Synthesis of New Trifluoromethylated Furans, Dihydrofurans and Butenolides Starting from γ-Ketothioesters and Diisopropylamine

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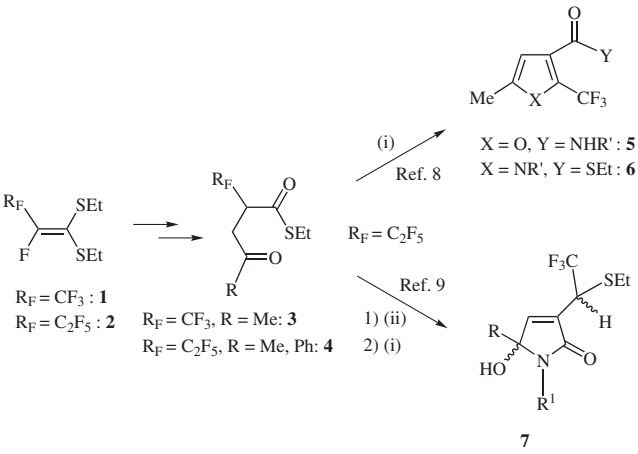
Abstract: γ-Ketothioesters were easily transformed into furans, dihydrofurans or butenolides by simple treatment with diisopropylamine in diethyl ether. The substitution pattern of the starting material has a great influence on the outcome of the reaction. Possible mechanisms for the formation of the heterocycles were proposed. The structures of all new compounds were ascribed using usual NMR data (^{19}F, ^{1}H, ^{13}C NMR), X-ray diffraction analysis and ^{1}H–^{1}H NOE experiments.

Key words: fluorine, heterocycle, furan, dihydrofuran, butenolide

The increasing interest in trifluoromethylated heterocycles[1,2] and the need of new fluorinated scaffolds for parallel synthesis prompted us to investigate the applications of perfluoroketene dithioacetals **1**, **2** and γ-ketothioesters **3**, **4** towards the synthesis of a large variety of heterocycles. Perfluoroketene dithioacetals **1**, **2** are versatile building blocks owing to the easy nucleophilic substitution of the vinylic fluoride and to the masked carboxylic function.[3,4] We have reported the convenient conversion of compounds **1**, **2** into the corresponding γ-ketothioesters **3**, **4** (Scheme 1).[5,6] The thioester **3** was shown to be an excellent precursor for the preparation of trifluoromethyl γ-lactones,[5] γ-lactams,[6] pyridazin-3-ones[7] and pyridazines.[7] The higher homologues **4** offered further developments, since an additional HF elimination easily occurred under basic conditions. Indeed, when **4** (R = Me) was treated with primary amines (which are basic as well as nucleophilic reagents), trifluoromethylated furans **5** and pyrroles **6** were obtained in good yields (Scheme 1).[8] More recently, γ-ketothioesters **4** (R = Me, Ph) were used in a one-pot synthesis to prepare new α,β-unsaturated γ-lactams **7** (Scheme 1).[9]

As previously reported,[8] the reaction of γ-ketothioester **4** (R = Me) with non-nucleophilic diisopropylamine led to the furan thioester **8** in moderate yield (Scheme 2). Surprisingly, when the same reaction was done with the aromatic γ-ketothioester analogue (Scheme 2, R^1 = Ph), the new heterocyclic compound **9** was isolated as a mixture (53:47) of stereoisomers, instead of the expected furan.



Scheme 1 *Reagents and conditions*: (i) R^1NH_2, Et_2O, r.t., 24 h; (ii) *i*-Pr_2NH, Et_2O, r.t. or reflux, 22–24 h.

The present paper reports on the full investigation of this new transformation, especially the influence of substituents of the starting material on the outcome of the reaction.

The new γ-ketothioesters **16**–**19** were obtained according to the following two-step procedure: nucleophilic substitution[5] of the vinylic fluoride of perfluoroketene dithioacetal **10** or **11** (prepared from heptafluorobutanal hydrate)[3] by potassium enolates of ketones, followed by acid hydrolysis[6] of intermediates **12**–**15** (Scheme 3, Table 1). This methodology allows us to introduce structural diversity at the initial step (using various aromatic thiols) as well as at the vinylic substitution step (both aliphatic and aromatic enolates worked well).

Only a few analogues of arylsulfanyl perfluoroketene dithioacetals **10**, **11** were reported in the literature.[10]

The γ-ketothioesters **16**–**19** were then reacted with diisopropylamine. We used our reported procedure[8] using two equivalents of diisopropylamine in diethyl ether at room temperature overnight. The reactions led to different types of compounds, in moderate to good yields (Scheme 4, Table 2), depending on the substitution pattern of the starting material.

The first experiment carried out on the γ-ketothioester **4** (R = Me) bearing an ethylsulfanyl group gave the furan **8**

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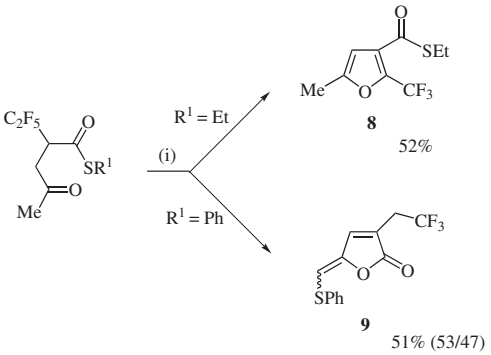
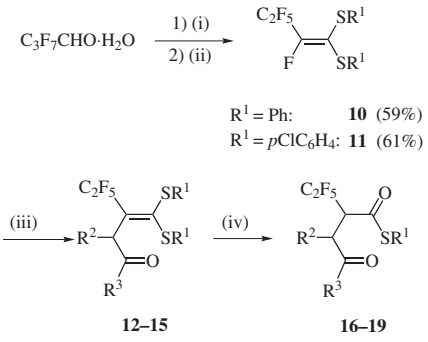


Scheme 2 *Reagents and conditions*: (i) *i*-Pr_2NH, Et_2O, r.t., 14 h.

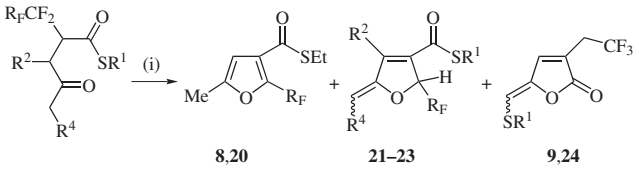


Scheme 3 *Reagents and conditions*: (i) R^1SH, $TiCl_4$, CH_2Cl_2; (ii) aq KOH, Bu_4NBr, CH_2Cl_2; (iii) $R^2CH_2COR^3$, KH, THF, 0 °C; (iv) TFA, H_2O, Δ.

and its tautomeric methylene form **21** (Scheme 4, Table 2, entry 1).[8] These two trifluoromethylated heterocycles were easily separated by silica gel column chromatography. Similar behavior was also observed for a higher perfluoroalkyl chain analogue [Scheme 4, $R_F = (CF_2)_2H$] leading to a mixture of furan **20** and dihydrofuran **22** (Table 2, entry 2).[9] Although we have not studied this issue further, we assume that the reaction occurs under thermodynamic control owing to the acido-basic (*i*-$Pr_2NH_2^+$/*i*-Pr_2NH) medium. As a consequence, the fully conjugated methylene derivatives **21** and **22** would have a resonance energy only slightly lower than those of the corresponding furans **8** and **20**, respectively. It is worth noting that perfluoroalkyl substituent (R_F) has no significant influence on the outcome of the reaction.

Most of the syntheses of 2-(trifluoromethyl)furans described in the literature are based on direct fluorination,[11] trifluoromethylation methodology,[12] or building-block strategies.[8,13] Fluorinated or non-fluorinated dihydrofuran derivatives such as **21**–**23** have not yet been reported.

In order to determine the effect of the thioester moiety, the phenylsulfanyl thioester **16** was reacted with diisopropylamine using the same conditions. Instead of furan or its tautomer, the butenolide **9** was obtained as a mixture (53:47) of stereoisomers (Table 2, entry 3). The reaction was also extended to *p*-ClC_6H_4 substituted derivative **19** which gave the new unsaturated γ-lactone **24** as a mixture (71:29) of stereoisomers. Therefore, this unexpected behavior of arylsulfanyl γ-ketothioesters seemed to be general. The stereoisomers of **9** and **24** were separated by silica gel column chromatography, major stereoisomers being identified with the letter **a**.



Scheme 4 *Reagents and conditions*: (i) *i*-Pr_2NH, Et_2O, 25 °C, 14 h.

It is worth noting that spontaneous isomerization of compound **9** or **24** occurred in solution, even at room temperature. For example, a $CDCl_3$ solution of stereoisomers of **9** ranged from 14:86 to 51:49 after one night at room temperature. Moreover, this isomerization process was favored when the solution was heated to 50 °C leading to a thermodynamic ratio of 85:15 after 24 hours.

To the best of our knowledge, compounds **9** and **24** are the first examples of such unsaturated arylsulfanyl trifluoromethyl butenolides. There is only one paper reporting on the synthesis of a non-fluorinated analogue which was prepared from Wittig reaction of cyclic anhydride.[14]

An important problem was the confirmation of the structure and the stereochemistry of the new butenolides **9** and

Table 1 Preparation of Ketene Dithioacetals **12**–**15** and γ-Ketothioesters **16**–**19**

Entry	Starting material	R^1	R^2	R^3	Ketene dithioacetal (%)	γ-Ketothioester (%)
1	**10**	Ph	H	Me	**12** (79)	**16** (75)
2	**10**	Ph	H	Ph	**13** (80)[a]	**17** (91)
3	**10**	Ph	Me	Et	**14** (66)	**18** (63)[b]
4	**11**	*p*-ClC_6H_4	H	Me	**15** (83)	**19** (62)

[a] Compound **13** was accompanied by small amount of undetermined fluorinated product.
[b] Compound **18** was obtained as a mixture (72:28) of diastereoisomers, undetermined configuration.

Table 2 Reactions of γ-Ketothioesters with Diisopropylamine

Entry	R_F	R^1	R^2	R^4	Furan (%)	Dihydrofuran (%)	Butenolide (%)
1	CF_3	Et	H	H	**8** (52)	**21** (16)	–
2	$(CF_2)_2H$	Et	H	H	**20** (51)	**22** (7)	–
3	CF_3	Ph	H	H	–	–	**9** (51)[a]
4	CF_3	*p*-ClC_6H_4	H	H	–	–	**24** (72)[b]
5	CF_3	Ph	Me	Me	–	**23** (46)[c]	–

[a] Mixture of stereoisomers (53:47).
[b] Mixture of stereoisomers (71:29).
[c] Mixture of stereoisomers (67:33).

24. We performed two types of experiments: X-ray diffraction analysis on **9a** and ^1H–^1H NOE study on **24a**.

After slow evaporation of a dichloromethane solution of the major stereomer **9a**, we obtained crystals that were suitable for X-ray diffraction analysis. The perspective view of **9a** is given in Figure 1. The X-ray clearly showed a *cis* relationship between the phenylsulfanyl group and the lactone moiety.

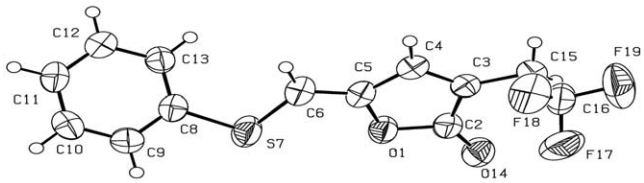


Figure 1 View and atom labeling of **9a**[15]

The comparison of ^{19}F, ^1H or ^{13}C NMR spectra of compounds **9** and **24** gave no useful evidence to ascribe the stereochemistry of the butenolide **24**. Therefore we recorded ^1H–^1H NOE spectra of the major stereoisomer **24a**. Irradiation of the olefinic proton H_a at δ = 6.21 ppm induced a 13% NOE on the olefinic proton H_b and a 4% NOE on the aromatic proton H_c, respectively (Figure 2). This observation confirmed the close relationship between the protons H_a and H_b, which was in good agreement with the *cis* configuration between the (*p*-chlorophenyl)sulfanyl group and the lactone moiety. Moreover, irradiation of the methylenic protons H_d at δ = 3.24 ppm induced a 4% NOE on the olefinic proton H_b (Figure 2).

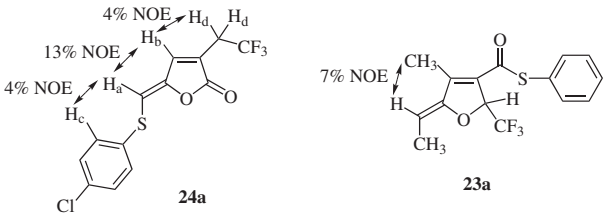


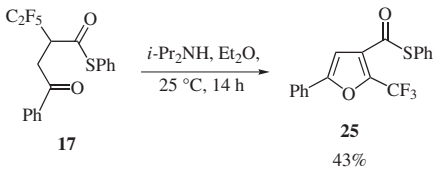
Figure 2 Selected ^1H–^1H NOE for compounds **23a** and **24a**

In order to study the influence of the substituents R^2 and R^4 of γ-ketothioesters (Scheme 4), the compound **18** was reacted with diisopropylamine in the standard conditions. Surprisingly, butenolide was not obtained, but the dihydrofuran **23** was isolated in a moderate yield as a mixture (67:33) of stereoisomers (Table 2, entry 5).

Heterocycle **23** showed similar spectroscopic data as its analogue **21**: two doublets at –67.8 ppm and –68.6 ppm ($^3J_{F,H}$ = 8.8 Hz) for the trifluoromethyl group (^{19}F NMR), a quartet at 5.54 ppm ($^3J_{H,H}$ = 7.5 Hz) for the olefinic proton (^1H NMR), and a singlet at 168.3 ppm which is characteristic of the α,β-unsaturated thioester carbonyl (^{13}C NMR). The configuration of the major stereoisomer **23a** was ascribed using NOE experiments. Irradiation of the methyl substituent at δ = 2.18 ppm induced a 7% NOE on the olefinic proton which proved their close relationship and confirmed the *Z* configuration (Figure 2).

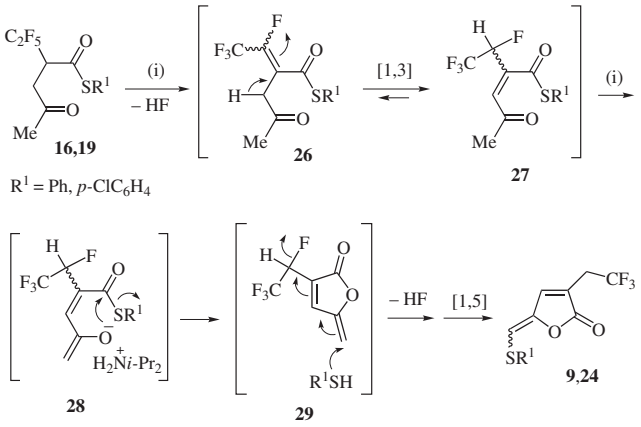
Then, to assess the scope and limitations of our methodology, the reaction was extended to 4-phenyl substituted γ-ketothioester **17**. As expected, the reaction of **17** with two equivalents of diisopropylamine afforded the new furan **25** in moderate yield (Scheme 5). This heterocycle was quite unstable and was spontaneously transformed, in $CDCl_3$ solution, into an unidentified trifluoromethyl compound, which itself quickly decomposed into a very complex mixture.

In order to explain the present results (Schemes 4 and 5), we had to examine the possible mechanisms for the cyclization reaction of γ-ketothioesters with diisopropylamine. The reaction pathways leading to the furan and butenolide derivatives have a common first step: the easy elimination of HF. Then, deprotonation by diisopropylamine, giving an enolate which undergoes an intramolecular Michael addition–fluoride elimination sequence,



Scheme 5

leads to the furans **8**, **20** and dihydrofurans **21**–**23**.[8] The formation of the new butenolides **9** and **24** may be explained by the mechanism depicted in Scheme 6, where the HF elimination is followed by a 1,3-proton shift leading to the intermediate **27**. Such a process was already observed during the treatment of γ-carboethoxythioester analogue with triethylamine affording ethyl 3-ethylsulfanyl-4-fluoro-5,5,5-trifluoropent-2-enoate.[16] A second deprotonation with diisopropylamine gives the enolate **28** which may substitute the arylsulfanyl group (Scheme 6). Then the highly conjugated γ-lactone **29** reacts as a Michael acceptor with the resulting thiol giving, after HF elimination and a 1,5-proton migration sequence, the desired butenolides **9**, **24**.



Scheme 6 *Reagents and conditions*: (i) *i*-Pr_2NH, Et_2O, 25 °C, 14 h.

In conclusion, this work extends the field of synthetic applications of perfluoroketene dithioacetals. The synthons **10** and **11** were easily converted into the corresponding γ-ketothioesters **16**–**19** which behave as useful building blocks for the synthesis of new heterocycles such as furans **8** and **20**, dihydro derivatives **21**–**23** as well as butenolides **9** and **24**. The selectivity depends on the sulfur substituent: ethylsulfanyl substitution favored the formation of furan derivatives whereas butenolides were obtained exclusively from aryl γ-ketothioester. The structures of compounds **9**, **23**, **24** were confirmed by X-ray diffraction analysis (for **9a**) and by homonuclear NOE experiments (for **23a** and **24a**). γ-Lactones **9**, **24** exhibit highly conjugated ester function which could be an interesting precursor for the synthesis of a new type of α,β-unsaturated lactams; this new aspect is under investigation.

For information on instruments used, see ref.[17] Compounds **10**, **11**[3], **12**–**15**[5] and **16**–**19**[6,8] were prepared according to reported procedures. For spectroscopic data of ketene dithioacetals **10**–**15** and γ-ketothioesters **16**–**19** see Table 3.

Reaction of γ-Ketothioesters with Diisopropylamine; General Procedure (Scheme 4, Table 2)

Diisopropylamine (0.33 mL, 2.44 mmol, 2.0 equiv) was added to a solution of γ-keto thioester **16**–**19** (1.22 mmol, 1.0 equiv) in Et_2O (6 mL). A white solid precipitated immediately. The mixture was stirred for 14 h at r.t., then diluted with Et_2O (10 mL) and washed with brine (10 mL). The aqueous phase was extracted with Et_2O (4 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with PE–EtOAc (96:4 for **9**, **24**, and 98:2 for **23**, **25**] to give the heterocycles **9**, **23**–**25** (Tables 2 and 4).

Table 3 Spectroscopic Data of Ketene Dithioacetals **10**–**15** and γ-Keto Thioesters **16**–**19**

Compd[a]	Solvent[b]	IR (cm^{-1})	GC/MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
10[d]	PE	3062, 1603, 1583, 1279, 1215	380 [M^+], 261, 227, 152, 127	–83.9 (m, 3 F), –100.1 (m, 1 F), –112.6 (m, 2 F)	7.0–7.1 (m, 4 H), 7.1–7.3 (m, 6 H)	109.1 (m, CF_2), 118.4 (qtd, $^1J_{C,F}$ = 287.5 Hz, $^2J_{C,F}$ = 37.1 Hz, $^3J_{C,F}$ = 3.2 Hz, CF_3), 127.3 (dm, $^2J_{C,F}$ = 20.1 Hz, C_q), 127.9 (s, CH), 128.7 (s, 2 × CH), 128.8 (s, 3 × CH), 129.2 (d, $^4J_{C,F}$ = 3.2 Hz, C_q), 131.0 (s, 2 × CH), 131.3 (s, C_q), 134.3 (s, 2 × CH), 144.5 (dt, $^1J_{C,F}$ = 267.6 Hz, $^2J_{C,F}$ = 26.6 Hz, CF)
11	PE	1605, 1573, 1476, 1391	450 [M + 1], 448, 305, 261, 186, 161, 107	–83.9 (m, 3 F), –98.6 (m, 1 F), –112.6 (m, 2 F)	6.92 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 6.96 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 7.12 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 7.15 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H)	108.4 (tq, $^1J_{C,F}$ = 260.1 Hz, $^2J_{C,F}$ = 39.4 Hz, CF_2), 118.3 (qt, $^1J_{C,F}$ = 287.6 Hz, $^2J_{C,F}$ = 38.7 Hz, CF_3), 126.1 (d, $^2J_{C,F}$ = 20.4 Hz, C_q), 127.4 (d, $^4J_{C,F}$ = 2.7 Hz, C_q), 129.0 (s, 2 × CH), 129.2 (s, 2 × CH), 129.5 (m, C_q), 132.1 (s, 2 × CH), 134.5 (s, C_q), 135.5 (s, 2 × CH), 135.6 (s, C_q), 145.1 (dt, $^1J_{C,F}$ = 269.7 Hz, $^2J_{C,F}$ = 26.9 Hz, CF)

Table 3 Spectroscopic Data of Ketene Dithioacetals **10–15** and γ-Keto Thioesters **16–19** (continued)

Compd[a]	Solvent[b]	IR (cm^{-1})	GC/MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
12[e]	PE–EtOAc (98:2)	3053, 2928, 1716, 1581, 1556	418 [M+], 375, 360, 308, 297, 123	–83.2 (t, $^{3}J_{F,F}$ = 3.6 Hz, 3 F), –107.3 (m, 2 F)	2.28 (s, 3 H), 3.90 (m, 2 H), 6.97 (d, $^{3}J_{H,H}$ = 7.6 Hz, 2 H), 7.07 (m, 2 H), 7.1–7.3 (m, 6 H)	29.4 (s, CH_3), 46.7 (t, $^{3}J_{C,F}$ = 2.5 Hz, CH_2), 113.2 (tq, $^{1}J_{C,F}$ = 257.0 Hz, $^{2}J_{C,F}$ = 39.2 Hz, CF_2), 119.2 (qt, $^{1}J_{C,F}$ = 288.0 Hz, $^{2}J_{C,F}$ = 39.5 Hz, CF_3), 126.2 (t, $^{2}J_{C,F}$ = 21.5 Hz, C_q), 127.5 (s, CH), 128.2 (s, CH), 128.4 (s, 2 × CH), 128.5 (s, 2 × CH), 131.2 (s, 2 × C_q), 131.7 (s, 2 × CH), 132.8 (s, 2 × CH), 147.7 (m, C_q), 202.1 (s, CO)
13[f]	PE–EtOAc (98:2)	3058, 2930, 1690, 1560, 1439	480 [M+], 375, 297, 110, 105, 77	–83.1 (t, $^{3}J_{F,F}$ = 3.6 Hz, 3 F), –107.5 (m, 2 F)	4.56 (s, 2 H), 7.06 (d, $^{3}J_{H,H}$ = 8.0 Hz, 2 H), 7.17–7.26 (m, 2 H), 7.28–7.36 (m, 6 H), 7.59 (d, $^{3}J_{H,H}$ = 7.7 Hz, 2 H), 7.69 (m, 1 H), 8.10 (d, $^{3}J_{H,H}$ = 7.7 Hz, 2 H)	42.5 (m, CH_2), 105–125 (m, CF_2 + CF_3), 126.5 (t, $^{2}J_{C,F}$ = 22.0 Hz, C_q), 127.5 (s, CH), 128.2 (s, 3 × CH), 128.5 (s, 4 × CH), 128.7 (s, 2 × CH), 131.4 (s, C_q), 131.7 (s, 2 × CH), 132.9 (s, 2 × CH), 133.0 (s, C_q), 133.5 (s, CH), 136.0 (s, C_q), 147.8 (s, C_q), 193.9 (s, CO)
14	PE–EtOAc (98:2)	3050, 2981, 1716, 1543, 1476	446 [M+], 389, 279, 160, 137, 109	–81.7 (m, 3 F), –99 to –102 (m, 1 F), –107.1 (dm, $^{2}J_{F,F}$ = 263.9 Hz, 1 F)	0.99 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H), 1.48 (d, $^{3}J_{H,H}$ = 6.9 Hz, 3 H), 2.4–2.7 (m, 2 H), 3.73 (q, $^{3}J_{H,H}$ = 6.9 Hz, 1 H), 6.8–6.9 (m, 4 H), 7.0–7.2 (m, 6 H)	7.8 (s, CH_3), 15.2 (s, CH_3), 33.0 (s, CH_2), 50.5 (s, CH), 114.1 (tq, $^{1}J_{C,F}$ = 270.9 Hz, $^{2}J_{C,F}$ = 39.5 Hz, CF_2), 119.1 (qt, $^{1}J_{C,F}$ = 288.3 Hz, $^{2}J_{C,F}$ = 39.5 Hz, CF_3), 127.8 (s, CH), 128.1 (s, CH), 128.4 (s, 2 × CH), 128.5 (s, 2 × CH), 131.2 (s, 2 × C_q), 132.0 (s, 2 × CH), 132.4 (s, 2 × CH), 133.0 (t, $^{2}J_{C,F}$ = 18.8 Hz, C_q), 147.0 (m, C_q), 207.8 (s, CO)
15[g]	PE–EtOAc (98:2)	3082, 2914, 1726, 1572, 1476	486 [M+], 331, 189, 157, 143, 108, 43	–83.3 (t, $^{3}J_{F,F}$ = 3.6 Hz, 3 F), –107.4 (m, 2 F)	2.18 (s, 3 H), 3.79 (s, 2 H), 6.83 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H), 6.91 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H), 7.10 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H), 7.11 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H)	29.5 (s, CH_3), 46.6 (t, $^{3}J_{C,F}$ = 4.3 Hz, CH_2), 113.0 (tq, $^{1}J_{C,F}$ = 257.9 Hz, $^{2}J_{C,F}$ = 39.0 Hz, CF_2), 119.0 (qt, $^{1}J_{C,F}$ = 288.0 Hz, $^{2}J_{C,F}$ = 39.5 Hz, CF_3), 127.3 (t, $^{2}J_{C,F}$ = 21.5 Hz, C_q), 128.8 (s, 2 × CH), 128.9 (s, 2 × CH), 129.5 (s, C_q), 131.2 (s, C_q), 132.8 (s, 2 × CH), 134.0 (s, C_q), 134.1 (s, 2 × CH), 134.8 (s, C_q), 146.5 (m, C_q), 201.7 (s, CO)
16	PE–Et_2O (98:2)	3064, 2933, 1724, 1703, 1479	344 [M + 1 + NH_3], 327 [M + 1], 193, 109, 94, 78[h]	–82.4 (m, 3 F), –115.0 (dd, $^{2}J_{F,F}$ = 273.8 Hz, $^{3}J_{F,H}$ = 14.4 Hz, 1 F), –116.4 (dd, $^{2}J_{F,F}$ = 273.8 Hz, $^{3}J_{F,H}$ = 14.4 Hz, 1 F)	2.23 (s, 3 H), 2.93 (dd, $^{2}J_{H,H}$ = 18.4 Hz, $^{3}J_{H,H}$ = 3.2 Hz, 1 H), 3.33 (dd, $^{2}J_{H,H}$ = 18.4 Hz, $^{3}J_{H,H}$ = 10.2 Hz, 1 H), 4.05 (m, 1 H), 7.4 (m, 5 H)	29.3 (s, CH_3), 39.5 (s, CH_2), 48.9 (t, $^{2}J_{C,F}$ = 21.0 Hz, CH), 113.3 (tq, $^{1}J_{C,F}$ = 259.5 Hz, $^{2}J_{C,F}$ = 38.2 Hz, CF_2), 118.6 (qt, $^{1}J_{C,F}$ = 286.9 Hz, $^{2}J_{C,F}$ = 36.0 Hz, CF_3), 126.3 (s, C_q), 129.3 (s, 2 × CH), 129.9 (s, CH), 134.3 (s, 2 × CH), 191.5 (s, COS), 202.9 (s, CO)
17	PE–Et_2O (98:2)	3063, 2931, 1691, 1598, 1582	389 [M + 1], 279, 259, 109, 105	–82.3 (m, 3 F), –114.7 (dd, $^{2}J_{F,F}$ = 274.1 Hz, $^{3}J_{F,H}$ = 14.6 Hz, 1 F), –116.4 (dd, $^{2}J_{F,F}$ = 274.1 Hz, $^{3}J_{F,H}$ = 14.6 Hz, 1 F)	3.43 (dd, $^{2}J_{H,H}$ = 18.2 Hz, $^{3}J_{H,H}$ = 2.8 Hz, 1 H), 3.95 (dd, $^{2}J_{H,H}$ = 18.2 Hz, $^{3}J_{H,H}$ = 10.3 Hz, 1 H), 4.29 (m, 1 H), 7.4–7.7 (m, 8 H), 8.00 (dm, $^{3}J_{H,H}$ = 7.7 Hz, 2 H)	35.5 (s, CH_2), 49.3 (t, $^{2}J_{C,F}$ = 20.7 Hz, CH), 110.0–125.0 (m, CF_3 + CF_2), 126.4 (s, C_q), 128.2 (s, 2 × CH), 128.8 (s, 2 × CH), 129.3 (s, 2 × CH), 129.9 (s, CH), 134.0 (s, CH), 134.4 (s, 2 × CH), 135.4 (s, C_q), 191.8 (m, COS), 194.7 (s, CO)
18a[i]	PE–Et_2O (98:2)	2982, 2936, 1712, 1479, 1461	355 [M + 1], 245, 225, 177, 109	–82.9 (m, 3 F), –110.9 (dd, $^{2}J_{F,F}$ = 272.9 Hz, $^{3}J_{F,H}$ = 4.5 Hz, 1 F), –120.6 (dd, $^{2}J_{F,F}$ = 272.9 Hz, $^{3}J_{F,H}$ = 22.4 Hz, 1 F)	1.02 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H), 1.17 (d, $^{3}J_{H,H}$ = 7.1 Hz, 3 H), 2.3–2.7 (m, 2 H), 3.24 (m, 1 H), 4.01 (ddd, $^{3}J_{H,F}$ = 22.2 Hz, *J* = 9.2, 5.7 Hz, 1 H), 7.1–7.5 (m, 5 H)	7.6 (s, CH_3), 15.1 (s, CH_3), 34.8 (s, CH_2), 41.9 (s, CH), 53.9 (t, $^{2}J_{C,F}$ = 19.1 Hz, CH), 105.0–115.0 (m, CF_2), 118.5 (qt, $^{1}J_{C,F}$ = 286.9 Hz, $^{2}J_{C,F}$ = 36.3 Hz, CF_3), 126.2 (s, C_q), 129.5 (s, 2 × CH), 130.2 (s, CH), 134.2 (s, 2 × CH), 190.5 (s, COS), 209.9 (s, CO)

Table 3 Spectroscopic Data of Ketene Dithioacetals **10–15** and γ-Keto Thioesters **16–19** (continued)

Compd[a]	Solvent[b]	IR (cm^{-1})	GC/MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
18b[i]			355 [M + 1], 245, 225, 177, 110, 91	–82.4 (m, 3 F), –107.8 (dd, $^{2}J_{F,F}$ = 278.2 Hz, $^{3}J_{F,H}$ = 8.1 Hz, 1 F), –115.8 (dd, $^{2}J_{F,F}$ = 278.2 Hz, $^{3}J_{F,H}$ = 19.9 Hz, 1 F)	0.97 (d, $^{3}J_{H,H}$ = 7.2 Hz, 3 H), 1.25 (d, $^{3}J_{H,H}$ = 7.1 Hz, 3 H), 2.3–2.7 (m, 2 H), 3.37 (m, 1 H), 3.83 (dm, $^{3}J_{H,F}$ = 20.0 Hz, 1 H), 7.1–7.5 (m, 5 H)	34.6 (s, CH_2), 44.9 (s, CH), 55.4 (t, $^{2}J_{C,F}$ = 19.9 Hz, CH), 110.0–125.0 (m, CF_2 + CF_3), 126.3 (s, C_q), 129.4 (s, 2 × CH), 130.0 (s, CH), 134.3 (s, 2 × CH), 190.4 (s, COS), 210.6 (s, CO)[j]
19	PE–Et_2O (98:2)	2929, 1725, 1705, 1478	361 [M^+], 217, 197, 169, 144, 108	–82.4 (m, 3 F), –114.9 (dd, $^{2}J_{F,F}$ = 274.7 Hz, $^{3}J_{F,H}$ = 14.4 Hz, 1 F), –116.3 (dd, $^{2}J_{F,F}$ = 274.4 Hz, $^{3}J_{F,H}$ = 13.5 Hz, 1 F)	2.20 (s, 3 H), 2.94 (dd, $^{2}J_{H,H}$ = 18.5 Hz, $^{3}J_{H,H}$ = 2.9 Hz, 1 H), 3.32 (dd, $^{2}J_{H,H}$ = 18.5 Hz, $^{3}J_{H,H}$ = 10.4 Hz, 1 H), 4.01 (m, 1 H), 7.34 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H), 7.40 (d, $^{3}J_{H,H}$ = 8.5 Hz, 2 H)	29.5 (s, CH_3), 39.7 (s, CH_2), 49.1 (t, $^{2}J_{C,F}$ = 21.0 Hz, CH), 113.3 (tq, $^{1}J_{C,F}$ = 259.5 Hz, $^{2}J_{C,F}$ = 38.2 Hz, CF_2), 118.6 (qt, $^{1}J_{C,F}$ = 286.9 Hz, $^{2}J_{C,F}$ = 36.0 Hz, CF_3), 124.8 (s, C_q), 129.6 (s, 2 × CH), 135.6 (s, 2 × CH), 136.5 (s, C_q), 191.3 (s, COS), 203.0 (s, CO)

[a] All compounds are oils except **12**, **13** and **15**. Satisfactory microanalyses or HRMS obtained.
[b] Solvent used for chromatographic separation (PE = petroleum ether).
[c] NMR solvent: $CDCl_3$.
[d] Bp 108–112 °C/0.05 mbar.
[e] Mp 92–93 °C.
[f] Mp 120–121 °C.
[g] Mp 111–112 °C.
[h] Chemical ionization (NH_3).
[i] Mixture (72:28) of diastereoisomers (major: **18a**, minor: **18b**). IR spectrum was recorded on the mixture.
[j] Selected data.

X-ray Crystal Structure Determination of Compound 9a (Figure 1)

$C_{13}H_9F_3O_2S$, Mr = 286.26, monoclinic, $P2_1/c$ (Nr 14), *a* = 8.534(2), *b* = 6.058(2), *c* = 24.590(7) Å, β = 99.35(2)°, *V* = 1254.4(6) $Å^3$, *Z* = 4, Dx = 1.52 gcm^{-3}. A total of 7409 reflections were collected using a MAR345 image plate detector and Mo Kα radiation (λ = 0.71069 Å), 2020 independent reflections (R_{int} = 0.065), $2\Theta_{max}$ = 49°. The structure was solved by direct methods with SHELXS-97[18] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97.[18] The H atoms were located by Fourier-difference synthesis and included in the refinement with a common isotropic temperature factor. The final *R* values are *R* = 0.047 for 1773 observed reflections and *wR*2 = 0.121. The data have been deposit with the Cambridge Crystallographic Data Centre (Nr CCDC276673). Selected bond lengths (Å): O(1)–C(2) = 1.390(3), C(2)–O(14) = 1.199(3), C(2)–C(3) = 1.461(3), C(3)–C(4) = 1.340(3), C(4)–C(5) = 1.430(3), O(1)–C(5) = 1.387(3), C(5)–C(6) = 1.334(3), C(6)–S(7) = 1.728(3).

Table 4 Spectroscopic Data of Compounds **9**, **23–25**

Compd[a]	Solvent[b]	IR (cm^{-1})	GC/MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
9a[d]	PE–EtOAc (96:4)	3060, 2924, 1767, 1621, 1607, 1577	286 [M^+], 189, 164, 121	–65.7 (t, $^{3}J_{F,H}$ = 10.3 Hz)	3.25 (q, $^{3}J_{H,F}$ = 10.3 Hz, 2 H), 6.32 (s, 1 H), 7.30 (s, 1 H), 7.3–7.4 (m, 3 H), 7.4–7.5 (m, 2 H)	30.0 (q, $^{2}J_{C,F}$ = 32.2 Hz, CH_2), 115.8 (s, CH), 120.2 (q, $^{3}J_{C,F}$ = 2.7 Hz, C_q), 124.9 (q, $^{1}J_{C,F}$ = 276.7 Hz, CF_3), 128.4 (s, CH), 129.6 (s, 2 × CH), 130.6 (s, 2 × CH), 133.0 (s, C_q), 138.7 (s, CH), 144.9 (s, C_q), 168.6 (s, CO_2)
9b[d]		3074, 2924, 1744, 1604, 1479	286 [M^+], 189, 164, 121, 110	–65.5 (t, $^{3}J_{F,H}$ = 10.2 Hz)	3.28 (q, $^{3}J_{H,F}$ = 10.2 Hz, 2 H), 6.63 (s, 1 H), 7.3–7.5 (m, 5 H), 7.76 (s, 1 H)	30.2 (q, $^{2}J_{C,F}$ = 32.2 Hz, CH_2), 112.5 (s, CH), 123.2 (t, $^{3}J_{C,F}$ = 3.2 Hz, C_q), 124.8 (q, $^{1}J_{C,F}$ = 277.3 Hz, CF_3), 127.8 (s, CH), 129.4 (s, 2 × CH), 129.5 (s, 2 × CH), 133.3 (s, C_q), 136.5 (s, CH), 148.6 (s, C_q), 168.7 (s, CO_2)
23a	PE–EtOAc (98:2)	2925, 2854, 1675, 1650, 1441	314 [M^+], 294, 205, 141, 110, 55	–67.8 (d, $^{3}J_{F,H}$ = 8.8 Hz)	1.99 (d, $^{3}J_{H,H}$ = 7.5 Hz, 3 H), 2.18 (s, 3 H), 4.66 (q, $^{3}J_{H,F}$ = 8.8 Hz, 1 H), 5.54 (q, $^{3}J_{H,H}$ = 7.5 Hz, 1 H), 7.2–7.4 (m, 3 H), 7.5–7.6 (m, 2 H)	10.9 (q, $^{n}J_{C,F}$ = 2.0 Hz, CH_3), 11.9 (s, CH_3), 46.9 (q, $^{2}J_{C,F}$ = 32.2 Hz, CH), 110.2 (s, CH), 120.2 (s, C_q), 125.3 (q, $^{1}J_{C,F}$ = 279.9 Hz, CF_3), 129.0 (s, CH), 129.4 (s, 2 × CH), 132.3 (s, C_q), 133.4 (s, 2 × CH), 150.2 (s, C_q), 151.7 (s, C_q), 168.3 (s, COS)

Table 4 Spectroscopic Data of Compounds **9**, **23**–**25** (continued)

Compd[a]	Solvent[b]	IR (cm^{-1})	GC/MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
23b[e]				–68.6 (d, $^{3}J_{H,F}$ = 8.8 Hz)	2.11 (s, 3 H), 4.38 (q, $^{3}J_{H,F}$ = 8.8 Hz, 1 H)	113.0 (s, CH)
24a	PE–EtOAc (96:4)	3056, 2924, 1733, 1613, 1596	320 [M+], 164, 155, 136, 108, 75, 69	–65.7 (t, $^{3}J_{F,H}$ = 10.4 Hz)	3.24 (q, $^{3}J_{H,F}$ = 10.4 Hz, 2 H), 6.21 (s, 1 H), 7.30 (s, 1 H), 7.36 (d, $^{3}J_{H,H}$ = 8.6 Hz, 2 H), 7.42 (d, $^{3}J_{H,H}$ = 8.6 Hz, 2H)	30.0 (q, $^{2}J_{C,F}$ = 32.3 Hz, CH_2), 114.6 (s, CH), 120.7 (q, $^{3}J_{C,F}$ = 4.0 Hz, C_q), 124.4 (q, $^{1}J_{C,F}$ = 277.2 Hz, CF_3), 129.7 (s, 2 × CH), 131.6 (s, C_q), 131.9 (s, 2 × CH), 134.7 (s, C_q), 138.7 (s, CH), 145.3 (s, C_q), 168.5 (s, CO_2)
24b[e]			320 [M+], 164, 155, 88, 75, 69, 45	–65.4 (t, $^{3}J_{F,H}$ = 10.4 Hz)	3.28 (q, $^{3}J_{H,F}$ = 10.2 Hz, 2 H), 6.55 (s, 1 H)	111.4 (s, CH), 129.6 (s, 2 × CH), 130.6 (s, 2 × CH), 136.5 (s, CH)
25	PE–EtOAc (98:2)	3055, 2924, 1798, 1610, 1562	348 [M+], 279, 239, 105, 77	–57.6 (s)	6.65 (s, 1 H), 7.3–7.5 (m, 8 H), 7.6–7.8 (m, 2 H)	101.1 (q, $^{4}J_{C,F}$ = 3.8 Hz, CH), 122.4 (q, $^{1}J_{C,F}$ = 277.2 Hz, CF_3), 125.8 (s, 2 × CH), 127.0 (s, C_q), 128.8 (s, CH), 129.0 (s, 2 × CH), 129.2 (s, 2 × CH), 130.5 (m, C_q), 131.5 (s, CH), 131.6 (s, C_q), 132.4 (s, 2 × CH), 132.5 (q, $^{2}J_{C,F}$ = 32.7 Hz, C_q), 157.0 (q, $^{4}J_{C,F}$ = 1.6 Hz, C_q), 164.3 (s, COS)

[a] Oil. Satisfactory microanalyses or HRMS obtained. The compounds **9**, **23**, **24** were obtained as a mixture of stereoisomers (major stereoisomers are recognized by the letter **a**).
[b] Solvent used for chromatographic separation (PE = petroleum ether).
[c] NMR solvent: $CDCl_3$.
[d] The stereoisomers of compound **9** were completely separated on silica gel chromatography. Compound **9a** (CH_2Cl_2): mp 127–129 °C; **9b** (CH_2Cl_2): mp 135–136 °C.
[e] Selected data.

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