Preparation and Reactions of 4-Alkoxy-2,2-bis(trifluoromethyl)-thietanes and 5-Alkoxy-3,3-bis(trifluoromethyl)dithiolanes

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4-Alkoxy-2,2-bis(trifluoromethyl)thietanes, **3** (R=Me and Et), were prepared by the reactions of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane with alkyl vinyl ethers in a KF–DMF system. A bimolecular condensation product, bis[4,4-bis(trifluoromethyl)thietan-2-yl]ether, **5**, was obtained by the treatment of **3** with concentrated sulfuric acid. On the other hand, when treated with sulfur in DMF in the presence of diethylamine, **3** gave 5-alkoxy-3,3-bis(trifluoromethyl)-1,2-dithiolanes, **8**, in rather good yields. Several reactions of these thietanes and 1,2-dithiolanes, including those with butyllithium, were examined.

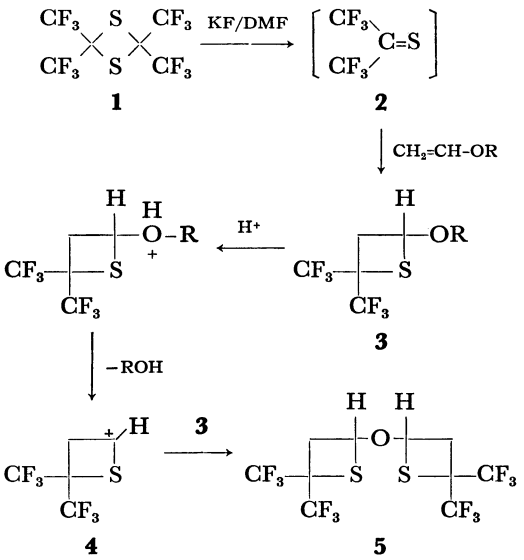
In our previous paper, it has been reported that hexafluorothioacetone (**2**) is liberated gently from its dimer, 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (**1**), in a potassium fluoride–*N,N*-dimethylformamide system.[1] Since the dimer is a stable liquid which can be prepared from hexafluoropropene and sulfur directly, the compound seemed to be a useful starting material for the hexafluorothioacetone derivatives. Thus, the earlier studies have been continued, and we now wish to report on the preparation of cycloadducts of hexafluorothioacetone liberated from **1**, with alkyl vinyl ethers and on several reactions of the cycloadducts, 4-alkoxy-2,2-bis(trifluoromethyl)thietanes, and its sulfurized dithiolane derivatives, 5-alkoxy-3,3-bis-(trifluoromethyl)-1,2-dithiolanes.

Results and Discussion

Preparation of 4-Alkoxy-2,2-bis(trifluoromethyl)thietanes (3). The cycloadduct of hexafluorothioacetone with ethyl vinyl ether, 3- or 4-ethoxy-2,2-bis(trifluoromethyl)-thietane, has been reported, though the structure has not been proved conclusively.[2] By the reaction of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (**1**) with ethyl vinyl ether in the presence of potassium fluoride in *N,N*-dimethylformamide, we obtained the same adduct in a good yield. On the basis of its mass spectrum, the structure was established as to be 4-ethoxy-2,2-bis-(trifluoromethyl)thietane (**3**, R=Et). That is, fragment peaks corresponding to $(CF_3)_2C{-}CH_2^+$ (*m/e* 164) and $EtO{-}CH{=}S^+$ (*m/e* 90), which resulted from the cleavage of the 4-ethoxythietane ring, as well as to the M^+ 254 molecular ion, were observed. However, the fragment peak corresponding to $EtO{-}CH{=}C^+(CF_3)_2$ (*m/e* 208), which should have resulted from another isomer, the 3-ethoxy compound, was not observed. When methyl vinyl ether was used in the above reaction, a similar 4-methoxy compound, **3** (R=Me), was obtained.

Thus, in this heterolytic cycloaddition, hexafluorothioacetone behaved as being normally polarized, *e.g.*, into a negative sulfur atom and a positive carbon atom, although a few examples have appeared in the literature in which hexafluorothioacetone reacts as if the thiocarbonyl group is polarized in the "reverse" direction.[3,4]

Reactions of 4-Alkoxy-2,2-bis(trifluoromethyl)thietanes. As cyclic monothioacetals, 4-alkoxy-2,2-bis(trifluoromethyl)thietanes were presumed to be susceptible to the attack of an acid or a base.



When a solution of the thietane **3** (R=Et) in concentrated sulfuric acid was kept at room temperature for several hours, a bimolecular condensation product was obtained. The structure of this compound was established from its spectral analysis as to be bis[4,4-bis(trifluoromethyl)thietan-2-yl]ether (**5**). In the IR spectrum, no absorption band due to either a OH or SH group was observed. In the ^{19}F NMR spectrum, only one multiplet signal due to CF_3 groups appeared, while in the ^1H NMR spectrum, two signals due to two unequivalent CH_2 protons and one triplet signal due to the CH proton were observed in the appropriate positions. In the mass spectrum, two fragment peaks, *m/e* 209 (base peak) and *m/e* 225, as well as the parent peak, M^+ 434, appeared; they resulted from the cleavage of the ether linkage.

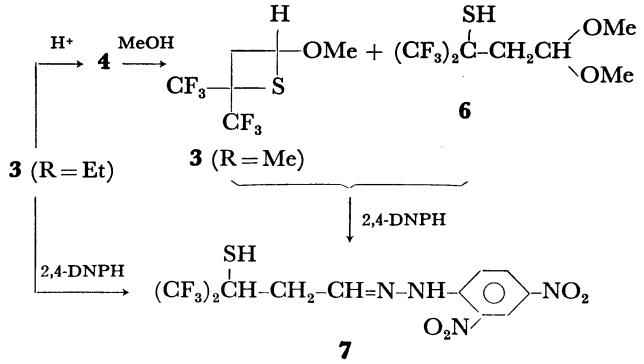
The pathway of the formation of **5** was presumed to be as is shown above. Protonation on the oxygen atom of **3**, followed by the loss of alcohol, gives a carbonium ion, **4**, which is stabilized by the adjacent sulfur atom. This carbonium ion finally attacks another molecule of **3** to give **5**. In order to confirm the formation of the cation, **4**, we carried out the following reactions.

In the presence of sulfuric acid, the ethoxythietane **3** (R=Et) was allowed to react with a large excess of methanol at room temperature. As reaction products, we thus obtained methoxythietane, **3** (R=Me), and

4,4,4-trifluoro-3-mercapto-3-(trifluoromethyl)butyraldehyde dimethyl acetal **6**, in yields of 17 and 30% respectively. The structure of **6** was elucidated from the spectral data. An absorption band due to SH appeared at 2550 cm^{-1} in its IR spectrum, and four signals due to the CH, OCH_3, SH, and CH_2 protons appeared appropriately in its NMR spectrum.

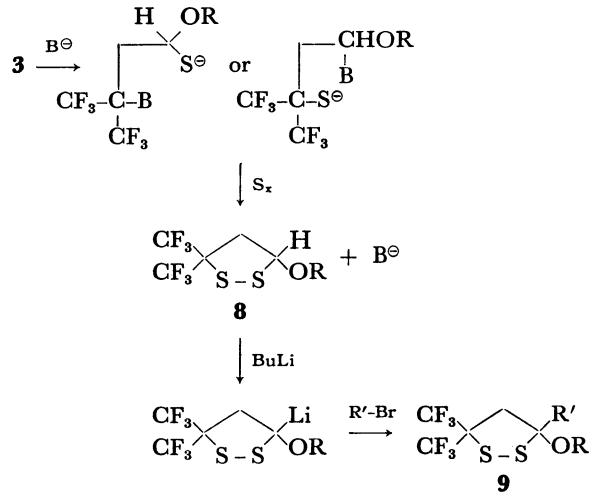
In this reaction, it was presumed that **3** (R=Me) was formed by an alkoxyl exchange *via* the carbonium ion, **4**, whereas **6** was formed by the further nucleophilic attack of a methanol molecule on **3**, which resulted in a cleavage of the thietane ring.

When the reaction mixture was treated with 2,4-dinitrophenylhydrazine and aqueous sulfuric acid, 2,4-dinitrophenylhydrazone of **6** was obtained in a 63% yield. This hydrazone, **7**, was also provided in a good yield (76%) directly from **3** (R=Et and Me) by treatment with 2,4-dinitrophenylhydrazine. These results mean that the cyclic monothioacetal **3**, as well as the dimethyl acetal **6**, behaved equivalently to an aldehyde, as had been expected.



When the ethoxythietane (**3**, R=Et) in a polar solvent was treated with diethylamine or potassium hydroxide at room temperature, 5-ethoxy-3,3-bis(trifluoromethyl)-1,2-dithiolane (**8**) was obtained as the main product. This base-catalyzed disproportionation seems to occur because the five-membered ring of 1,2-dithiolane is thermodynamically more stable than the four-membered ring of thietane.

Preparation of 5-Alkoxy-3,3-bis(trifluoromethyl)-1,2-dithiolanes. An example of the ring-expansion reaction of thietanes into 1,2-dithiolanes involving heating with sulfur has been reported.[5] This direct sulfurization was, however, applied in vain in the preparation of **8** from **3**. In the presence of a base such as diethylamine, however, the thietane, **3**, reacted with sulfur in *N,N*-dimethylformamide, and the 1,2-dithiolane **8** was obtained in a rather good yield:



The structure of this 1,2-dithiolane derivative, **8**, was evident from its ^{19}F NMR and mass spectra. The two trifluoromethyl groups of the dithiolane were nuclear-magnetically unequivalent, while those of the thietane compound, **3**, were equivalent, as has been described before. We assumed that, while the five-membered ring is not co-planar,[6] the four-membered ring is nearly co-planar or that its frequency between axial and equatorial vibrations is so quick that the NMR at room temperature is not distinguishable.

The Alkylation of Thietane, 3, and Dithiolane, 8. Because of the adjacent sulfur atom, the carbon atom of the 4-position of the thietane, **3**, and of the 5-position of the dithiolane, **8**, had been expected to be lithiated to give a carbanionic intermediate.

The five-membered 1,2-dithiolane compound, **8**, was easily lithiated with butyllithium in a hexane–tetrahydrofuran solution, and the resulting lithio compound reacted with alkyl bromides to give their 5-alkyl derivatives, **9** (Table 1).

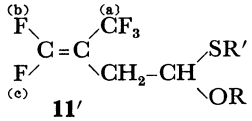
In contrast with the above-mentioned results, the four-membered thietane compound, **3**, gave ring-opened monothioacetal, 4-alkoxy-4-butylthio-1,1-difluoro-2-(trifluoromethyl)-1-butene, **11**, by the similar reaction. The structure of this compound, **11** (R=Et), was also evident from its spectral data. In the IR spectrum, the presence of the C=C double bond was revealed by the absorption at 1748 cm^{-1}. In the ^{19}F NMR spectrum, three signals due to the CF_2=C–CF_3 group appeared. In the ^1H NMR, two noticeable signals due to methine and methylene groups appeared, in addition to those due to butyl and ethyl groups.

Table 1. Preparation of the dithiolane **9**

R	R′	Yield (%)	Bp (°C/mmHg)	^{19}F NMR CF_3		J (Hz)	F Anal (%) Found	Calcd
Me	$CH_2CO_2CH_3$	45	147—150/4	−11.2 q	−11.6 q	10.2	33.3	33.1
Me	$CH_2(CH_2)_3CH_3$	59	120—122/3	−10.3 q	−11.8 q	11.8	33.5	33.3
Et	$CH_2CO_2CH_3$	62	155—156/3	−10.5 q	−11.2 q	9.0	31.6	31.8
Et	$CH_2(CH_2)_3CH_3$	79	125—127/3	−10.3 q	−12.0 q	9.4	32.0	32.0

a) Measured in neat. The values are given in δ ppm from ext. CF_3CO_2H.

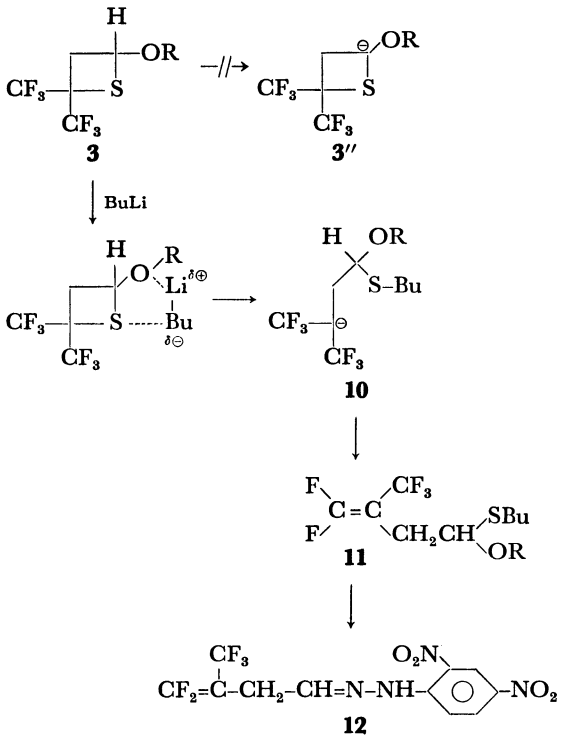
TABLE 2. PREPARATION OF THE MONOTHIOACETAL



11′

Product R	Product R′	Reactant	Reac. Temp (°C)	Yield (%)	Bp (°C/mmHg)	^{19}F NMR ppm[a] a	b	c	^{19}F NMR J (Hz) J_{ab}	J_{bc}	J_{ca}	F Anal (%) Found	Calcd
Me	*n*-Bu	*n*-BuLi	−60	59	87—90/27	−16.7	−1.0	2.3	20.7	16.9	10.5	34.3	34.1
		n-BuMgBr	r.t.	56									
Me	Ph	PhMgBr	r.t.	63	103—105/20	−17.3	−2.0	1.3	19.3	15.6	10.1	32.2	31.9
Et	*n*-Bu	*n*-BuLi	−60	53	94—95/19	−16.8	−0.7	2.6	19.7	18.3	9.9	32.3	32.5
		n-BuMgBr	r.t.	60									
Et	Ph	PhMgBr	r.t.	67	130—132/27	−17.4	−1.6	1.6	20.1	15.3	10.1	30.7	30.4
Et	Et	EtMgI	r.t.	37	86—90/17	−17.5	−1.8	0.7	19.5	16.8	9.8	36.1	36.0

a) See footnote a) of Table 1.



The reaction mechanism was presumed to be as is shown above. Thus, the thietane, **3**, did not give the expected carbanion, **3″**; instead the sulfur atom was attacked by the butyl anion. This must be ascribed to the low stability of the **3″** carbanion, which is too much strained to have a *p*-orbital occupied by two electrons at the 3-carbon atom. The attack of the butyl anion on the sulfur atom might have been promoted by the co-ordination of alkoxy oxygen on lithium, as is shown in the scheme. The reaction was terminated by the liberation of a fluoride ion from one of the trifluoromethyl groups, giving the α-olefin, (**11**).

In order to obtain a range of compounds of this type, we also carried out the reaction of alkoxythietanes (**3**) with Grignard reagents. The corresponding monothioacetals (**11′**) were obtained in good yields (Table 2).

Further, these nomothioacetals yielded a hydrazone, **12**, by a reaction with 2,4-dinitrophenylhydrazine, thus behaving like acetals,[4] as had been expected.

Experimental

4-Ethoxy-2,2-bis(trifluoromethyl)thietane (3, R=Et). A mixture of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (36.4 g, 0.1 mol), ethyl vinyl ether (14.4 g, 0.2 mol), potassium fluoride (5.8 g, 0.1 mol) and *N,N*-dimethylformamide (70 ml) was stirred for 24 h at room temperature. The whole was poured into water, and the separated oily material was extracted with diethyl ether. The extract was dried over magnesium sulfate, and the solvent was removed. The residue was then subjected to vacuum distillation, giving **3** (R=Et) (18.3 g) (bp 78—80 °C/70 mmHg (lit,[2] bp 43 °C/10 mmHg)) in a 72% yield.

Found: F, 44.4%. Calcd for $C_7H_8F_6OS$: F, 44.9%. ^{19}F NMR*: δ −3.1 (s). MS: M$^+$ 254, *m/e* 164 ($(CF_3)_2C$–CH_2), *m/e* 90 (EtO–CH=S), *m/e* 145 (CF_2=C(CF_3)CH_2).

4-Methoxy-2,2-bis(trifluoromethyl)thietane (3, R=Me). (bp 145—148 °C/760 mmHg) was obtained in a 68% yield by using methyl vinyl ether instead of ethyl vinyl ether in the above procedure.

Found: F, 47.7%. Calcd for $C_6H_6F_6OS$: F, 47.5%. ^{19}F NMR: δ −3.0 (s).

Bis[4,4-bis(trifluoromethyl)thietan-2-yl] Ether (5). Alkoxythietane **3** (R=Et or Me) (0.04 mol) was dissolved in concd sulfuric acid (10 ml), after which the solution was allowed to stand for 1 h at room temperature. The reaction mixture was then poured into ice water and worked up as has been described above. The crude product solidified upon being stored in an ice-box; it was recrystallized from petroleum ether to give **5**, mp 91—92 °C. Yield: 76% from **3** (R=Et) and 82% from **3** (R=Me).

Found: C, 27.5; H, 1.13; F, 52.4%. Calcd for $C_{10}H_6F_{12}OS_2$: C, 27.7; H, 1.39; F, 52.2%. ^{19}F NMR (in CCl_4): δ-6.5 (m). ^{1}H NMR ($CDCl_3$): τ 6.95 and 7.28 (d of d each, $C\underline{H}_2$, J_{gem}=15.0 Hz), 4.55 (t, $C\underline{H}$, J_{vic}=9.0 Hz). MS: M$^+$ 434, *m/e* 225 ($C_5H_3F_6SO$), *m/e* 209 ($C_5H_3F_6S$).

Reaction of 3 (R=Et) with Methanolic Sulfuric Acid. A mixture of **3** (R=Et, 10.16 g, 0.04 mol), concd sulfuric acid (8 ml), and methanol (40 ml) was stirred for 11 days at room

* All the ^{19}F NMR chemical shifts throughout this article are given in δ ppm from external trifluoroacetic acid. They were measured in neat unless the solvent is indicated.

temperature. The reaction mixture was then poured into water, and a separated oily material was extracted with diethyl ether. Two products, 4-methoxy-2,2-bis(trifluoromethyl)-thietane (**3**, R=Me) and 4,4,4-trifluoro-3-mercapto-3-(trifluoromethyl)butyraldehyde dimethyl acetal, **6**, were separated from each other by means of gas chromatography. The yields, 17% for **3** (R=Me) and 30% for **6**, were determined by GLC, using nitrobenzene as the internal standard.

Thiol **6**: Found: F, 41.7%. Calcd for $C_7H_{10}F_6O_2S$: F, 41.9%. IR: 2550 (S–H), 1070, 1050 (C–O–C) cm^{-1}. ^{19}F NMR: δ −5.6 (s). ^1H NMR τ 5.45 ($CH_2C\underline{H}$, t, J=5.5 Hz), 6.80 (2×$OC\underline{H}_3$, s), 6.89 ($S\underline{H}$, s), 7.80 ($C\underline{H}_2CH$, d).

4,4,4-Trifluoro-3-mercapto-3-(trifluoromethyl) butyraldehyde 2,4-Dinitrophenylhydrazone (**7**). 2,4-Dinitrophenylhydrazine (2.18 g, 0.011 mol) was dissolved in a mixture of ethanol (47 ml), water (14 ml), and concd sulfuric acid (10 ml). Ethoxythietane **3** (R=Et, 2.54 g, 0.01 mol) was added to this solution, and the whole was stirred for 24 h at room temperature. The precipitated product was collected by filtration and recrystallized from benzene to give the 2,4-dinitrophenylhydrazone; mp 131—132 °C (3.08 g, 76%).

Found: C, 32.4; H, 1.42; N, 13.8; F, 28.0%. Calcd for $C_{11}H_8F_6N_4O_4S$: C, 32.5; H, 1.47; N, 13.8; F, 28.1%. IR: 3305 (NH), 2570 (SH), 1615 (C=N), 1510, 1340 (NO_2) cm^{-1}. ^{19}F NMR ($CHCl_3$): δ −6.5 (s).

5-Alkoxy-3,3-bis(trifluoromethyl)-1,2-dithiolane (**8**). *a) By the Disproportionation of* **3**: Ethoxythietane **3** (R=Et, 5.08 g, 0.02 mol) was dissolved in *N,N*-dimethylformamide (15 ml), and then diethylamine (1.63 g, 0.02 mol) was added to this solution. The whole was stirred for 72 h at room temperature. The reaction mixture was worked up as usual, giving 5-ethoxy-3,3-bis(trifluoromethyl)-1,2-dithiolane (**8**, R=Et) (bp 73—75 °C/11 mmHg, 1.57 g) in a yield of 55%. In the potassium hydroxide–methanol system, the same product was obtained in a 55% yield.

Found: C, 29.5; H, 2.67; F, 39.6%. Calcd for $C_7H_8F_6OS_2$: C, 29.4; H, 2.82; F, 39.8%. ^{19}F NMR: δ −6.4 (q), −8.6 (q). J_{F-F}=10.4 Hz.

No other identifiable products were separated from the distillation residue.

b) By the Sulfurization of **3**: A mixture of ethoxy thietane (**3**, R=Et) (20.3 g, 0.08 mol), sulfur (3.07 g, 0.09 mol), diethylamine (2.92 g, 0.04 mol), and dimethylformamide (50 ml) was refluxed for 1 h. The reaction mixture was then poured into water, and the separated oily material was extracted with diethyl ether. The usual work-up gave the dithiolane (**8**, R=Et) (13.0 g) in a yield of 57%.

When methoxythietane (**3**, R=Me) was sulfurized in a similar way, methoxy dithiolane (**8**, R=Me) (bp 103—105 °C/50 mmHg) was obtained in a 46% yield.

Found: F, 42.1%. Calcd for $C_6H_6F_6OS_2$: F, 41.9%. ^{19}F NMR: δ −6.5 (q), −7.5 (q). J_{F-F}=10.2 Hz.

4-Alkoxy-4-alkyl(or phenyl)thio-1,1-difluoro-2-(trifluoromethyl)-1-butene (**11′**). *a) Reaction of Alkoxythietane* **3** *and Butyllithium*: A hexane solution of butyllithium (1.71 N, 13 ml, 0.022 mol) was stirred into a solution of ethoxythietane (**3**, R=Et) (5.08 g, 0.02 mol) in dry tetrahydrofuran (50 ml) with the temperature kept at −50——60 °C. After 2 h of stirring at −60 °C, the reaction mixture was poured into water and worked up as usual. Vacuum distillation gave a 1-butene compound, **11** (R=Et) (3.10 g, 53%); bp 94—95 °C/19 mmHg.

Found: F, 32.3%. Calcd for $C_{11}H_{17}F_5OS$: F, 32.5%. IR: 1748 (C=C) cm^{-1}. ^1H NMR: τ 5.60 (t, $CH_2C\underline{H}<$), 6.1—6.9 (m, S–$CH_2C\underline{H}_2C\underline{H}_2$), 7.3—7.7 (m, $OC\underline{H}_2$), 8.3—8.7 (m, $SC\underline{H}_2$) 8.85 (t, $OCH_2C\underline{H}_3$), 8.98 (t, $S(CH_2)_3C\underline{H}_3$). ^{19}F NMR: (Table 2). MS: M^+ (not observed), *m/e* 203 (M^+−SBu), *m/e* 147 (EtO–CH–SBu).

The reaction with methoxythietane **3** (R=Me) gave a similar product, **11** (R=Me), in a 59% yield (Table 2).

b) Reaction of Alkoxythietane **3** *with a Grignard Reagent.* Intoa solution of a Grignard reagent prepared from phenyl bromide (6.91 g, 0.044 mol), magnesium (1.15 g, 0.04 mol), and dry tetrahydrofuran (30 ml), 4-ethoxy-2,2-bis(trifluoromethyl)-thietane **3** (R=Et) (10.16 g, 0.04 mol) was added in the course of 30 min at room temperature. After 3 h of stirring at that temperature, the reaction mixture was worked up as usual. The distillation of the crude product gave an oil, **11′** (R=Et, R′=Ph) (8.23 g, 67%); bp 130—132 °C/27 mmHg.

Found: F, 30.7%. Calcd for $C_{13}H_{13}F_5OS$: F, 30.4%. ^1H NMR: τ 2.5—2.9 (m, Ar$\underline{H}$), 5.37 (t, $CH_2C\underline{H}<$), 5.9—6.9 (d of q, $C\underline{H}_2CH_3$), 7.38 (d, $C\underline{H}_2CH<$), 8.80 (t, $CH_2C\underline{H}_3$). ^{19}F NMR: (Table 2).

Similar reactions with other Grignard reagents were also carried out (Table 2).

4,4-Difluoro-3-(trifluoromethyl)-3-butanal 2,4-Dinitrophenylhydrazone (**12**). Into a solution of 2,4-dinitrophenylhydrazine (2.18 g, 0.011 mol) in ethanol (47 ml), **11′** (R=Et, R′=Bu) (2.92 g, 0.01 mol) and dilute sulfuric acid (concd H_2SO_4 10 ml and H_2O 14 ml) were added. The whole was stirred for 24 h at room temperature, and then worked up as usual. The crude product was recrystallized from acetone to give 2,4-dinitrophenylhydrazone (3.40 g, 96%); mp 120—120.5 °C.

Found: C, 37.4; H, 1.97; N, 16.1; F, 26.9%. Calcd for $C_{11}H_7N_4O_4F_5$: C, 37.3; H, 1.99; N, 15.8; F, 26.8%. IR: 3280 (N–H), 1755 (C=C), 1505, 1365 (NO_2) cm^{-1}. ^{19}F NMR: δ −16.7 (d of d, CF_3), −1.67 (q of d, CF_2), 2.00 (d of q, CF_2).

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