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Synthesis of trifluoromethyl-substituted salicylates by cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one

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ABSTRACT

A formal [3+3] cyclocondensation of 1,3-bis(silyl enol ethers) with the little-known 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one was studied. In contrast to 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one, this α-oxoketene dithioacetal reacts with 1,3-bis(trimethylsilyloxy)-1,3-butadienes in the presence of $TiCl_4$ to give mainly 6-methylthio-4-(trifluoromethyl)salicylates via 1,2-addition. The scope and limitations of the reaction are discussed.

1. Introduction

Polysubstituted aromatic compounds are useful intermediates in organic syntheses. However, their preparation by classical synthetic methods is restrained by the customary long synthetic routes and the difficult separation of positional isomers which are often formed. Besides, it has not been possible so far to introduce a perfluoroalkyl group using Friedel–Crafts type electrophilic substitution reactions. At the same time, fluorinated arenes represent important molecules in organic and medicinal chemistry [1]. In fact, undesirable metabolic transformations are often avoided, due to the high chemical and biological stability of the fluoro group. Thus, the preparation of specific positional isomers of polysubstituted trifluoromethylated arenes is of considerable current interest [1,2].

Chan and co-workers developed [3] a convenient synthesis of salicylates by cyclocondensation of 1,3-bis(silyl enol ethers) [4] with 3-silyloxy-2-en-1-ones. In recent years, we have extended the scope of this chemistry and studied its application to the synthesis of a variety of functionalized arenes [5]. For example, formal [3+3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **1** with 3-alkoxy-1-alkyl-2-en-1-ones [6], 3-alkoxy-1-trifluoromethyl-2-en-1-ones [7], and related enones [8], in particular with 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one **2** [9], to afford new aromatic compounds has been described. In most reactions developed so far, the products – functionalized salicylates – contain CF_3 group located at C-6 as in compounds **3**. 3,3-Bis(methylthio)propenones **4** have also been successfully applied in reactions with **1** and salicylates **5** have been prepared [10]. In this case, the regioselectivity (initial 1,2-addition) is opposite to the one observed for cyclocondensations of 1,3-bis(silyl enol ethers) **1** with 3-alkoxy- and 3-silyloxypropenones (initial 1,4-addition). In keeping with the greater ability of α-oxoketene dithioacetals to afford products of 1,2-addition with C-nucleophiles (for example, Junjappa–Ila annulation [11]), we envisaged that the reaction of 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one **6** with **1** would

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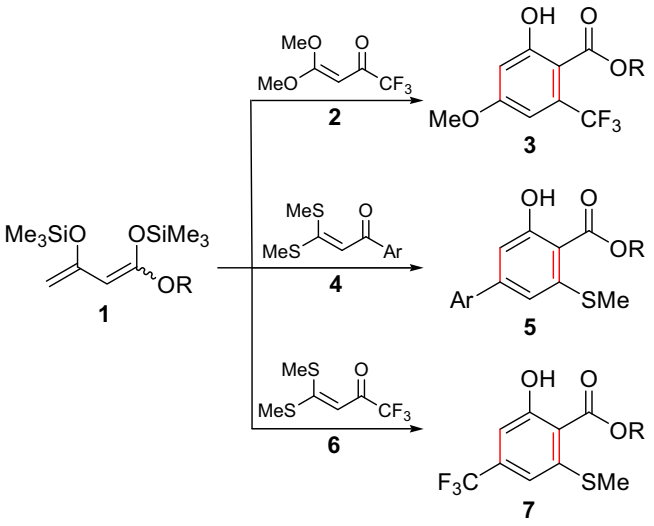
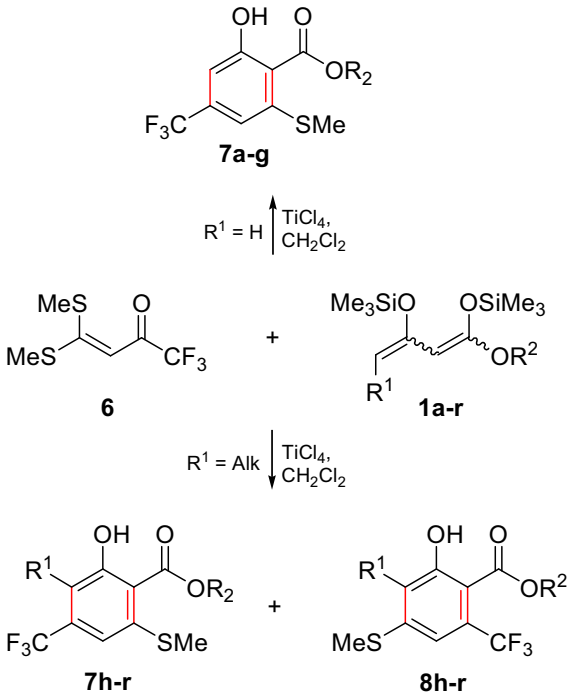


Scheme 1.



Scheme 2.

produce the corresponding 4-trifluoromethyl-substituted salicylates **7**. Indeed, we found that 6-methylthio-4-(trifluoromethyl)salicylates **7** can be obtained by reaction of 1,3-bis(silyl enol ethers) **1**, prepared according to the literature from the corresponding β-ketoesters in two steps [3,12], with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one **6**. The latter was synthesized, following a known procedure [13], by base-mediated reaction of 1,1,1-trifluoroacetone with carbon disulfide and methyl iodide (Scheme 1).

The easy accessibility and high electrophilicity make dithioacetal **6** an attractive candidate for further synthetic elaboration. However, little effort has been devoted to trifluoroacetylketene dithioacetals, especially with respect to C-nucleophiles. To the best of our knowledge, there are only two reports on the reactions of **6** with amines, which proceed via nucleophilic 1,4-addition, followed by elimination [13,14].

2. Results and discussion

It is evident from the reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **1** with a number of electrophiles that the nucleophilic site at C-4 is more reactive than that at C-2 [3–6]. On the other hand, it is known that the allyl and heteroallyl anions add to the α-oxoketene dithioacetals mainly by 1,2-addition [11a,b] (the electron-donating sulfur atoms increase the negative charge of C-4 atom compared with that of electron-withdrawing oxygen atom, which rationalizes their 1,2-addition preference [11c]). In accordance with this, we found that the $TiCl_4$-mediated cyclocondensation of **6** with **1a–g** derived from unsubstituted alkyl acetoacetates afforded the products of 1,2-addition, namely 6-methylthio-4-(trifluoromethyl)salicylates **7a–g**, in 49–56% yields (Scheme 2). The reaction conditions have been optimized for the synthesis of derivative **7d** (Table 1), the structure of which was elucidated by 2D NMR spectroscopic methods (NOESY and COSY). During the optimization, the concentration and the stoichiometry play an important role. The best yield is obtained when the solution is slowly warmed from −78 to 20 °C, when the reaction is carried out in a highly concentrated solution, and when an excess (2.0 equiv.) of **1** is employed. Products **7a–g**, containing the CF_3 group located *para* to the ester group, are formed with excellent regioselectivity. The formation of the other regioisomer, containing the CF_3 group located *ortho* to the ester group, is not observed in these examples. It should be emphasized that acetals **2** and **6** are quite similar in their reactivities with ammonia and primary amines [14], however, their reaction with 1,3-bis(silyl enol ethers) **1** gave completely different products. The reaction of **1** with dithioacetal **6** gave 4-(trifluoromethyl)salicylates **7**, while the reaction of **1** with acetal **2** afforded 6-(trifluoromethyl)salicylates **3** [9].

Having established that the 1,2-addition is the major mechanistic pathway for the reaction of dithioketeneacetal **6** with **1a–g**, it was interesting to study the reaction of **6** with 1,3-bis(silyloxy)-1,3-butadienes **1h–r** containing a terminal substituent. As expected, the regioselectivity of the nucleophilic attack depends on the steric effects of the substituents. In fact, the regioselectivity dropped, however, the 1,2-attack is still dominant. The reaction of dienes **1h–r** with enone **6**, in the presence of $TiCl_4$, afforded mixtures of two regioisomeric products. The expected 6-methylthio-4-(trifluoromethyl)salicylates **7h–r** were formed by 1,2-addition, and the 4-methylthio-6-(trifluoromethyl)salicylates **8h–r** were formed by 1,4-addition in variable proportions and yields (23–69%) (Scheme 2, Table 2).

It is noteworthy that the regioselectivity decreased with increasing steric hindrance of the 1,3-bis(silyl enol ether). This fact suggests that the steric effect of the R^1 group located at the carbon atom C-4 of the diene influences the course of the annulation reaction. The moderate yields can be explained by hydrolysis and $TiCl_4$-mediated oxidative dimerization of dienes **1**. This type of process has been previously reported [15]. Note

Table 1
Optimization of the synthesis of **7d**.

Ratio of **6**:**1d** (mmol)	CH_2Cl_2 (mL)	Yield[a] of **7d** (%)
1:2	0	26
1:1	1	33
1:2	1	56
1:3	1	21
1:2	2	38
1:2	5	39

[a] Yields of the isolated product.

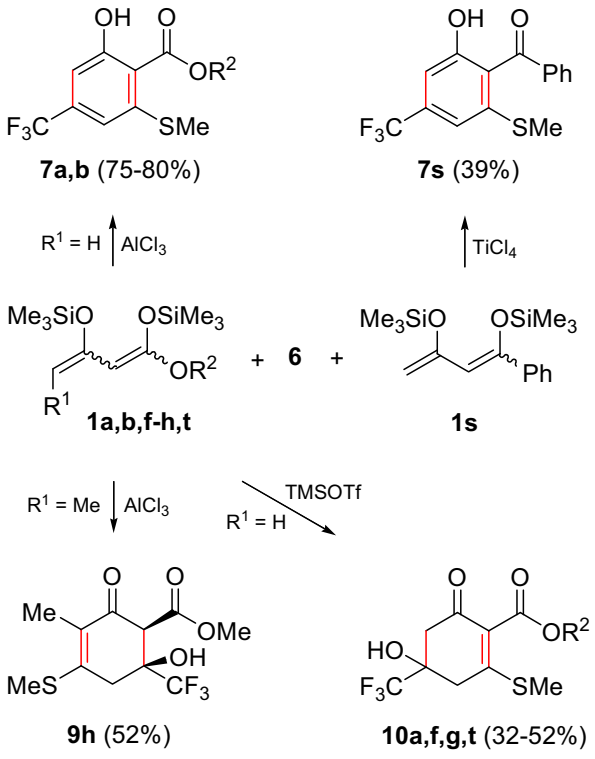
Table 2
Synthesis of salicylates **7** and **8**.

Bissilyl **1**	R^1	R^2	Arenes **7**, **8**	Ratio of **7**:**8**	Yield[a] (%)
a	H	Me	**7a**		52
b	H	Et	**7b**		51
c	H	Bn	**7c**		51
d	H	*i*-Pr	**7d**		56
e	H	*i*-Bu	**7e**		49
f	H	*i*-Pent	**7f**		56
g	H	*n*-Oct	**7g**		55
h	Me	Me	**7h**+**8h**	1:0.1	69
i	Et	Me	**7i**+**8i**	1:0.1	54
j	*n*-Pr	Me	**7j**+**8j**	1:0.1	39
k	*i*-Pr	Et	**7k**+**8k**	1:0.4	50
l	*n*-Bu	Et	**7l**+**8l**	1:0.5	30
m	*n*-Pent	Et	**7m**+**8m**	1:0.7	36
n	*n*-Hept	Et	**7n**+**8n**	1:0.7	34
o	*n*-Oct	Me	**7o**+**8o**	1:0.7	50
p	Allyl	Me	**7p**+**8p**	1:0.5	44
q	$(CH_2)_3Cl$	Me	**7q**+**8q**	1:0.4	54
r	$(CH_2)_3Ph$	Et	**7r**+**8r**	1:1	23

[a] Yields of isolated products.

that regioisomers **7** and **8** could be easily distinguished by the chemical shift of the phenolic proton in a $CDCl_3$ solution. For **7j**,**m**,**o**, this signal is observed as a singlet at δ 11.77–11.86 ppm, whereas for **8j**,**m**,**o** the protons are more shielded (δ 11.17–11.31 ppm).

In an analogous manner the less reactive benzoylacetone-derived diene **1s** gave, by initial 1,2-addition, the benzophenone **7s** as the only isolated product in 39% yield (Scheme 3). This result clearly shows that the present methodology could be applicable to various types of 1,3-bis(silyl enol ethers), providing a rapid route to the synthesis of a great variety of CF_3-containing arenes. The structures of **7a** and **7s** are independently confirmed by X-ray



Scheme 3.

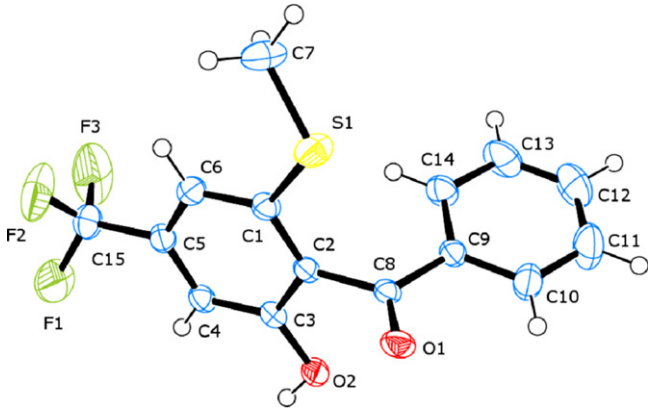


Fig. 1. Molecular structure of compound **7a**.

crystal structure analyses [16] (Figs. 1 and 2). Thus, we have shown that, while the addition of 1,3-bis(silyl enol ethers) to β-alkoxy-α,β-unsaturated fluorinated ketones proceeds by a 1,4-pathway, additions to α-oxoketene dithioacetals occur by preferential 1,2-addition. Obviously, the change in the regioselectivity is a result of the replacement of the methoxy groups by methylthio groups in the 1,1,1-trifluorobut-3-en-2-one. Taking into account that the methylthio substituent can easily be removed by desulfurization [17], this is also a method for preparing 4-CF_3-substituted derivatives of salicylic acid. Given the actual interest in fluoroarenes as pharmaceutical intermediates [1,2], this simple entry to novel fluorinated arenes is useful and complements the published synthetic methods.

When the reaction of **6** with **1a**,**b** was catalyzed by $AlCl_3$ (1.0 equiv.), salicylates **7a**,**b** were isolated in high yield (75–80%), however the other bis-silyls gave no results with $AlCl_3$. The terminal substituted diene **1h** under $AlCl_3$ conditions gave the stable cyclohexenone **9h** in 52% yield. Similar compounds have been observed earlier [9]. The X-ray crystal structure analysis of **9h** allows to unambiguously prove the relative configuration of this molecule [16]. The hydroxyl and the ester group are located *cis* to each other and an intramolecular hydrogen bond O–H···O=C is present (Fig. 3). In this case, there is a preference for 1,4-addition, followed by elimination of methanethiol (the conjugative position is more reactive than the carbonyl function). This might be explained by the steric influence of the methyl group, which results in a change of the reaction route with regard

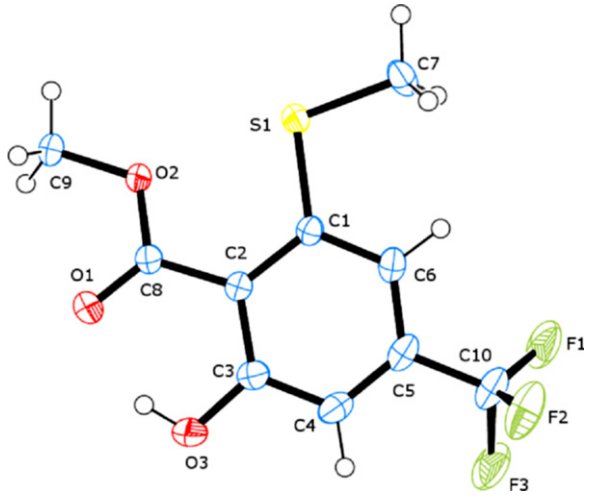


Fig. 2. Molecular structure of compound **7s**.

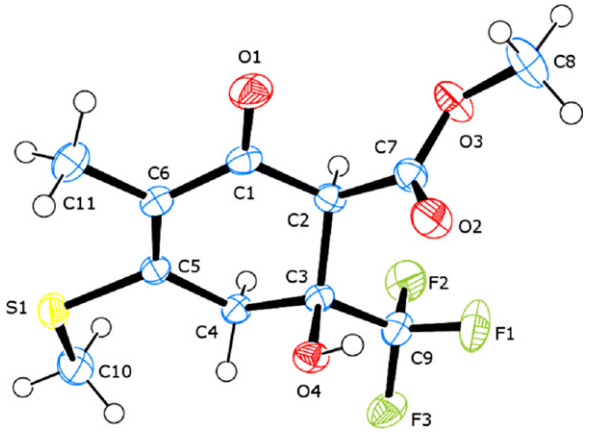


Fig. 3. Molecular structure of compound **9h**.

to unsubstituted dienes **1a–g**. Attempts to synthesize other derivatives **9** in the presence of $AlCl_3$/DCM as well as arenes **7** using BF_3/DCM or $ZnCl_2$/THF failed.

Next, we have made efforts to increase the yield of salicylates **7** by changing the catalyst to Me_3SiOTf (1.0 equiv.). Starting with dienes **1a**,**f**,**g**,**t**, which do not contain a substituent located at carbon C-4 (R^1 = H), the trifluoromethylated cyclohexenones **10a**,**f**,**g**,**t**, which are regioisomeric to **9h**, were obtained in 32–52% yields. The formation of these products proceeds by 1,2-addition of the diene to the enone **6** with subsequent ring closure (Scheme 3). In contrast to the formation of salicylates **7**, no elimination of the hydroxyl group and aromatization occurs. This result is surprising since the aromatization should be a facile process. It might be explained by the assumption that the intermediate containing a titanium alkoxide moiety readily undergoes an elimination of $TiCl_3OH$ and aromatization, while the analogous intermediate containing a silanolate moiety is more stable and no elimination occurs. The aromatization of **10** by elimination of water is difficult because of the destabilisation of a carbocationic intermediate by the electron-withdrawing CF_3 group. The regiochemistry of **10a** is independently confirmed by X-ray crystal structure analysis (Fig. 4) [16]. The structures of cyclohexenones **10f**,**g**,**t** were firmly established by comparison of their spectra with the spectra of **10a**.

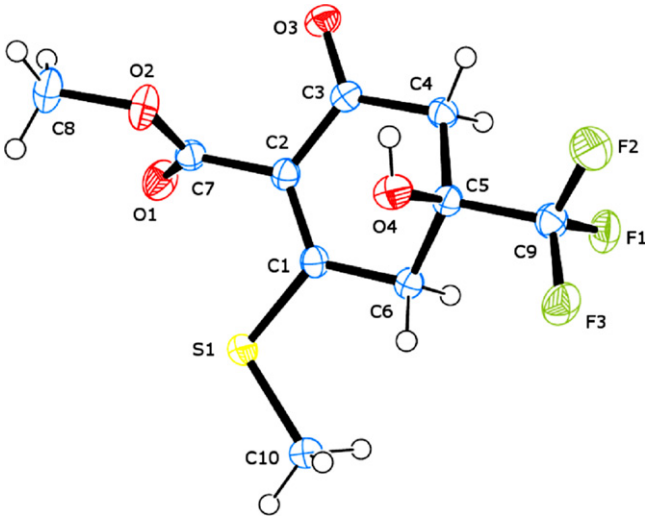
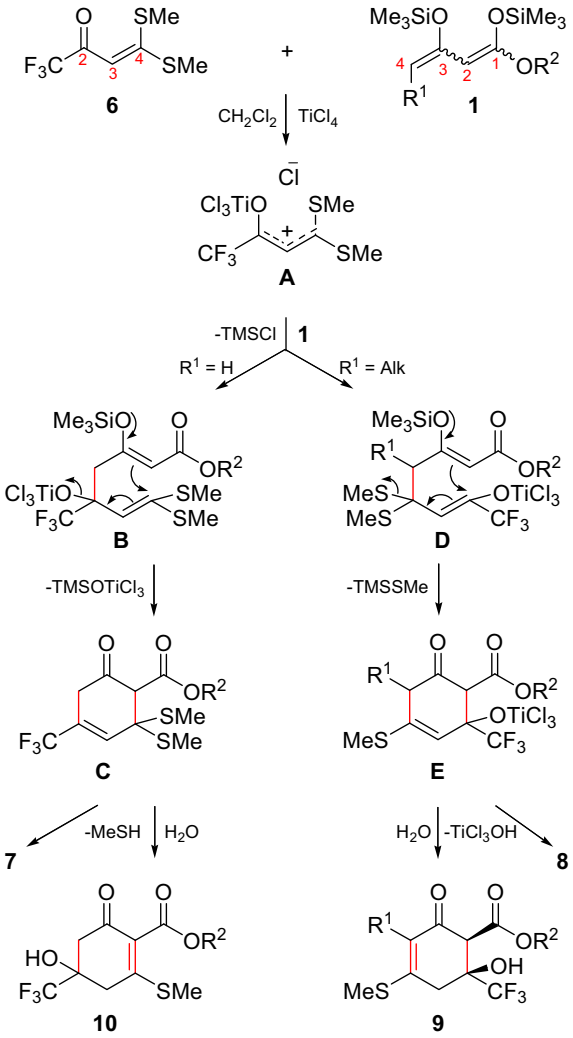


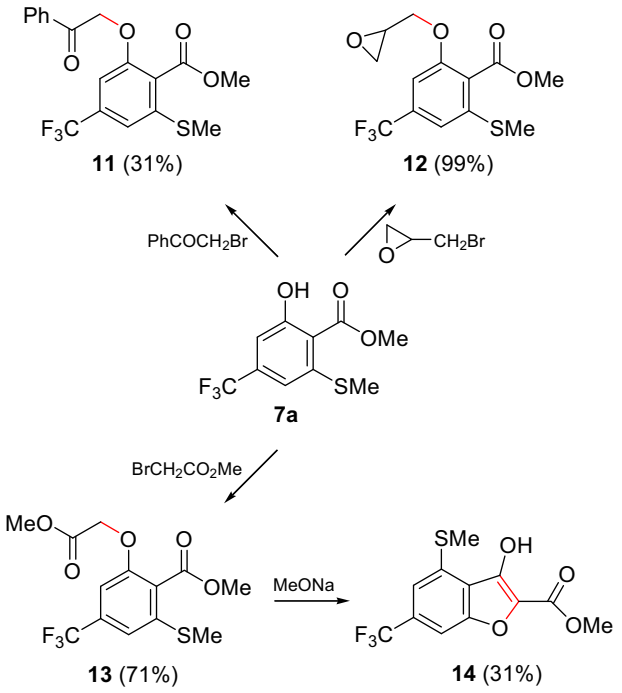
Fig. 4. Molecular structure of compound **10a**.



Scheme 4.

The formation of product **7** can be explained by reaction of **6** with a Lewis acid, for example $TiCl_4$, to give cation **A** containing an allylic carbon unit. The attack of the terminal carbon atom of **1** onto the activated carbonyl group of **A** (1,2-addition, intermediate **B**), cyclization (intermediate **C**), and subsequent aromatization by extrusion of methanethiol give 4-CF_3-substituted salicylates **7**. The formation of the other regioisomer **8**, containing the CF_3 group located *ortho* to the ester group, proceeds by attack of the substituted terminal carbon atom of **1** onto the β-carbon atom of **A** to give intermediate **D**; the elimination of Me_3SiSMe and subsequent cyclization afforded intermediate **E** (l,4-addition–elimination sequence). The elimination of titanium hydroxide (before or during the aqueous workup) and aromatization results in the formation of product **8**. It is evident that compounds **9** ($AlCl_3$ conditions) and **10** (Me_3SiOTf conditions) are formed by the sequence of reactions shown in Scheme 4.

Derivatives of *ortho*-acylated phenols and thiophenols have recently been used for the synthesis of various benzofurans and benzothiophenes [18]. We therefore investigated the synthesis of a benzofuran derivative starting from arene **7a**. First, **7a** was alkylated by 2-bromoacetophenone, 2-(bromomethyl)oxirane or methyl bromoacetate as representative examples to give compounds **11–13** in 31–99% yields. When **13** was heated in methanol in the presence of sodium methoxide for **6h**, cyclization took place



Scheme 5.

to give the previously unknown benzofuran **14** in 31% yield (Scheme 5).

3. Conclusion

In conclusion, we reported a convenient and short synthesis of functionalized 6-methylthio-4-(trifluoromethyl)salicylates by the formal [3+3] cyclocondensation of 1,3-bis(silyl enol ethers) with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one. The products constitute an important structural subunit of a variety of biologically active compounds, which are not readily available by other methods. They could serve as versatile and useful building blocks in the construction of functionalized heterocycles bearing a trifluoromethyl group.

4. Experimental

NMR spectra were recorded on a Brucker AVANCE 250 II, Brucker AV 300 and Brucker AV 400. IR spectra were recorded on a Perkin Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained on a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F_{254} plates were used for TLC. All solvents were purified and dried by standard methods. The starting 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one **6** was prepared according to described procedure [13].

4.1. General procedure for the synthesis of salicylates 7 and 8

To a solution of 1,1,1-trifluoro-4,4-bis(methylthio)but-3-en-2-one **6** (1.0 mmol) in CH_2Cl_2 (1 mL) was added bissilyl **1** (2.0 mmol) and, subsequently, $TiCl_4$ (0.11 mL, 1.0 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12–14 h with stirring. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography.

4.1.1. Methyl 6-methylthio-4-(trifluoromethyl)salicylate (7a)

Starting with **6** (0.216 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1a** (0.521 g, 2.0 mmol), product **7a** was isolated as a colorless solid. Yield 0.138 g (52%), mp 91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H, SMe), 4.04 (s, 3H, OMe), 6.86 (br s, 1H, CH), 6.99 (d, ^4J = 1.1 Hz, 1H, CH), 11.46 (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.4 (SMe), 52.4 (OMe), 110.7 (q, $J_{C,F}$ = 3.8 Hz, C-3), 111.3 (q, $J_{C,F}$ = 3.8 Hz, C-5), 112.5 (C-1), 123.1 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 135.4 (q, $J_{C,F}$ = 32.8 Hz, C-4), 146.0, 163.4 (C), 170.2 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.2 (CF_3); IR (ATR, cm^{-1}) ν 3041 (w), 2960 (w), 2922 (w), 1667 (w), 1610 (w), 1575 (w), 1557 (w), 1441 (w), 1416 (w), 1351 (w), 1338 (w), 1292 (w), 1107 (m), 929 (m), 799 (m), 744 (m), 699 (m); GC–MS (EI, 70 eV) *m/z* (%) 266 (M^+, 52), 236 (11), 235 (18), 234 (100), 206 (47), 191 (39), 163 (7); HRMS (EI, 70 eV): calcd for $C_{10}H_9F_3O_3S$ (M^+) 266.02190, found 266.021597. Anal. Calcd. for $C_{10}H_9F_3O_3S$: C, 45.11; H, 3.41. Found: C, 45.30; H, 3.09.

4.1.2. Ethyl 6-methylthio-4-(trifluoromethyl)salicylate (7b)

Starting with **6** (0.216 g, 1.0 mmol) and 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1b** (0.549 g, 2.0 mmol), product **7b** was isolated as a colorless solid. Yield 0.143 g (51%), mp 65–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (t, ^3J = 7.1 Hz, 3H, Me), 2.46 (s, 3H, SMe), 4.52 (q, ^3J = 7.2 Hz, 2H, OCH_2), 6.85 (br s, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.57 (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1 (Me), 16.4 (SMe), 62.8 (CH_2), 110.7 (q, $J_{C,F}$ = 3.8 Hz, C-3), 111.2 (q, $J_{C,F}$ = 3.8 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C,F}$ = 273.3 Hz, CF_3), 135.3 (q, $J_{C,F}$ = 32.7 Hz, C-4), 146.2, 163.4 (C), 169.8 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1 (CF_3); IR (ATR, cm^{-1}) ν 3000 (w), 2925 (w), 1661 (w), 1607 (w), 1576 (w), 1466 (w), 1450 (w), 1412 (w), 1374 (w), 1349 (m), 1289 (m), 1221 (m), 1014 (w), 956 (m), 801 (m), 773 (w), 698 (m); GC–MS (EI, 70 eV) *m/z* (%) 280 (M^+, 40), 235 (21), 234 (100), 206 (42), 191 (29); HRMS (EI, 70 eV): calcd for $C_{11}H_{11}F_3O_3S$ (M^+) 280.03755, found 280.03832. Anal. Calcd. for $C_{11}H_{11}F_3O_3S$: C, 47.14; H, 3.96. Found: C, 47.08; H, 3.33.

4.1.3. Benzyl 6-methylthio-4-(trifluoromethyl)salicylate (7c)

Starting with **6** (0.216 g, 1.0 mmol) and 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1c** (0.673 g, 2.0 mmol), product **7c** was isolated as a slight yellow solid. Yield 0.175 g (51%), mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, SMe), 5.50 (s, 2H, CH_2), 6.85 (br s, 1H, CH), 6.98 (d, ^4J = 0.9 Hz, 1H, CH), 7.36–7.53 (m, 5H, Ph), 11.48 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (SMe), 68.0 (OCH_2), 110.7 (q, $J_{C,F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C,F}$ = 3.9 Hz, C-5), 112.5 (C-1), 123.1 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 128.5, 128.7, 128.7 (CH), 134.4 (C), 135.4 (q, $J_{C,F}$ = 32.8 Hz, C-4), 146.3, 163.5 (C), 169.6 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.2 (CF_3); IR (ATR, cm^{-1}) ν 3031 (w), 2988 (w), 2956 (w), 2925 (w), 1731 (w), 1698 (w), 1663 (m), 1611 (w), 1600 (w), 1577 (m), 1496 (m), 1455 (w), 1428 (m), 1412 (m), 1387 (m), 1342 (m), 1289 (s), 1218 (s), 1182 (s), 1116 (s), 964 (s), 909 (s), 860 (s), 846 (s), 799 (s), 762 (m), 746 (s), 695 (s); GC–MS (EI, 70 eV): *m/z* (%) = 342 (M^+, 33), 92 (9), 91 (100); HRMS (EI, 70 eV): calcd for $C_{16}H_{13}F_3O_3S$ (M^+) 342.05320, found 342.05339.

4.1.4. Isopropyl 6-methylthio-4-(trifluoromethyl)salicylate (7d)

Starting with **6** (0.216 g, 1.0 mmol) and 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1d** (0.577 g, 2.0 mmol), product **7d** was isolated as a colorless oil. Yield 0.164 g (42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, ^3J = 6.2 Hz, 6H, 2 Me), 2.45 (s, 3H, SMe), 5.31–5.44 (m, 1H, OCH), 6.85 (br s, 1H, CH), 6.97 (d, ^3J = 1.1 Hz, 1H, CH), 11.65 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (SMe), 22.1 (Me), 71.8 (CH), 110.6 (q, $J_{C,F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C,F}$ = 3.9 Hz, C-

5), 113.0 (C-1), 123.2 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 135.1 (q, $J_{C,F}$ = 32.6 Hz, C-4), 146.2, 163.4 (C), 169.4 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1 (CF_3); IR (ATR, cm^{-1}) ν 2985 (w), 2925 (w), 1724 (w), 1660 (m), 1609 (m), 1575 (m), 1468 (w), 1455 (w), 1412 (s), 1373 (m), 1342 (s), 1289 (s), 1276 (m), 1221 (s), 1190 (s), 1123 (s), 1097 (s), 959 (s), 907 (m), 805 (m), 758 (m), 699 (s); GC–MS (EI, 70 eV) *m*/*z* (%) 294 (M^+, 24), 252 (17), 235 (22), 234 (100), 206 (27), 191 (16); HRMS (EI, 70 eV): calcd for $C_{12}H_{13}F_3O_3S$ (M^+) 294.05320, found 294.053170. Anal. Calcd. for $C_{12}H_{13}F_3O_3S$: C, 48.97; H, 4.45. Found: C, 48.99; H, 4.32.

4.1.5. Isobutyl 6-methylthio-4-(trifluoromethyl)salicylate (7e)

Starting with **6** (0.216 g, 1.0 mmol) and 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1e** (0.605 g, 2.0 mmol), product **7e** was isolated as a colorless solid. Yield 0.150 g (49%), mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, ^3J = 6.8 Hz, 6H, 2 Me), 2.12–2.25 (m, 1H, CH), 2.47 (s, 3H, SMe), 4.25 (d, ^3J = 6.4 Hz, 2H, OCH_2), 6.86 (br s, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.69 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (SMe), 19.3 (Me), 27.6 (CH), 73.1 (CH_2), 110.7 (q, $J_{C,F}$ = 3.9 Hz, C-3), 111.1 (q, $J_{C,F}$ = 3.9 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 135.3 (q, $J_{C,F}$ = 32.6 Hz, C-4), 146.1, 163.3 (C), 170.1 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1 (CF_3); IR (ATR, cm^{-1}) ν 3067 (w), 2967 (w), 2924 (w), 2873 (w), 1666 (s), 1610 (w), 1571 (m), 1465 (w), 1414 (m), 1381 (m), 1369 (m), 1342 (s), 1222 (m), 1184 (s), 1114 (s), 956 (m), 938 (s), 776 (m), 697 (s); GC–MS (EI, 70 eV) *m*/*z* (%) 308 (M^+, 27), 252 (11), 235 (25), 234 (100), 206 (20), 191 (12); HRMS (EI, 70 eV): calcd for $C_{13}H_{15}F_3O_3S$ (M^+) 308.06885, found 308.06864. Anal. Calcd. for $C_{13}H_{15}F_3O_3S$: C, 50.64; H, 4.90. Found: C, 49.96; H, 4.77.

4.1.6. Isopentyl 6-methylthio-4-(trifluoromethyl)salicylate (7f)

Starting with **6** (0.216 g, 1.0 mmol) and 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1f** (0.633 g, 2.0 mmol), product **7f** was isolated as a colorless solid. Yield 0.180 g (56%), mp 32–33 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, ^3J = 6.4 Hz, 6H, 2 Me), 1.71–1.93 (m, 3H, CH_2CH), 2.46 (s, 3H, SMe), 4.49 (t, ^3J = 6.8 Hz, 2H, OCH_2), 6.85 (br s, 1H, CH), 6.98 (br s, 1H, CH), 11.63 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (SMe), 22.4 (Me), 25.0 (CH), 37.1 (CH_2), 65.5 (OCH_2), 110.7 (q, $J_{C,F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C,F}$ = 3.9 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 135.3 (q, $J_{C,F}$ = 32.6 Hz, C-4), 146.1, 163.5 (C), 170.0 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1 (CF_3); IR (ATR, cm^{-1}) ν 2959 (w), 2929 (w), 2872 (w), 1726 (w), 1665 (m), 1608 (w), 1575 (m), 1464 (w), 1412 (s), 1349 (s), 1289 (s), 1220 (s), 1189 (s), 1118 (s), 963 (m), 934 (m), 803 (m), 758 (m), 699 (s); GC–MS (EI, 70 eV) *m*/*z* (%) 322 (M^+, 28), 252 (11), 235 (32), 234 (100), 206 (18), 191 (11); HRMS (EI, 70 eV): calcd for $C_{14}H_{17}F_3O_3S$ (M^+) 322.08450, found 322.08462. Anal. Calcd. for $C_{14}H_{17}F_3O_3S$: C, 52.16; H, 5.32. Found: C, 52.25; H, 5.30.

4.1.7. Octyl 6-methylthio-4-(trifluoromethyl)salicylate (7g)

Starting with **6** (0.216 g, 1.0 mmol) and 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1g** (0.717 g, 2.0 mmol), product **7g** was isolated as a colorless solid. Yield 0.200 g (55%), mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, ^3J = 6.7 Hz, 3H, Me), 1.26–1.54 (m, 11H, $(CH_2)_5$), 1.54–1.80 (m, 2H, CH_2), 2.46 (s, 3H, SMe), 4.45 (t, ^3J = 6.6 Hz, 2H, OCH_2), 6.86 (br s, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.63 (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1 (Me), 16.5 (SMe), 22.6, 26.0, 28.4, 29.1, 29.1, 31.7 $(CH_2)_6$, 67.0 (OCH_2), 110.7 (q, $J_{C,F}$ = 3.8 Hz, C-3), 111.2 (q, $J_{C,F}$ = 3.8 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C,F}$ = 273.4 Hz, CF_3), 135.2 (q, $J_{C,F}$ = 32.7 Hz, C-4), 146.1, 163.5 (C), 170.0 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.1 (CF_3); IR (ATR, cm^{-1}) ν 2956 (w), 2924 (m), 2855 (w), 2158 (w), 1976 (w), 1665 (m), 1636 (w), 1608 (w), 1575 (m), 1457 (w), 1412 (m), 1346 (s), 1289 (s), 1220 (s), 1189 (s), 1118 (s), 961 (m), 938 (m), 804 (m), 756 (m), 699 (s); GC–MS (EI, 70 eV) *m*/*z* (%) 364 (M^+, 17), 252 (11), 235 (28), 234 (100), 206 (11); HRMS (EI, 70 eV): calcd for $C_{17}H_{23}F_3O_3S$ (M^+) 364.13145, found 364.13071. Anal. Calcd. for $C_{17}H_{23}F_3O_3S$: C, 56.03; H, 6.36. Found: C, 56.20; H, 6.39.

4.1.8. Methyl 6-methylthio-3-propyl-4-(trifluoromethyl)salicylate (7j) and methyl 4-methylthio-3-propyl-6-(trifluoromethyl)salicylate (8j)

Starting with **6** (0.216 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-heptadiene **1j** (0.605 g, 2.0 mmol), a mixture of regioisomers **7j** and **8j** (1:0.2) was isolated as a colorless oil. Yield 0.119 g (39%); ^{1}H NMR (300 MHz, $CDCl_3$) for **7j** δ 1.01 (t, ^3J = 7.4 Hz, 3H, Me), 1.51–1.65 (m, 2H, CH_2), 2.45, (s, 3H, SMe), 2.70 (t, ^3J = 8.0 Hz, 2H, CH_2), 4.03 (s, 3H, OMe), 6.90, (br s, 1H, Ar), 11.78 (s, 1H, OH), for **8j** δ 1.00, (t, ^3J = 7.4 Hz, 3H, Me), 1.51–1.65 (m, 2H, CH_2), 2.51 (s, 3H, SMe), 2.76 (t, ^3J = 7.9 Hz, 2H, CH_2), 3.96, (s, 3H, OMe), 7.07 (br s, 1H, Ar), 11.18, (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) for **7j** δ 14.5 (Me), 16.2 (SMe), 22.7, 28.6 ($(CH_2)_2$), 52.4, (OMe), 112.1, 111.5 (q, $J_{C,F}$ = 6.4 Hz, CH_{Ar}), 123.8 (q, $J_{C,F}$ = 275.1 Hz, CF_3), 126.3 (q, $J_{C,F}$ = 31.9 Hz, CCF_3), 133.1 (q, $J_{C,F}$ = 29.3 Hz, CCF_3), 141.4, 162.3 (C), 170.8 (C=O), for **8j** δ 14.3 (Me), 14.8 (SMe), 20.9, 29.1 ($(CH_2)_2$), 52.7 (OMe), 106.5, 113.9 (q, $J_{C,F}$ = 7.2 Hz), 123.5 (q, $J_{C,F}$ = 273.3 Hz, CF_3), 131.9, 127.8 (q, $J_{C,F}$ = 31.9 Hz, CCF_3), 145.6, 159.3 (C), 170.2 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) for **7j** δ −60.5 (CF_3), for **8j** δ −58.7 (CF_3).

4.1.9. Ethyl 6-methylthio-3-pentyl-4-(trifluoromethyl)salicylate (7m) and ethyl 4-methylthio-3-pentyl-6-(trifluoromethyl)salicylate (8m)

Starting with **6** (0.216 g, 1.0 mmol) and 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-nonadiene **1m** (0.689 g, 2.0 mmol), a mixture of regioisomers **7m** and **8m** (1:1) was isolated as a colorless oil. Yield 0.127 g (36%); ^{1}H NMR (300 MHz, $CDCl_3$) for **7m** δ 0.91 (t, ^3J = 7.1 Hz, 3H, Me), 1.36–1.59 (m, 9H, $Me(CH_2)_3$), 2.44 (s, 3H, SMe), 2.71 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.52 (q, ^3J = 7.2 Hz, 2H, OCH_2), 6.90 (br s, 1H, Ar), 11.86 (s, 1H, OH), for **8m** δ 0.91 (t, ^3J = 7.1 Hz, 3H, Me), 1.36–1.59 (m, 9H, $Me(CH_2)_3$), 2.51 (s, 3H, SMe), 2.77 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.42 (q, ^3J = 7.2 Hz, 2H, OCH_2), 7.07 (br s, 1H, Ar), 11.31, (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) for **7m** δ 14.0, 14.2 (2 Me), 16.3 (SMe), 22.4, 26.6, 29.1, 32.3 ($(CH_2)_4$), 62.7 (OCH_2), 112.3 (C_{Ar}), 111.4 (q, $J_{C,F}$ = 6.3 Hz, CH_{Ar}), 123.9 (q, $J_{C,F}$ = 275.1 Hz, CF_3), 126.5 (C_{Ar}), 132.9 (q, $J_{C,F}$ = 29.3 Hz, CCF_3), 141.5, 162.3 (C_{Ar}), 170.4 (C=O), for **8m** δ 13.5, 14.0 (2Me), 14.8 (SMe), 22.5, 27.1, 27.2, 32.0 ($(CH_2)_4$), 62.3 (OCH_2), 106.7 (C_{Ar}), 113.9 (q, $J_{C,F}$ = 7.3 Hz, CH_{Ar}), 123.5 (q, $J_{C,F}$ = 273.3 Hz, CF_3), 132.1, (C_{Ar}), 127.7 (q, $J_{C,F}$ = 31.6 Hz, CCF_3), 145.2, 159.4 (C_{Ar}), 169.8 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) for **7m** δ −0.4 (CF_3), for **8m** δ −57.9 (CF_3).

4.1.10. Methyl 6-methylthio-3-octyl-4-(trifluoromethyl)salicylate (7o) and methyl 4-methylthio-3-octyl-6-(trifluoromethyl)salicylate (8o)

Starting with **6** (0.216 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-dodecadiene **1o** (0.745 g, 2.0 mmol), a mixture of regioisomers **7o** and **8o** (1: 0.7) was isolated as a colorless oil. Yield 0.190 g (50%); ^{1}H NMR (300 MHz, $CDCl_3$) for **7o** δ 0.89 (t, ^3J = 6.7 Hz, 3H, Me), 1.28–1.58 (m, 12H, $(CH_2)_6$), 2.44 (s, 3H, SMe), 2.77 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.03 (s, 3H, OMe), 6.90 (br s, 1H, Ar), 11.77 (s, 1H, OH), for **7o** δ 0.88 (t, ^3J = 6.7 Hz, 3H, Me), 1.28–1.58 (m, 12H, $(CH_2)_6$), 2.51 (s, 3H, SMe), 2.71 (t, ^3J = 8.0 Hz, 2H, CH_2), 3.96 (s, 3H, OMe), 7.07 (br s, 1H, Ar), 11.17 (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) for **7o** δ 14.1 (Me), 16.2 (SMe), 22.7, 26.5, 29.2, 29.3, 29.4, 30.1, 31.9 ($(CH_2)_7$), 52.4 (OMe), 112.1 (C_{Ar}), 111.5 (q, $J_{C,F}$ = 6.4 Hz, CH_{Ar}), 123.8 (q, $J_{C,F}$ = 275.1 Hz, CF_3), 126.5 (C_{Ar}), 132.0 (q, $J_{C,F}$ = 29.6 Hz, CCF_3), 141.3, 162.3 (C_{Ar}), 170.8 (C=O), for **8o** δ 14.1 (Me), 14.8 (SMe), 22.7, 27.2, 27.5, 29.2, 29.4, 29.9, 31.9

($(CH_2)_7$), 52.7 (OMe), 106.5 (C_{Ar}), 113.9 (q, $J_{C,F}$ = 7.2 Hz, CH_{Ar}), 123.5 (q, $J_{C,F}$ = 273.3 Hz, CF_3), 131.9 (C_{Ar}), 127.8 (q, $J_{C,F}$ = 31.7 Hz, (CCF_3), 145.6, 159.4 (C_{Ar}), 170.2 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) for **7o** δ −60.5 (CF_3), for **8o** δ −58.7 (CF_3).

4.1.11. 2-Hydroxy-6-methylthio-4-(trifluoromethyl)benzophenone (7s)

Starting with **6** (0.216 g, 1.0 mmol) and 1-phenyl-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1s** (0.613 g, 2.0 mmol), product **7s** was isolated as a brown solid. Yield 0.120 g (38%), mp 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H, SMe), 7.07 (s, 1H, CH), 7.08 (s, 1H, CH), 7.45–7.50 (m, 2H, Ph), 7.59–7.65 (m, 1H, Ph), 7.75–7.79 (m, 2H, Ph), 8.13 (br s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.5 (SMe), 111.6 (q, $J_{C,F}$ = 3.8 Hz, C-3), 115.5 (q, $J_{C,F}$ = 4.0 Hz, C-5), 123.2 (q, $J_{C,F}$ = 273.1 Hz, CF_3), 126.3 (C-1), 128.8, 129.5, 133.9 (CH), 134.1 (q, $J_{C,F}$ = 33.0 Hz, C-4), 137.6, 141.5, 157.0 (C), 197.9 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.5 (CF_3); IR (ATR, cm^{-1}) ν 3331 (w), 3081 (w), 3064 (w), 2928 (w), 1679 (w), 1653 (m), 1594 (w), 1579 (w), 1484 (m), 1448 (m), 1416 (w), 1345 (w), 1324 (w), 1309 (w), 1284 (w), 1265 (w), 1244 (w), 1128 (m), 1087 (m), 954 (m), 924 (m), 856 (m), 713 (m), 683 (m), 626 (w); GC–MS (EI, 70 eV) *m*/*z* (%) 312 (M^+, 14), 311 (10), 297 (21), 295 (18), 294 (72), 293 (100), 235 (14), 105 (22), 77 (39), 51 (10), 32 (20), 91 (100); HRMS (EI, 70 eV): calcd for $C_{15}H_{11}F_3O_2S$ (M^+) 312.04264, found 312.042315. Anal. Calcd. for $C_{15}H_{11}F_3O_2S$: C, 57.69; H, 3.55. Found: C, 57.51; H, 3.57.

4.1.12. Methyl 6-hydroxy-3-methyl-4-methylthio-2-oxo-6-(trifluoromethyl)cyclohex-3-enecarboxylate (9h)

To a solution of **6** (0.216 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene **1h** (0.549 g, 2.0 mmol) and, subsequently, $AlCl_3$ (0.134 g, 1.0 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12–14 h with stirring. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography to give **9h** as a colorless solid. Yield 0.154 g (52%), mp 93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3H, Me), 2.44 (s, 3H, SMe), 2.80 (dq, ^2J = 17.8 Hz, $^4J_{H,F}$ = 2.1 Hz, 1H, H-5a), 2.97 (br d, ^2J = 17.8 Hz, 1H, H-5b), 3.72 (s, 1H, CH), 3.87 (s, 3H, OMe), 5.35 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6 (Me), 14.0 (SMe), 33.1 (CH_2), 53.1 (CH), 53.3 (OMe), 74.7 (q, $J_{C,F}$ = 28.8 Hz, C-6), 124.4 (q, $J_{C,F}$ = 287.0 Hz, CF_3), 127.0, 154.0, 171.0 (C), 184.8 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.6 (CF_3); IR (ATR, cm^{-1}) ν 3431 (w), 3285 (w), 3024 (w), 2962 (w), 2935 (w), 2919 (w), 2858 (w), 2635 (w), 1737 (m), 1651 (m), 1574 (m), 1441 (w), 1414 (w), 1372 (w), 1356 (w), 1333 (m), 1301 (m), 1267 (m) 1222 (w), 1200 (m), 1162 (m), 1129 (m), 1068 (m), 1003 (m), 630 (m), 569 (m); GC–MS (EI, 70 eV) *m*/*z* (%) 298 (M^+, 13), 281 (13), 280 (100), 265 (30), 248 (16), 223 (27), 221 (49), 197 (24), 193 (22), 175 (16), 85 (16), 81 (22), 69 (33), 59 (19), 53 (18); HRMS (EI, 70 eV): calcd for $C_{11}H_{13}F_3O_4S$ (M^+) 298.04812, found 298.048772. Anal. Calcd. for $C_{11}H_{13}F_3O_4S$: C, 44.29; H, 4.39. Found: C, 44.34; H, 4.67.

4.2. General procedure for the synthesis of compounds 10

To a solution of **6** (0.216 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added **1** (2.0 mmol) and, subsequently, Me_3SiOTf (0.18 mL, 1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12–14 h with stirring. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography.

4.2.1. Methyl 4-hydroxy-2-methylthio-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (10a)

Starting with **6** (0.216 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1a** (0.520 g, 2.0 mmol), product **10a** was isolated as a colorless solid. Yield 0.110 g (39%), mp 142–143 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 2.53 (s, 3H, SMe), 2.60–2.88 (m, 2H, CH_2), 3.07–3.23 (m, 2H, CH_2), 3.74 (s, 3H, OMe), 5.69 (s, 1H, OH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 14.1 (SMe), 34.6, 42.0 (CH_2), 52.1 (OMe), 73.7 (q, $J_{C,F}$ = 29.5 Hz, C-4), 126.2 (q, $J_{C,F}$ = 283.0 Hz, CF_3), 129.1, 159.7, 166.3 (C), 187.5 (C=O); ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ −83.7 (CF_3); IR (ATR, cm^{-1}) ν 3429 (m), 3252 (w), 3011 (w), 2957 (w), 2930 (w), 2850 (w), 1721 (s), 1640 (s), 1549 (s), 1431 (m), 1403 (m), 1164 (s), 1044 (s), 813 (m), 552 (m); HRMS (ESI-TOF/MS): calcd for $C_{10}H_{12}F_3O_4S$ ($[M+H]^+$) 285.0402, found 285.0400; calcd. for $C_{10}H_{11}F_3NaO_4S$ ($[M+Na]^+$) 307.0222, found 307.0221. Anal. Calcd. for $C_{10}H_{11}F_3O_4S$: C, 42.25; H, 3.90; S, 11.28. Found: C, 42.45; H, 4.26; S, 11.16.

4.2.2. Isopentyl 4-hydroxy-2-methylthio-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (10f)

Starting with **6** (0.216 g, 1.0 mmol) and 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1f** (0.633 g, 2.0 mmol), product **10f** was isolated as a colorless solid. Yield 0.110 g (32%), mp 130–132 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 0.91 (s, 3H, Me), 0.94 (s, 3H, Me), 1.53–1.59 (m, 2H, CH_2), 1.72–1.81 (m, 1H, CH), 2.53 (s, 3H, SMe), 2.58–2.88 (m, 2H, CH_2), 3.05–3.24 (m, 2H, CH_2), 4.21 (t, ^3J = 6.7 Hz, 2H, OCH_2), 5.69 (s, 1H, OH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 14.1 (SMe), 22.6 (Me), 25.5 (CH), 34.4, 38.0, 42.0, 64.1 (OCH_2), 73.7 (q, $J_{C,F}$ = 29.0 Hz, C-4), 126.2 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 129.3, 159.3, 165.9 (C), 187.6 (C=O); ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ −83.7 (CF_3); IR (ATR, cm^{-1}) ν 3312 (m), 2946 (w), 2811 (w), 1720 (s), 1643 (s), 1547 (s), 1430 (m), 1403 (m), 1267 (s), 1043 (s), 786 (m), 533 (m); HRMS (ESI-TOF/MS): calcd for $C_{14}H_{20}F_3O_4S$ ($[M+H]^+$) 341.1029, found 341.1029; calcd for C_{14} $H_{19}F_3NaO_4S$ ($[M+Na]^+$) 363.0848, found 363.0857. Anal. Calcd. for $C_{14}H_{19}F_3O_4S$: C, 49.40; H, 5.63; S, 9.42. Found: C, 50.05; H, 5.88; S, 9.45.

4.2.3. Octyl 4-hydroxy-2-methylthio-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (10g)

Starting with **6** (0.216 g, 1.0 mmol) and 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1g** (0.717 g, 2.0 mmol), product **10g** was isolated as a colorless solid. Yield 0.130 g (34%), mp 98–99 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 0.88 (t, ^3J = 6.8 Hz, 3H, Me), 1.28–1.45 (m, 10H, $(CH_2)_5$), 1.64–1.71 (m, 2H, CH_2), 2.53 (s, 3H, SMe), 2.60–2.87 (m, 2H, CH_2), 3.07–3.23 (m, 2H, CH_2), 4.18 (t, ^3J = 6.4 Hz, 2H, OCH_2), 5.68 (s, 1H, OH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 14.1 (SMe), 14.3 (Me), 23.2, 26.6, 29.8, 29.9, 32.5, 34.4, 42.0, 65.6 (OCH_2), 73.7 (q, $J_{C,F}$ = 29.2 Hz, C-4), 126.2 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 129.3, 159.1, 165.8 (C), 187.5 (C=O); ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ −83.6 (CF_3); IR (ATR, cm^{-1}) ν 3348 (m), 2935 (m), 2855 (w), 1712 (s), 1653 (s), 1564 (s), 1464 (w), 1437 (w), 1318 (s), 1159 (s), 1045 (s), 938 (m), 544 (m), 488 (m); HRMS (ESI-TOF/MS): calcd for $C_{17}H_{26}F_3O_4S$ ($[M+H]^+$) 383.1498, found 383.1503; calcd. for $C_{17}H_{25}F_3NaO_4S$ ($[M+Na]^+$) 405.1318, found 405.1324. Anal. Calcd. for $C_{17}H_{25}F_3O_4S$: C, 53.39; H, 6.59; S, 8.38. Found: C, 54.26; H, 6.53; S, 9.20.

4.2.4. Butyl 4-hydroxy-2-methylthio-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (10t)

Starting with **6** (0.216 g, 1.0 mmol), 1-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **1t** (0.605 g, 2.0 mmol), product **10t** was isolated as a colorless solid. Yield 0.170 g (52%), mp 137–138 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 0.93 (t, ^3J = 7.5 Hz, 3H,

Me), 1.36–1.49 (m, 2H, CH_2), 1.60–1.70 (m, 2H, CH_2), 2.53 (s, 3H, SMe), 2.59–2.88 (m, 2H, CH_2), 3.05–3.24 (m, 2H, CH_2), 4.41 (t, ^3J = 6.6 Hz, 2H, CH_2), 5.68 (s, 1H, OH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 13.9 (Me), 14.1 (SMe), 19.7, 31.3, 34.5, 42.0, 65.3 (OCH_2), 73.7 (q, $J_{C,F}$ = 29.2 Hz, C-4), 126.2 (q, $J_{C,F}$ = 283.1 Hz, CF_3), 129.4, 159.1, 165.8 (C), 187.5 (C=O); ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ −83.7 (CF_3); IR (ATR, cm^{-1}) ν 3294 (m), 2963 (w), 2934 (w), 2874 (w), 1707 (s), 1648 (s), 1558 (m), 1470 (w), 1405 (m), 1180 (s), 1043 (s), 946 (m), 540 (m); HRMS (ESI-TOF/MS): calcd. for $C_{13}H_{18}F_3O_4S$ ($[M+H]^+$) 327.0872, found 327.0869; calcd for $C_{13}H_{17}F_3NaO_4S$ ($[M+Na]^+$) 349.0692, found 349.0694.

4.3. General procedure for the synthesis of compounds 11, 12 and 13

To a solution of methyl 6-methylthio-4-(trifluoromethyl)salicylate **7a** (0.275 g, 1.1 mmol) in acetone (2–3 mL) was added K_2CO_3 (0.172 g, 1.3 mmol) and 2-bromoacetophenone, 2-(bromomethyl)oxirane or methyl bromoacetate (1.3 mmol). The mixture was then heated to 55 °C for 8 h and the resulting suspension was filtered and washed with diethyl ether. The ether solution was washed with Brine (4 × 15 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography.

4.3.1. Methyl 2-methylthio-6-phenacyloxy-4-(trifluoromethyl)benzoate (11)

Starting with **7a** (0.275 g, 1.1 mmol) and 2-bromoacetophenone (0.247 g, 1.3 mmol), product **11** was isolated as a colorless solid. Yield 0.121 g (32%), mp 82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, SMe), 3.89 (s, 3H, OMe), 5.31 (s, 2H, CH_2), 6.87 (br s, 1H, CH), 7.18 (br s, 1H, CH), 7.47–7.52 (m, 2H, Ph), 7.60–7.65 (m, 1H, Ph), 7.94–7.97 (m, 2H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.7 (SMe), 52.6 (OMe), 71.7 (CH_2), 106.6 (q, $J_{C,F}$ = 3.7 Hz, C-5), 117.0 (q, $J_{C,F}$ = 3.8 Hz, C-3), 123.2 (q, $J_{C,F}$ = 273.1 Hz, CF_3), 128.2, 128.8, 128.9, 132.8 (q, $J_{C,F}$ = 32.8 Hz, C-4), 134.1 (CH), 134.1, 139.7, 155.3 (C), 165.9 (OC=O), 192.9 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.0 (CF_3); IR (ATR, cm^{-1}) ν 3084 (w), 3009 (w), 2959 (w), 2925 (w), 2908 (w), 2841 (w), 1710 (m), 1597 (w), 1579 (w), 1468 (w), 1448 (w), 1421 (m), 1325 (m), 1278 (w), 1255 (m), 1224 (m), 1180 (w), 1159 (m), 1122 (m), 1093 (m), 1074 (m), 984 (m), 760 (m), 670 (m); GC–MS (EI, 70 eV) m/z (%) 384 (M^+, 22), 353 (13), 106 (8), 105 (100), 91 (11), 77 (24), 45 (9); HRMS (EI, 70 eV): calcd for $C_{18}H_{15}F_3O_4S$ (M^+) 384.06377, found 384.06394.

4.3.2. Methyl 2-methylthio-6-(oxiran-2-ylmethoxy)-4-(trifluoromethyl)benzoate (12)

Starting with **7a** (0.275 g, 1.1 mmol) and 2-(bromomethyl) oxirane (0.170 g, 1.3 mmol), product **12** was isolated as a colorless solid. Yield 0.330 g (99%), mp 45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3H, SMe), 2.73 (dd, ^2J = 4.9 Hz, ^3J = 2.6 Hz, 1H, OC*H*H), 2.87 (dd, ^2J = 4.9 Hz, ^3J = 4.2 Hz, 1H, OCH*H*), 3.28–3.33 (m, 1H, CH), 3.94 (s, 3H, OMe), 4.02 (dd, ^2J = 11.1 Hz, ^3J = 5.5 Hz, 1H, OC*H*H), 4.33 (dd, ^2J = 11.3 Hz, ^3J = 2.6 Hz, 1H, OCH*H*), 6.99 (br s, 1H, CH), 7.16 (br s, 1H, CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.7 (SMe), 44.2 (OCH_2), 49.7 (CH), 52.6 (OMe), 69.8 (OCH_2), 106.9 (q, $J_{C,F}$ = 3.7 Hz, C-5), 116.6 (q, $J_{C,F}$ = 4.0 Hz, C-3), 123.3 (q, $J_{C,F}$ = 273.0 Hz, CF_3), 127.1 (C), 132.9 (q, $J_{C,F}$ = 32.7 Hz, C-4), 139.3, 155.7 (C), 166.0 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.1 (CF_3); IR (ATR, cm^{-1}) ν 3078 (w), 3003 (w), 2960 (w), 2930 (w), 2854 (w), 1714 (m), 1605 (w), 1573 (w), 1464 (w), 1432 (w), 1425 (w), 1387 (m), 1322 (m), 1283 (m), 1250 (m), 1201 (m), 1169 (m), 1120 (s), 1086 (m), 1074 (m), 1024 (m), 993 (m), 842 (s), 704 (m); GC–MS (EI, 70 eV) m/z (%) 322 (M^+, 100), 303 (21), 291 (60), 235 (42), 234 (85), 206 (38), 191 (44), 163 (12), 57 (49) 45 (54), 31 (23), 29 (45); HRMS (EI, 70 eV): calcd for $C_{13}H_{13}F_3O_4S$ (M^+) 322.04812, found 322.04821. Anal. Calcd. for $C_{13}H_{13}F_3O_4S$: C, 48.45; H, 4.07. Found: C, 48.70; H, 4.06.

4.3.3. Methyl 2-(2-methoxy-2-oxoethoxy)-6-methylthio-4-(trifluoromethyl)benzoate (13)

Starting with **7a** (0.400 g, 1.5 mmol), methyl bromoacetate (0.549 g, 2.0 mmol) and K_2CO_3 (0.249 g, 1.8 mmol) in acetone (3.0 mL), product **13** was isolated as a yellow solid. Yield 0.362 g (71%), mp 64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, SMe), 3.79, 3.96 (both s, 3H, OMe), 4.68 (s, 2H, CH_2), 6.83 (br s, 1H, CH), 7.19 (br s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (SMe), 52.4, 52.7 (OMe), 66.2 (OCH_2), 106.6 (q, $J_{C,F}$ = 3.7 Hz, C-3), 117.2 (q, $J_{C,F}$ = 3.9 Hz, C-5), 123.2 (q, $J_{C,F}$ = 273.1 Hz, CF_3), 127.3 (C), 135.9 (q, $J_{C,F}$ = 32.8 Hz, C-4), 139.8, 155.1 (C), 165.8 (OC = O), 168.0 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.1 (CF_3); IR (ATR, cm^{-1}) ν 3457 (w), 3188 (w), 3098 (w), 3010 (w), 2961 (w), 2915 (w), 2860 (w), 1733 (m), 1698 (w), 1605 (w), 1580 (w), 1557 (w), 1471 (w), 1449 (w), 1417 (m), 1389 (w), 1330 (w), 1303 (m), 1249 (m), 1206 (w), 1161 (m), 1120 (m), 1078 (m), 1066 (m), 1018 (m), 935 (m), 864 (m), 705 (m); GC–MS (EI, 70 eV) m/z (%) 338 (M^+, 47), 319 (17), 307 (51), 279 (27), 249 (19), 248 (16), 247 (100), 246 (31), 219 (14), 218 (37), 191 (22), 189 (12), 45 (92); HRMS (ESI-TOF/MS): calcd for $C_{13}H_{14}F_3O_5S$ ($[M+H]^+$) 339.0509, found 339.0508; calcd for $C_{13}H_{13}F_3NaO_5S$ ($[M+Na]^+$) 361.0328, found 361.0329. Anal. Calcd. for $C_{13}H_{13}F_3O_5S$: C, 46.15; H, 3.87. Found: C, 46.27; H, 3.77.

4.3.4. Methyl 3-hydroxy-4-methylthio-6-(trifluoromethyl)benzofuran-2-carboxylate (14)

To a solution of **13** (0.160 g, 0.5 mmol) in MeOH/CH_2Cl_2 (1:1, 3.0 mL) was added MeONa (0.065 g, 0.6 mmol). The reaction mixture was then heated to 50 °C for 6 h. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography to give **14** as an yellow solid. Yield 0.045 g (31%), mp 179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3H, SMe), 4.02 (s, 3H, OMe), 7.16 (br s, 1H, CH), 7.44 (s, 1H, CH), 8.26 (br s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.9 (SMe), 52.3 (OMe), 106.4 (q, $J_{C,F}$ = 4.4 Hz, C-7), 114.6 (q, $J_{C,F}$ = 3.7 Hz, C-5), 116.8 (q, $J_{C,F}$ = 275 Hz), 136.1, 138.9 (q, $J_{C,F}$ = 33.5 Hz), 142.2, 145.3, 150.9, 152.5, 162.4 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.2 (CF_3); IR (ATR, cm^{-1}) ν 3331 (w), 3087 (w), 3003 (w), 2959 (w), 2930 (w), 2864 (w), 1688 (w), 1604 (w), 1575 (w), 1499 (w), 1455 (w), 1377 (w), 1335 (m), 1258 (w), 1216 (m), 1198 (m), 1148 (m), 1115 (m), 1074 (m), 966 (m), 849 (m), 658 (m); GC–MS (EI, 70 eV) m/z (%) 306 (M^+, 100), 275 (15), 274 (49), 273 (15), 247 (17), 246 (65), 217 (21), 190 (17), 189 (33), 143 (15), 121 (15); HRMS (EI, 70 eV): calcd for $C_{12}H_9F_3O_4S$ (M^+) 306.01682, found 306.01591.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.04.011.

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