FIRST SYNTHESIS OF *gem*-DIFLUOROTHIIRANES FROM CYCLOALIPHATIC THIOKETONES AND DIFLUOROCARBENE[1]

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Abstract - The reaction of sterically crowded cycloaliphatic thioketones with phenyl(trifluoromethyl)mercury and sodium iodide in boiling benzene yielded *gem*-difluorothiiranes in fair yields whereas in the case of aromatic thioketones *gem*-difluoroalkenes were obtained. The formation of these products is rationalized by an addition of difluorocarbene onto the C,S-double bond, followed by the extrusion of sulfur.

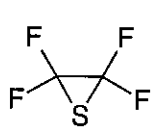
INTRODUCTION

Reports on syntheses and properties of fluorinated thiiranes are very rare. An old protocol concerns the preparation of tetrafluorothiirane (**1**) starting with difluorothiophosgene and perfluoropropylene oxide.[3] The yield of **1** was very low, however, and the product was contaminated with perfluorocyclobutane as reported by another group.[4] Another access to a fluorinated thiirane based on the rather hardly available bis(perfluoropentyl) disulfide, which upon treatment with tris(diethylamino)phosphane was converted into 2-fluoro-3-hexafluoroisopropylidene-2-(trifluoromethyl)thiirane (**2**).[5] The same research group described the synthesis of 2,2-difluoro-3,3-bis(trifluoromethyl)thiirane (**4**) *via* the cyclization of sulfenyl chloride (**3**) with borontrifluoride-triethylamine complex[6] (*Scheme 1*).

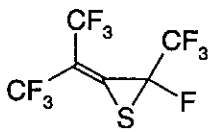
On the other hand, thiocarbonyl compounds are versatile starting materials for simple preparation of various thiiranes. In the first place, the 1,3-dipolar cycloaddition of diazo compounds followed by N_2 extrusion should be mentioned.[7-9] In the case of less reactive diazo compounds, thiiranes are formed in Rh-catalyzed reactions with thiocarbonyl

compounds, in which a carbenoid is involved.[10] A mechanism *via* a thiocarbonyl ylide was postulated for reactions of thioketones with a free carbene generated photolytically at low temperature in an argon matrix.[11] Recently, we elaborated a preparative method for the synthesis of *gem*-dichlorothiiranes from non-enolizable thioketones under two-phase conditions.[12] In this case, a plausible reaction mechanism involving dichlorocarbene was postulated.

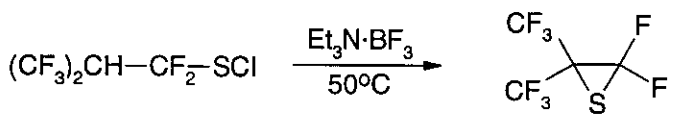
Scheme 1



1



2



3 **4**

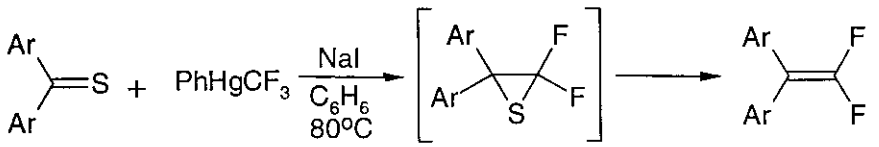
Fluorinated thioethers attract considerable attention due to their unusual properties; many of them were involved in the design of biologically active compounds.[13] In view of the structural similarity of aliphatic thioethers and thiiranes we decided to develop a synthetically useful method for the preparation of fluorinated thiiranes. The most simple approach seemed to be the addition of difluorocarbene onto thioketones. Difluorocarbene is a widely used halogenated carbene and its chemistry has been reviewd by Dehmlov.[14] Phenyl-(trifluoromethyl)mercury ($PhHgCF_3$, Seyferth's reagent) is recommended as the most convenient precursor. Whereas additions of $:CF_2$ onto C,C-double bonds are well documented, attempts to accomplish similar reactions with C,O-, C,N-, and C,S-double bonds failed.[15] In the present paper, we describe first successful additions of $:CF_2$ with thioketones yielding *gem*-difluorothiiranes.

RESULTS AND DISCUSSION

Generally, the reactions of non-enolizable thioketones (**5a-d**) with $PhHgCF_3$ were carried out in boiling benzene in the presence of *ca.* equimolar amounts of dried NaI. Under these conditions, reactions were completed after 24-48 h and the products were isolated after chromatographic workup. Reactions with aromatic thioketones (**5a**,**b**) did not afford the

expected thiiranes. Instead, *gem*-difluoroalkenes (**7a**,**b**) were obtained in 55 and 72% yields, respectively (*Scheme 2*).

Scheme 2



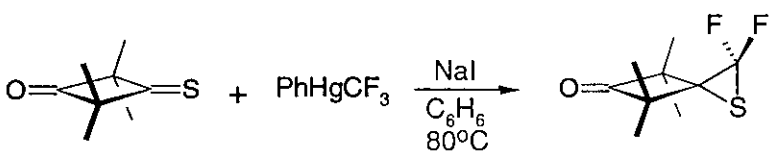
5a, b **6a, b** **7a, b**

a: Ar = C_6H_5 **b**: Ar = 4-$MeOC_6H_4$

The formation of ethylene derivatives (**7**) results from a desulfurization of unstable 2,2-difluoro-3,3-diarylthiiranes (**6a**,**b**) which are believed to be primarily formed adducts. The instability of thiiranes of type (**6**) was also observed when they were prepared from **5a**,**b** and CF_3SiMe_3 (Ruppert's reagent) in the presence of specially dried tetrabutylammonium fluoride at room temperature.[16] It is worth mentioning that 2,2-dichloro-3,3-diphenylthiirane is a fairly stable compound at room temperature[12] whereas the replacement of chlorine by fluorine atoms results in an easier elimination of sulfur.

In the case of the sterically crowded aliphatic 2,2,4,4-tetramethyl-3-thioxocyclobutane (**5c**) we were able to isolate the expected thiirane (**6c**) in 50% yield as a thick colorless oil (*Scheme 3*). The IR spectrum (neat) showed a very strong band at 1790 cm^{-1} for the unchanged C=O group of cyclobutanone. In the ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz), two signals for the methyl groups appeared, one of them as a singlet (1.23 ppm) and the other one as a triplet (1.39 ppm) with J = *ca.* 1 Hz. This coupling results from a 'through-space-interaction' with the fluorine atoms which absorb at -94.9 ppm in the ^{19}F-NMR spectrum ($CDCl_3$). Finally, the ^{13}C-NMR spectrum revealed the presence of a triplet with $^1J_{C,F}$ = 307.8 Hz at 121.1 ppm which is attributed to C(2). The signal of C(3) was identified also as a triplet at 62.1 ppm ($^2J_{C,F}$ = 9.3 Hz). The other signals are typical for the tetramethylcyclobutanone ring.[17] The structure of **6c** shows that difluorocarbene reacted exclusively with the C=S group of **5c**.

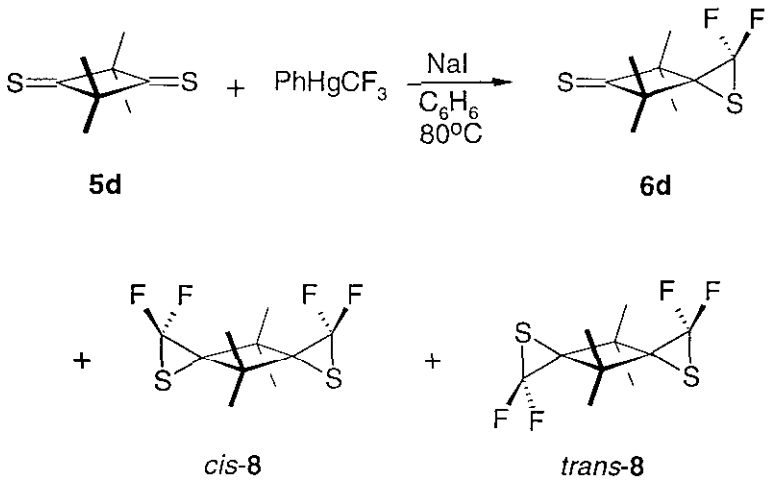
Scheme 3



5c **6c**

The next thioketone selected for our studies was 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**5d**). The typical red-orange color of this compound disappeared after heating the mixture with $PhHgCF_3$ for 48 h. Separation of the reaction mixture by column chromatography afforded mono-adduct (**6d**) (18%) and a mixture of the bis-adducts *cis*- and *trans*-**8** (40%, *Scheme 4*).

Scheme 4



Spectral data of **6d** were similar to those of **6c**; the signal of the C=S group in the ^{13}C-NMR spectrum appeared typically at *ca.* 273 ppm.[18] The separation of *cis*- and *trans*-**8** was not achieved, neither by column chromatography nor *via* crystallization. Identification and characterization of both isomers were possible, however, due to the different symmetry of the two molecules. The centrosymmetric *trans*-**8** showed only one Me resonance in the ^1H- and ^{13}C-NMR spectra (1.29 and 24.7 ppm, respectively). In the ^1H-NMR, the signal of the Me groups appeared as a triplet with a 'through-space coupling' of *ca.* 1 Hz. For *cis*-**8**, with a mirror symmetry, the Me groups resonated in the ^1H- and ^{13}C-NMR spectra as two signals at 1.52/1.12 and 28.5/21.3 ppm, respectively.

In view of our successful protocol for the preparation of *gem*-dichlorothiiranes from thioketones and $CHCl_3$/NaOH/TEBA,[12,19] we became interested in elaboration of a similar two-phase procedure for corresponding *gem*-difluorothiiranes. Recently, Balcerzak and Jończyk succeeded in preparation of a series of *gem*-difluorinated cyclopropanes using $CHBr_3/CBr_2F_2$/KOH/TBAHS[20] recognized as a convenient source of $:CF_2$.[14,21] In our experiments with thiobenzophenone (**5a**), however, we could not obtain the expected *gem*-difluorothiirane (**6a**). Therefore, we conclude that Seyferth's reagent is the reagent of choice to convert thioketones into fluorinated thiiranes.

EXPERIMENTAL

Melting points were determined in a capillary on a *Büchi-SMP-125* apparatus and are uncorrected. IR spectra were recorded on a *Perkin-Elmer 781* instrument (cm-1), ^{1}H-NMR and ^{13}C-NMR spectra on a *Bruker AC-300* (^{1}H, 300 MHz) and *Bruker ARX-300* instrument (^{13}C, 75.5 MHz), respectively, in $CDCl_3$; chemical shifts in ppm, TMS as internal standard, *J* in Hz. ^{19}F-NMR spectra were taken on a *Bruker AMX-600* Instrument (564.7 MHz) in $CDCl_3$; chemical shifts in ppm, $CFCl_3$ as internal standard. EI-MS spectra were recorded on a *Varian-MAT-112S* spectrometer at 70 eV; CI-MS with NH_3 as carrier gas. Microanalyses were performed at the microanalytical laboratory of the University of Zurich.

Starting materials. They were prepared according to known protocols: thiobenzophenone (**5a**) and 4,4'-dimethoxythiobenzophenone (**5b**) from corresponding ketones and Lawesson's reagent in boiling toluene,[22] 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**5c**) and 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**5d**) from commercially available 2,2,4,4-tetramethylcyclobutane-1,3-dione using P_4S_{10} in pyridine.[23] Phenyl(trifluoromethyl)mercury was prepared according to Seyferth *et al.*[24] Commercial NaI has been dried overnight in high vacuum at 150°C.

Reactions of thioketones with phenyl(trifluoromethyl)mercury; general procedure. To a solution of thioketone **5** (2 mmol) in dry benzene (5 mL), $PhHgCF_3$ (767.7 mg, 2.2 mmol) and NaI (314.8 mg, 2.1 mmol) were added at rt. The stirred mixture was heated to reflux under N_2 atmosphere. When the reaction came to an end, the solution was cooled to rt and the solvent was evaporated. The residues were purified chromato-graphically (SiO_2, pentane with increasing amounts of CH_2Cl_2).

Reaction with thiobenzophenone (**5a**). After 36 h, the reaction mixture was colorless. *1,1-Difluoro-2,2-diphenylethene* (**7a**). 238 mg (55%), colorless, viscous oil. IR (neat): 3060*w*, 3020*w*, 1710*vs*, 1500*m*, 1450*s*, 1250*s* (br), 1210*m*, 1000*m*, 990*s*, 910*m*, 760*s*, 700*s*, 630*m*. ^{1}H-NMR: 7.35-7.25 (*m*, 10 arom. H). ^{13}C-NMR: 153.8 (*t*, ^1J(C,F) = 294.0, $=CF_2$); 134.4 (*s*, 2 arom. C); 129.6 (*dt*, ^4J(C,F) = 3.0, 4 arom. CH); 128.4, 127.6 (2*d*, 6 arom. CH); 96.3 (*t*, ^2J(C,F) = 16.0, $C=CF_2$). ^{19}F-NMR: -88.3 (*s*, $=CF_2$). EI-MS: 216 (100, $M^{+\cdot}$), 196 (32), 167 (16), 165 (84), 82 (11). Anal. Calcd for $C_{14}H_{10}F_2$: C, 77.76; H 4.66. Found: C, 76.97; H, 4.86.

Reaction with 4,4'-dimethoxythiobenzophenone (**5b**). After 24 h, the reaction mixture was colorless. *1,1-Difluoro-2,2-bis(4-methoxyphenyl)ethene* (**7b**). 397 mg (72%), colorless crystals, mp 53-54°C (pentane). IR (KBr): 1700*s*, 1610*s*, 1510*vs*, 1310*m*, 1280*s*, 1240*vs*, 1210*m*, 1180*s*, 1110*m*, 1030*s*, 980*m*, 840*vs*. ^{1}H-NMR: 6.83, 6.20 (*AB*, *J*(A,B) = 7.0, 8 arom. H); 3.79 (*s*, 2 MeO). ^{13}C-NMR: 158.9 (*s*, 2 arom. C); 153.8 (*t*, ^1J(C,F) = 294.0, $=CF_2$); 137.3 (*s*,

2 arom. C); 130.7, 113.8 (2*d*, 8 arom. CH); 95.3 (*t*, ^2J(C,F) = 16.0, *C*=CF_2); 55.3 (*q*, 2 MeO). ^{19}F-NMR: -90.2 (*s*, =CF_2). CI-MS: 277 ([*M*+1]$^+$). Anal. Calcd for $C_{16}H_{14}O_2F_2$: C, 69.56; H 5.11. Found: C, 68.94; H, 5.47.

Reaction with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**5c**). After 24 h, the reaction mixture was colorless. Chromatography yielded a small amount of starting material and *2,2-difluoro-4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexan-5-one* (**6c**) as the less polar fraction: 140 mg (50%), colorless oil. IR (neat): 2970*m*, 2930*m*, 1790*vs* (C=O), 1460*m*, 1380*s*, 1150*s*, 1100*m*, 1030*m*, 1000*s*, 960*m*, 790*s*. ^{1}H-NMR: 1.39 (*t*, *J*(H,F) = *ca.* 1.0, 2 Me); 1.23 (*s*, 2 Me). ^{13}C-NMR: 216.4 (*s*, C=O); 121.1(*t*, ^1J(C,F) = 307.8, CF_2); 62.5 (*t*, ^3J(C,F) = 3.3, C(4), C(6)); 62.1 (*t*, ^2J(C,F) = 9.3, C(3)); 22.9, 20.3 (2*q*, 4 Me). ^{19}F-NMR: -94.9 (br *s*, CF_2). EI-MS: 206 (3, $M^{+\cdot}$), 163 (45), 146 (100), 131 (65), 81 (75), 70 (70).

Reaction with 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**5d**). After 48 h, the reaction mixture was colorless. A preliminary separation by column chromatography (SiO_2) yielded a mixture of 1:1 and 1:2 adducts. Additional separation on PLC plates coated with SiO_2 and pentane as eluent gave the 1:1 adduct **6d** as the minor component (R_f = 0.7) along with an inseparable mixture of two 1:2 adducts as the major fraction (R_f = 0.8). *2,2-Difluoro-4,4,6,6-tetramethyl-1-thiaspiro[2.3]hexane-5-thione* (**6d**): 80 mg (18%), pale red crystals, mp 115-117°C (after sublimation). IR (neat): 2970*s*, 2920*s*, 1460*s* (br), 1390*s*, 1300*m*, 1140*s*, 1090*m*, 1010*m*, 990*s*, 950*m*, 790*s*. ^{1}H-NMR: 1.44 (*t*, *J*(H,F) = *ca.* 1.0, 2 Me); 1.30 (*s*, 2 Me). ^{13}C-NMR: 273.2 (*s*, C=S); 121.0 (*t*, ^1J(C,F) = 310.0, CF_2); 66.0 (*s*, C(3)); 64.6 (*s*, C(4), C(6)); 26.9, 24.2 (2*q*, 4 Me). EI-MS: 222 (37, $M^{+\cdot}$), 207 (31), 189 (30), 175 (20), 86 (100, [Me_2C=C=S]$^{+\cdot}$).
cis- *and* trans-*2,2,7,7-Tetrafluoro-4,4,8,8-tetramethyl-1,6-dithiadispiro[2.1.2.1]octanes* (*cis*- and *trans*-**8**): 220 mg (40%) of a 4:1 mixture, colorless solid, mp 155-162°C (pentane). IR (KBr): 2980*m*, 1460*m*, 1390*m*, 1370*m*, 1350*vs* (br), 1180*m*, 1130*s*, 1110*m*, 1030*m*, 1020*m*, 950*s*, 790*s*. ^{1}H-NMR: 1.52, 1.12 (2*s*, 4 Me of *cis*-**8**); 1.29 (*t*, *J*(H,F) = *ca.* 1.0, 4 Me of *trans*-**8**). ^{13}C-NMR: 120.7, 120.5 (2*t*, ^1J(C,F) = 310, 2 CF_2 of *cis*-**8** and 2 CF_2 of *trans*-**8**); 65.3, 64.9 (2*s*, C(3), C(5) of *cis*/*trans*-**8**); 46.7, 46.2 ((2*s*, C(4), C(8) of *cis*/*trans*-**8**); 28.5, 21.3 (2*q*, 4 Me of *cis*-**8**); 24.7 (*q*, 4 Me of *trans*-**8**). ^{19}F-NMR: -94.2 (*s*, 2 CF_2 of *cis*-**8**); -93.6 (*s*, 2 CF_2 of *trans*-**8**). CI-MS: 272 (82, $M^{+\cdot}$), 257 (100), 256 (19), 255 (37), 198 (82), 190 (37), 187 (59), 175 (56). Anal. Calcd for $C_{10}H_{12}F_4S_2$: C, 44.11; H 4.44. Found: C, 44.38; H, 4.58.

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REFERENCES

1. Presented in preliminary form by *G.M.* at the '12th European Symposium on Fluorine Chemistry', Berlin, 1998.
2. Postdoctoral stay at the Institute of Organic Chemistry of the University of Zurich, February, 1997 - July, 1998.
3. W.R. Brasen, H.N. Cripps, C.G. Bottomley, M.W. Farlow, and C.G. Krespan, *J. Org. Chem.*, **1965**, *30*, 4188.
4. B. Beagley, R. Calladine, R.G. Pritchard, and S.F. Taylor, *J. Mol. Structure*, **1987**, *158*, 309.
5. V.Ya. Popkova, M.V. Galakhov, and J.L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1989**, 116 (*Chem. Abstr.*, **1989**, *111*, 77762t).
6. R.A. Bekker, V.Ya. Popkova, and J.L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1980**, 1692 (*Chem. Abstr.*, **1980**, *93*, 186054u).
7. D.C. Dittmer, in 'Comprehensive Heterocyclic Chemistry', ed. by A.R. Katritzky and C.W. Rees, Vol. 7, Pergamon Press, Oxford, 1984, p. 131.
8. A.V. Fokin and A.F. Kolomiets, *Russ. Chem. Rev.* (Engl. Transl.), **1975**, *44*, 138; **1976**, *45*, 25.
9. G. Mlostoń, M. Petit, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, **1994**, *77*, 435; M. Petit, A. Linden, G. Mlostoń, and H. Heimgartner, *ibid.*, **1994**, *77*, 1076.
10. G. Mlostoń and H. Heimgartner, *Helv. Chim. Acta*, **1996**, *79*, 1785, and refs. cited therein.
11. G. Mlostoń, J. Romański, C. Schmidt, H.P. Reisenauer, and G. Maier, *Chem. Ber.*, **1994**, *127*, 2527.
12. G. Mlostoń, J. Romański, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, **1998**, *81*, in the press.
13. T. Billard and B.R. Langlois, *Tetrahedron Lett.*, **1996**, *37*, 6865, and refs. cited therein.
14. E.V. Dehmlov, in 'Methoden der organischen Chemie (Houben-Weyl)', ed. by M. Regitz, Thieme Verlag, Stuttgart 1989, Band E19/b, p. 1467.
15. D. Seyferth and S.P. Hopper, *J. Org. Chem.*, **1972**, *37*, 4070.
16. G.A. Olah, G.K.S. Prakash, and G. Mlostoń, '18th International Symposium on the Organic Chemistry of Sulfur', Firenze (Italy), 1998, Abstracts P-47, p. 145.
17. R. Huisgen, G. Mlostoń, and C. Fulka, *Heterocycles*, **1985**, *23*, 2207.
18. G. Mlostoń and H. Heimgartner, *Helv. Chim. Acta*, **1995**, *78*, 1298; G. Mlostoń, J. Romański, A. Linden, and H. Heimgartner, *ibid.*, **1995**, *78*, 1499.

19. TEBA = benzyltriethylammonium chloride.
20. TBAHS = tetrabutylammonium hydrosulfate.
21. P. Balcerzak and A. Jończyk, *J. Chem. Res. (S)*, **1994**, 200.
22. L. Spruce, *Phosphorus, Sulfur and Silicon*, **1985**, *22*, 337.
23. E.W. Elam, *J. Org. Chem.*, **1967**, *32*, 1563.
24. D. Seyferth, S.P. Hopper, and G.J. Murphy, *J. Organometal. Chem.*, **1972**, *46*, 201.

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