: C, 43.37; H, 5.95.

4.2.2. Ethyl 4,4-bis(ethylsulfanyl)-3-pentafluoroethylbut-3-enoate (2b). Yield: 91%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 and 1.25 and 1.26 (t, $^3J_{H,H}$=7.2 Hz, 9H, 2× SCH_2CH_3+OCH_2CH_3), 2.84 and 2.86 (q, $^3J_{H,H}$=7.2 Hz, 4H, 2×SCH_2CH_3), 3.66 (s, 2H, H-2), 4.15 (q, $^3J_{H,H}$=7.2 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 and 14.6 and 14.8 (s, 2×SCH_2CH_3+OCH_2CH_3), 28.3 and 29.3 (s, 2×SCH_2CH_3), 38.1 (t, $^3J_{C,F}$=4.3 Hz, C-2), 61.2 (s, OCH_2CH_3), 113.3 (tq, $^1J_{C,F}$=257.4, $^2J_{C,F}$=39.0 Hz, CF_2), 119.2 (qt, $^1J_{C,F}$=288.0, $^2J_{C,F}$=39.0 Hz, CF_3), 127.2 (t, $^2J_{C,F}$=20.7 Hz, C-3), 148.8 (t, $^3J_{C,F}$=3.2 Hz, C-4), 169.3 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −107.1 (m, 2F, CF_2), −83.3 (m, 3F, CF_3); IR (film) 2982, 2931, 1741, 1197, 1130 cm^{-1}; GCMS (EI) *m/e* (%) 352 (M^+), 323, 303, 279 (100), 189, 75.

4.3. Typical procedure for acid hydrolysis of compounds (2a,b and 4) (Scheme 4)

To a solution of ketene dithioacetal **2a** (6.64 g, 22.0 mmol, 1 equiv) in trifluoroacetic acid (15 mL, 0.2 mol, 9 equiv) was added water (1.2 mL, 66.0 mmol, 3 equiv). The mixture was refluxed until complete conversion of **2a** (10 h). After cooling, water (30 mL) was added and the medium was basified using a saturated aqueous solution of $NaHCO_3$ (20 mL). The resulting aqueous phase was extracted twice with CH_2Cl_2 (2×40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether–EtOAC (95/5) to give the compound **3a** (4.71 g, 83%).

4.3.1. Ethyl 3-(ethylsulfanylcarbonyl)-4,4,4-trifluorobutyrate (3a). Yield: 83%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, SCH_2CH_3), 2.73 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=4.0 Hz, 1H, H-2), 2.97 (qd, $^3J_{H,H}$=7.4, J=1.5 Hz, 2H, SCH_2CH_3), 3.08 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=10.3 Hz, 1H, H-2), 3.82 (dqd, $^3J_{H,H}$=10.3, $^3J_{H,F}$=8.5, $^3J_{H,H}$=4.0 Hz, 1H, H-3), 4.15 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, SCH_2CH_3 or OCH_2CH_3), 14.1 (s, SCH_2CH_3 or OCH_2CH_3), 24.2 (s, SCH_2CH_3), 31.0 (q, $^3J_{C,F}$=2.5 Hz, C-2), 52.7 (q, $^2J_{C,F}$=27.0 Hz, C-3), 61.4 (s, OCH_2CH_3), 123.6 (q, $^1J_{C,F}$=280.8 Hz, CF_3), 169.4 (s, C-1), 192.4 (q, $^3J_{C,F}$=2.1 Hz, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −68.2 (d, $^3J_{F,H}$=8.5 Hz); IR (film) 2984, 2937, 1742, 1686, 1306, 1259, 1170, 1123 cm^{-1}; GCMS (EI) *m/e* (%) 259 (M+1), 213, 197 (100), 169, 149, 121, 101. Anal. Calcd for $C_9H_{13}F_3O_3S$: C, 41.86; H, 5.07. Found: C, 42.06; H, 5.08.

4.3.2. Ethyl 3-(ethylsulfanylcarbonyl)-4,4,5,5,5-pentafluoropentanoate (3b). Yield: 84%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, $^3J_{H,H}$=7.1 Hz, 3H, OCH_2CH_3 or SCH_2CH_3), 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, OCH_2CH_3 or SCH_2CH_3), 2.80 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=3.6 Hz, 1H, H-2), 2.9–3.2 (m, 3H, SCH_2CH_3 and H-2), 3.84 (m, 1H, H-3), 4.17 (q, $^3J_{H,H}$=7.1 Hz, 2H, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.87 and 13.92 (s, SCH_2CH_3 and OCH_2CH_3), 24.2 (s, SCH_2CH_3), 30.7 (m, C-2), 50.5 (t, $^2J_{C,F}$=20.7 Hz, C-3), 61.4 (s, OCH_2CH_3), 113.1 (tq, $^1J_{C,F}$=257.5, $^2J_{C,F}$=37.9 Hz, CF_2), 118.5 (qt, $^1J_{C,F}$=287.1, $^2J_{C,F}$=37.8 Hz, CF_3), 169.3 (s, C-1), 192.4 (m, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −82.6 (m, 3F, CF_3), −115.6 (dd, $^2J_{F,F}$=274.1, $^3J_{F,H}$=13.8 Hz, 1F, CF_2), −117.5 (dd, $^2J_{F,F}$=274.1, $^3J_{F,H}$=13.8 Hz, 1F, CF_2); IR (film) 2983, 2936, 1743, 1686, 1276, 1210 cm^{-1}; GCMS (EI) *m/e* (%) 309 (M+1), 263, 247, 219, 199 (100), 151, 77.

4.3.3. 3-(Ethylsulfanylcarbonyl)-4,4,4-trifluorobutanoic acid (5). Yield: 87%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, $^3J_{H,H}$=7.4 Hz, 3H, SCH_2CH_3), 2.80 (dd, $^2J_{H,H}$=17.8, $^3J_{H,H}$=3.9 Hz, 1H, H-2), 2.97 (q, $^3J_{H,H}$=7.4 Hz, 2H, SCH_2CH_3), 3.16 (dd, $^2J_{H,H}$=17.8, $^3J_{H,H}$=10.1 Hz, 1H, H-2), 3.80 (m, 1H, H-3), 11.3 (brs, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0 (s, SCH_2CH_3), 24.3 (s, SCH_2CH_3), 30.7 (q, $^3J_{C,F}$=2.0 Hz, C-2), 52.4 (q, $^2J_{C,F}$=27.4 Hz, C-3), 123.5 (q, $^1J_{C,F}$=280.8 Hz, CF_3), 175.8 (s, C-1), 192.2 (q, $^3J_{C,F}$=1.5 Hz, *C*OS); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −68.1 (d, $^3J_{F,H}$=8.6 Hz); IR (film) 3053, 2971, 2937, 1720, 1684, 1260, 1171, 1124 cm^{-1}; GCMS (EI) *m/e* (%) 231 (M+1), 169, 149, 121, 101, 95, 62 (100); HRMS (ESI) calcd for $C_7H_9F_3O_3NaS$ *m/e*=253.0122; found 253.0122.

4.4. Preparation of compound (4) (Scheme 4)

To a solution of compound **2a** (9.97 g, 33.0 mmol) in EtOH (50 mL) was added an aqueous solution of KOH 3 M (50 mL). The mixture was heated at 80 °C for 3 h. After cooling at 0 °C and acidification with hydrochloric acid 1 M (30 mL) until pH=1, the mixture was extracted with ether (3×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized using a mixture of petroleum ether–EtOAc to give the compound **4** (8.9 g, 98%).

4.4.1. 4,4-Bis(ethylsulfanyl)-3-trifluoromethylbut-3-enoic acid (4). Solid: mp 79–80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, $^3J_{H,H}$=7.2 Hz, 3H, SCH_2CH_3), 1.26 (t, $^3J_{H,H}$=7.2 Hz, 3H, SCH_2CH_3), 2.84 (q, $^3J_{H,H}$=7.2 Hz, 2H, SCH_2CH_3), 2.87 (q, $^3J_{H,H}$=7.2 Hz, 2H, SCH_2CH_3), 3.79 (s, 2H, H-2), 11.5 (s, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.6 and 14.9 (s, 2×SCH_2CH_3), 28.0 and 28.9 (s, SCH_2CH_3), 37.3 (m, C-2), 122.7 (q, $^1J_{C,F}$=275.6 Hz, CF_3), 129.1 (q, $^2J_{C,F}$=29.4 Hz, C-3), 147.0 (m, C-4), 176.2 (s, C-1); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −57.0 (s); IR (KBr) 3100, 2965, 1697, 1570, 1411 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}F_3O_2S_2$ *m/e*=275.0387; found 275.0374.

4.5. Typical procedure for preparation of succinimides (7a–d) (Scheme 5, path a)

To a solution of γ-carboxy-thioester **5** (0.23 g, 1.00 mmol, 1.00 equiv) in toluene (6 mL) was added benzylamine (0.11 g, 1.04 mmol, 1.05 equiv). The mixture was heated first at 110 °C for 2 h (formation of intermediate **6a**). After evaporation of toluene, the residue was heated to 200 °C for 1–3 h. After cooling, the crude mixture was diluted with ether (8 mL) and washed with brine (5 mL). After separation, the aqueous phase was extracted with ether (3×5 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using a mixture of petroleum ether/EtOAc (85/15) to give the succinimide **7a** (0.19 g, 73%).

4.5.1. 3-Benzylcarbamoyl-4,4,4-trifluoro-butanoic acid (6a). Yield: 68%; Solid: mp 167–169 °C; ^{1}H NMR (250 MHz, CD_3OD) δ 2.75 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=3.4 Hz, 1H, H-2), 3.09 (dd, $^2J_{H,H}$=17.2, $^3J_{H,H}$=11.1 Hz, 1H, H-2), 3.7 (m, 1H, H-3), 4.4 (m, 2H, $NHCH_2$), 7.3 (m, 5H, Ph), NH and OH not visible; ^{13}C NMR (62.9 MHz, CD_3OD) δ 31.1 (m, C-2), 44.4 (s, $NHCH_2$), 47.7 (q, $^2J_{C,F}$=26.7 Hz, C-3), 126.5 (q, $^1J_{C,F}$=279.2 Hz, CF_3), 128.2 (s, CH Ph), 128.4 (s, 2×CH Ph), 129.5 (s, 2×CH Ph), 139.3 (s, C_q Ph), 167.6 (m, *C*ON), 173.2 (s, C-1); ^{19}F NMR (235.4 MHz, CD_3OD) δ −68.2 (d, $^3J_{F,H}$=8.6 Hz); IR (KBr) 3297, 3098, 2971, 2941, 1710, 1656, 1242, 1169 cm^{-1}; MS (ESI) *m/e* (%) 314 $(M+K)^+$, 298 $(M+Na)^+$, 276 $((M+H)^+$, 100). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 51.82; H, 4.24; N, 4.94.

4.5.2. 1-Benzyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7a). Yield: 73%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.4 Hz, 1H, H-4), 2.99 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.4 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 4.68 (d, $^2J_{H,H}$=17.2 Hz, 1H, NCH_2), 4.73 (d, $^2J_{H,H}$=17.2 Hz, 1H, NCH_2), 7.3 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=1.7 Hz, C-4), 43.1 (s, NCH_2), 44.4 (q, $^2J_{C,F}$=30.0 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 128.3 (s, CH Ph), 128.7 (s, 2×CH Ph), 128.8 (s, 2×CH Ph), 134.8 (s, C_q Ph), 169.3 (q, $^3J_{C,F}$=2.6 Hz, C-2), 173.0 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3036, 2954, 1789, 1716, 1456, 1402 cm^{-1}; GCMS (EI) *m/e* (%) 258 (M+1), 257 (M^+), 160, 104, 95, 77 (100), 51; HRMS (ESI) calcd for $C_{12}H_{11}F_3NO_2$ *m/e*=258.0742; found 258.0736.

4.5.3. 1-(*n*-Pentyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7b). Yield: 71%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, $^3J_{H,H}$=6.9 Hz, 3H, CH_3), 1.3 (m, 4H, 2×CH_2), 1.6 (m, 2H, NCH_2CH_2), 2.83 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.2 Hz, 1H, H-4), 2.98 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.4 Hz, 1H, H-4), 3.54 (t, $^3J_{H,H}$=7.4 Hz, 2H, NCH_2), 3.5–3.6 (m, 1H, H-3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.8 (s, CH_3), 22.1 (s, CH_2), 27.0 (s, CH_2), 28.7 (s, CH_2), 29.4 (m, C-4), 39.5 (s, NCH_2), 44.3 (q, $^2J_{C,F}$=29.9 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 169.6 (q, $^3J_{C,F}$=3.0 Hz, C-2), 173.4 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.4 (d, $^3J_{F,H}$=8.6 Hz); IR (film) 2960, 2874, 1716, 1405, 1353, 1256, 1186 cm^{-1}; GCMS (EI) *m/e* (%) 238 (M+1), 237 (M^+), 181, 168 (100), 41; HRMS (ESI) calcd for $C_{10}H_{15}F_3NO_2$ *m/e*=238.1055; found 238.1064.

4.5.4. 1-Isopropyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7c). Yield: 56%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (d, $^3J_{H,H}$=6.9 Hz, 6H, CH_3), 2.78 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.1 Hz, 1H, H-4), 2.93 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.5 (m, 1H, H-3), 4.40 (sept, $^3J_{H,H}$=6.9 Hz, 1H, NC*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.9 (s, CH_3), 29.3 (q, $^3J_{C,F}$=1.8 Hz, C-4), 44.0 (q, $^2J_{C,F}$=29.5 Hz, C-3), 44.7 (s, NCH), 123.8 (q, $^1J_{C,F}$=278.7 Hz, CF_3), 169.5 (m, C-2), 173.4 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.6 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 2982, 1785, 1716, 1404, 1369 cm^{-1}; GCMS (EI) *m/e* (%) 210 (M+1), 209 (M^+), 194, 168 (100), 123, 95, 44; HRMS (ESI) calcd for $C_8H_{11}F_3NO_2$ *m/e*=210.0742; found 210.0740.

4.5.5. 1-(1′-Phenylethyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7d). Yield: 76%; mixture (50/50) of diastereomers; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.82 (d, $^3J_{H,H}$=7.3 Hz, 3H+3H, CH_3), 2.78 and 2.79 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=5.0 Hz, 1H+1H, H-4), 2.90 and 2.92 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H+1H, H-4), 3.5 (m, 1H+1H, H-3), 5.45 and 5.46 (q, $^3J_{H,H}$=7.3 Hz, 1H+1H, NC*H*), 7.2–7.5 (m, 5H+5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.1 and 16.4 (s, CH_3), 29.3 (m, C-4), 44.0 (q, $^2J_{C,F}$=29.9 Hz, C-3), 51.0 and 51.2 (s, NCH), 123.7 and 123.8 (q, $^1J_{C,F}$=278.8 Hz, CF_3), 127.3 and 127.5 (s, 2×CH Ph), 128.0 and 128.1 (s, CH Ph), 128.5 (s, 2×CH Ph), 138.5 and 138.7 (s, C_q Ph), 169.3 (m, C-2), 173.1 and 173.2 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.5 and −69.4 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 2981, 1713, 1606, 1505, 1455, 1385 cm^{-1}.

4.6. General procedure for preparation of succinimides (7e–i) (Scheme 5, path b)

The same procedure as described for path a (Scheme 5), except that the mixture was heated at 110 °C for 2 h, gave after work-up and purification by silica gel chromatography (mixture of petroleum ether–ethyl acetate) the succinimides **7e–i**.

4.6.1. 1-Phenyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7e). Yield: 81%; solid: mp 117 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.86 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.5 Hz, 1H, H-4), 2.99 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 7.1 (dm, $^3J_{H,H}$=7.5 Hz, 2H, 2×CH Ph), 7.4 (m, 3H, 3×CH Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=2.0 Hz, C-4), 44.4 (q, $^2J_{C,F}$=29.9 Hz, C-3), 123.7 (q, $^1J_{C,F}$=278.5 Hz, CF_3), 126.3 (s, 2×CH Ph), 129.2 (s, CH

Ph), 129.3 (s, 2×CH Ph), 131.0 (s, C_q Ph), 168.7 (q, $^3J_{C,F}$= 2.7 Hz, C-2), 172.5 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.2 (d, $^3J_{F,H}$=9.5 Hz); IR (KBr) 3074, 2960, 1717, 1406, 1212 cm^{-1}; GCMS (EI) *m/e* (%) 243 (M^+), 174, 120, 95, 91 (100), 77. Anal. Calcd for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.56; H, 3.13; N, 5.72.

4.6.2. 1-(*p*-Methoxyphenyl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7f). Yield: 81%; solid: mp 148–150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.95 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.3 Hz, 1H, H-4), 3.09 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$= 9.6 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 3.82 (s, 3H, CH_3), 6.98 (d, $^3J_{H,H}$=8.6 Hz, 2H, 2×CH Ar), 7.15 (d, $^3J_{H,H}$=8.6 Hz, 2H, 2×CH Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (q, $^3J_{C,F}$=2.0 Hz, C-4), 44.3 (q, $^2J_{C,F}$=30.1 Hz, C-3), 55.4 (s, CH_3), 114.5 (s, 2×CH Ar), 123.5 (s, NC_q Ar), 123.7 (q, $^1J_{C,F}$=279.1 Hz, CF_3), 127.5 (s, 2×CH Ar), 159.8 (s, OC_q Ar), 169.0 (q, $^3J_{C,F}$=3.2 Hz, C-2), 172.8 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$=8.6); IR (KBr) 3020, 2955, 1714, 1609, 1445, 1411 cm^{-1}; GCMS (EI) *m/e* (%) 273 (M^+, 100), 204, 122. Anal. Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.75; H, 3.69; N, 5.13. Found: C, 52.89; H, 3.63; N, 4.80.

4.6.3. 1-(Pyridin-2-yl)-3-trifluoromethyl-pyrrolidine-2,5-dione (7g). Yield: 31%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.04 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=5.4 Hz, 1H, H-4), 3.20 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=9.7 Hz, 1H, H-4), 3.8 (m, 1H, H-3), 7.30 (dd, $^3J_{H,H}$=7.9, $^4J_{H,H}$=0.9 Hz, 1H, CH Ar), 7.41 (ddd, $^3J_{H,H}$=7.9, $^3J_{H,H}$=4.9, $^4J_{H,H}$=0.9 Hz, 1H, CH Ar), 7.89 (ddd, $^3J_{H,H}$=7.9, $^3J_{H,H}$=7.9, $^4J_{H,H}$=1.8 Hz, 1H, CH Ar), 8.65 (dm, $^3J_{H,H}$=4.9 Hz, 1H, CH Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.8 (m, C-4), 44.7 (q, $^2J_{C,F}$= 30.1 Hz, C-3), 122.2 (s, CH Ar), 123.7 (q, $^1J_{C,F}$=278.8 Hz, CF_3), 124.6 (s, CH Ar), 138.7 (s, CH Ar), 145.3 (s, C_q Ar), 149.9 (s, CH Ar), 168.2 (m, C-2), 171.9 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.0 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3064, 2930, 1798, 1736, 1594, 1472, 1439, 1387 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8F_3N_2O_2$ *m/e*=245.0538; found 245.0534.

4.6.4. 1-Amino-3-trifluoromethyl-pyrrolidine-2,5-dione (7h). Yield: 45%; oil; ^{1}H NMR (250 MHz, CD_3OD) δ 2.86 (dd, $^2J_{H,H}$=18.3, $^3J_{H,H}$=4.8 Hz, 1H, H-4), 3.09 (dd, $^2J_{H,H}$=18.3, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.97 (qdd, $^3J_{H,F}$= 9.5, $^3J_{H,H}$=9.5, $^3J_{H,H}$=4.8 Hz, 1H, H-3), NH_2 not visible; ^{13}C NMR (62.9 MHz, CD_3OD) δ 29.5 (q, $^3J_{C,F}$=2.1 Hz, C-4), 44.8 (q, $^2J_{C,F}$=29.9 Hz, C-3), 126.5 (q, $^1J_{C,F}$= 277.4 Hz, CF_3), 170.8 (q, $^3J_{C,F}$=3.2 Hz, C-2), 174.7 (s, C-5); ^{19}F NMR (235.4 MHz, CD_3OD) δ −68.7 (d, $^3J_{F,H}$= 9.5 Hz); GCMS (EI) *m/e* (%) 183 (M+1), 156, 123, 95 (100), 77, 69; HRMS (ESI) calcd for $C_5H_6F_3N_2O_2$ *m/e*= 183.0381; found 183.0376.

4.6.5. 1-Methylamino-3-trifluoromethyl-pyrrolidine-2,5-dione (7i). Yield: 47%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.71 (d, $^3J_{H,H}$=5.2 Hz, 3H, CH_3), 2.83 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$=4.8 Hz, 1H, H-4), 3.00 (dd, $^2J_{H,H}$=18.6, $^3J_{H,H}$= 9.5 Hz, 1H, H-4), 3.6 (m, 1H, H-3), 4.73 (q, $^3J_{H,H}$=5.2 Hz, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.8 (q, $^3J_{C,F}$= 2.1 Hz, C-4), 37.5 (s, CH_3), 42.7 (q, $^2J_{C,F}$=30.1 Hz, C-3), 123.5 (q, $^1J_{C,F}$=279.0 Hz, CF_3), 167.0 (q, $^3J_{C,F}$=3.2 Hz, C-2), 170.9 (s, C-5); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.5 (d, $^3J_{F,H}$=9.5 Hz); IR (film) 3497, 3303, 2944, 1717, 1361, 1259, 1178 cm^{-1}; GCMS (EI) *m/e* (%) 197 (M+1), 168, 95, 77, 69 (100); HRMS (ESI) calcd for $C_6H_8F_3N_2O_2$ *m/e*=197.0538; found 197.0543.

4.7. Preparation of the succinimide (7j) (Scheme 6)

To a suspension of sodium ethoxide (68 mg, 1.00 mmol, 2.00 equiv) in dry toluene (3 mL) was added *N*,*N*′-dimethylhydrazine dihydrochloride (69 mg, 0.52 mmol, 1.05 equiv). The mixture was stirred at room temperature for 1 h. The γ-carboxy thioester **5** (0.12 g, 0.50 mmol, 1.00 equiv) was then added. The resulting mixture was heated at 110 °C for 2 h and gave after work-up and purification by silica gel chromatography (mixture of petroleum ether–EtOAc (80/20)) the succinimide **7j** (27 mg, 30%).

4.7.1. 1-Methyl-3-trifluoromethyl-pyrrolidine-2,5-dione (7j). Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.87 (dd, $^2J_{H,H}$= 18.5, $^3J_{H,H}$=5.3 Hz, 1H, H-4), 3.01 (dd, $^2J_{H,H}$=18.5, $^3J_{H,H}$=9.5 Hz, 1H, H-4), 3.07 (s, 3H, NCH_3), 3.6 (m, 1H, H-3); ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −69.3 (d, $^3J_{F,H}$= 8.6 Hz); GCMS (EI) *m/e* (%) 182 (M+1), 181 (M^+), 124, 96 (100).

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