Tetrahedron Vol 46, No. 12, pp. 4261–4264, 1990
Printed in Great Britain

0040–4020/90 $3.00+.00

α-FLUORO- AND α,α-DIFLUOROALKANALS BY SUBSTITUTION OF VICINAL BROMOFLUOROALKANES AND SUBSEQUENT PUMMERER REARRANGEMENT

Hiroaki SUGA and Manfred SCHLOSSER*

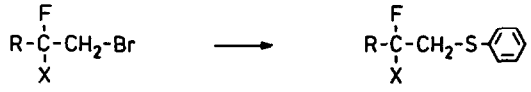
Institut de Chimie organique de l'Université

Rue de la Barre 2, CH-1005 Lausanne, Switzerland

(*Received in Belgium* 27 *March* 1990)

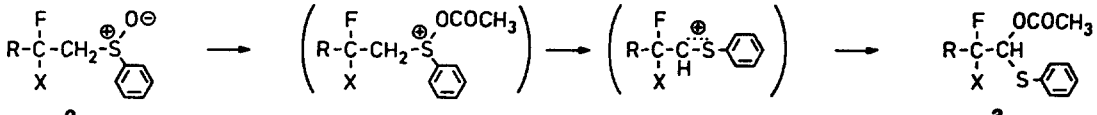
Summary : 2-Fluoro- or 2,2-difluoro-1-bromoalkanes readily undergo nucleophilic substitution by sodium thiophenolate to give 2-fluoro- or 2,2-difluoroalkyl phenyl sulfides (**1a - 1c**). The latter may be oxidized to the corresponding sulfoxides (**2a - 2c**). Heating with acetic anhydride produces 2-fluoro- and 2,2-difluoro-1-(phenylthio)alkyl acetates (**3a - 3b**) which may then be cleaved to give 2-fluoro- and 2,2-difluoro-1-phenylthio-1-alkanols (**5b - 5c**) or the 2-fluoro- and 2,2-difluoroalkanals (**4a - 4c**) if not reduced to give 2-fluoro- or 2,2-difluoro-1-alkanols (**6b - 6c**).

Fluorine decreases the reactivity of adjacent electrophilic centers towards nucleophilic substitution. Thus, potassium iodide in acetone promotes a Finkelstein halide exchange with 2,2,2-trifluoroethyl bromide [1] $2.5 \cdot 10^5$ times more slowly than with propyl bromide [2] under identical conditions. (1-Fluorocyclohexyl)methyl bromide was found to be too inert towards sodium acetate to allow replacement of the bromine atom to occur [3]. Therefore, a more powerful nucleophile deemed preferable if we wanted to submit the readily available 2-fluoro- and 2,2-difluoro-1-bromoalkanes [4] to substitution reactions. Indeed, with sodium thiophenolate high yields of the 2-fluoro- and 2,2-difluoroalkyl phenyl sulfides **1a - 1c** were obtained.



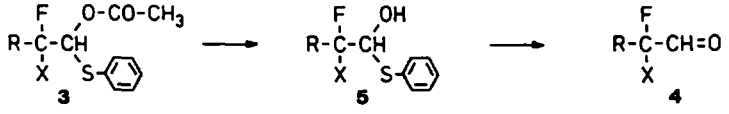
a: R = $H_{17}C_8$, X = H **b:** R = $H_{17}C_8$, X = F **c:** R = H_5C_6, X = F

Peracid oxidation produced the corresponding sulfoxides **2a - 2c**. When heated with acetic anhydride, the latter smoothly underwent the Pummerer rearrangement [5] to afford the 2-fluoro- or 2,2-difluoro-1-(phenylthio)alkyl acetates **3a - 3c**. The fact that no β-elimination of fluoride is observed disproves the transient existence of a sulfonia ylid species [6] and advocates for the intermediacy of a carbenium-sulfonium ion.



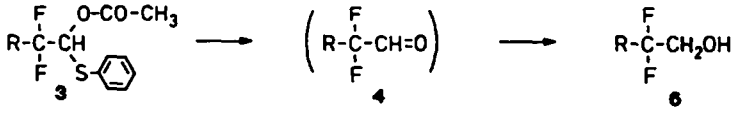
a: R = $H_{17}C_8$, X = H **b:** R = $H_{17}C_8$, X = F **c:** R = H_5C_6, X = F

The ester group of the α-phenylthioalkyl acetates **3** could be easily removed by reduction with diisobutylaluminum hydride. Only the monofluorinated hemithioacetal **5a**, however, spontaneously decomposed under elimination of thiophenol to set free the 2-fluorodecanal **4a**. The cleavage of the difluorinated analogs **5b** and **5c** had to be brought about by a combination of chromatography and dehydration.



a: R = $H_{17}C_8$, X = H **b:** R = $H_{17}C_8$, X = F **c:** R = H_5C_6, X = F

The aldehydes **4** proved to be too labile to be kept at ordinary temperature. On the other hand, they may be generated any time from their precursors **3** which can be indefinitely stored. Moreover, the fluorinated 1-(phenylthio)alkyl acetates **3** can be used in many reactions as if they were the free aldehydes. For example, treatment of **3b** and **3c** with lithium aluminum hydride led immediately to the 2,2-difluoro-1-alkanols **6b** and **6c**.



b: R = $H_{17}C_8$ **c:** R = H_5C_6

So far, only a few saturated α-fluoro- and α,α-difluoroaldehydes were reported in literature [7]. In most cases, they are derived from atypical polyhalogenated starting materials. Our approach appears to present the first systematic entry to this class of compounds [8]. Fluorinated aldehydes merit particular attention because of their potential biological properties [9].

EXPERIMENTAL PART

General remarks: see the first article of this series of three [10]. - The (di)fluorofluoroalkyl phenyl sulfides and (di)fluoro-1-alkanols show similar NMR anomalies as the corresponding bromides [4].

1. 2-Fluoro- and 2,2-Difluoroalkyl Phenyl Sulfides

A solution of the 2-fluoro- or 2,2-difluoroalkyl bromide (50 mmol) and sodium thiophenolate (7.9 g, 60 mmol) in anhydrous *N,N*-dimethyl formamide (100 mL) was kept 2 h at 25 °C. Water (200 mL) was added and the mixture was extracted with hexane (3 x 50 mL). The organic layers were combined, washed with a 10% aqueous solution of sodium carbonate (2 x 50 mL) and evaporated. The product was isolated by distillation under reduced pressure.

2-Fluorodecyl phenyl sulfide (1a) : 89%; mp 17 - 18 °C; bp 175 - 177 °C/5 mmHg; n_D^{20} 1.5134. - ^{1}H-NMR ($CDCl_3$) : 7.3 (5 H, m), 4.60 (1 H, d of symm. m, *J* 48.5), 3.20 (1 H, ddd, *J* 16.4, 14.0, 6.6), 3.07 (1 H, ddd, *J* 21.0, 14.0, 5.6), 1.7 (2 H, m), 1.4 (2 H, m), 1.3 (10 H, s-like m), 0.88 (3 H, t, *J* 7.0). - Analysis : calc. for $C_{16}H_{25}FS$ (268.43) C 71.59, H 9.39; found C 71.82, H 9.12%.

2,2-Difluorodecyl phenyl sulfide (1b) : 94%; mp -20 to -19 °C; bp 166 - 169 °C/5 mmHg; n_D^{20} 1.5025. - ^{1}H-NMR ($CDCl_3$) : 7.4 (2 H, m), 7.3 (3 H, m), 3.29 (2 H, t, *J* 14.1), 1.96 (2 H, symm. m), 1.4 (2 H, m), 1.3 (10 H, s-like m), 0.88 (3 H, t, *J* 6.9). - Analysis : calc. for $C_{16}H_{24}F_2S$ (286.42) C 67.16, H 8.45; found C 67.16, H 8.21%.

2,2-Difluoro-2-phenylethyl phenyl sulfide (1c) : 99%; bp 122 - 124 °C/5 mmHg; n_D^{20} 1.5695. - ^{1}H-NMR ($CDCl_3$): 7.5 (2 H, m), 7.4 (3 H, m), 7.3 (2 H, m), 7.2 (3 H, m), 3.56 (2 H, t, *J* 14.6). - Analysis : calc. for $C_{14}H_{12}F_2S$ (250.31) C 67.18, H 4.83; found C 67.11, H 5.01%.

2. 2-Fluoro- and 2,2-Difluoroalkyl Phenyl Sulfoxides

General procedure : A mixture of the 2-fluoro- or 2,2-difluoroalkyl phenyl sulfide (35 mmol) and *m*-chloroperbenzoic acid hydrate (55% techn. quality, 12 g, 38 mmol) in dichloromethane (100 mL) was stirred 3 h at -40 °C. The solution was thoroughly washed with 20% aqueous sodium hydroxide (3 x 20 mL), dried and evaporated. The residue was purified by recrystallization (**2a, 2b**) or chromatography (**2c**).

2-Fluorodecyl phenyl sulfoxide (2a) : 65%; mp 40 - 41 °C (from hexane). Before recrystallization, two diastereoisomers were present in a roughly 1 : 1 ratio. - ^{1}H-NMR ($CDCl_3$) : 7.7 (2 H, m), 7.6 (3 H, m), 5.12 (0.5 × 1 H, d of symm. m, *J* 49.5), 4.74 (0.5 × 1 H, d of symm. m, *J* 48.5), 3.28 (0.5 × 1 H, ddd, *J* 15.8, 13.7, 7.3), 3.00 (0.5 × 1 H, ddd, *J* 20.5, 13.7, 4.5), 2.9 (0.5 × 2 H, m), 1.8 (2 H, m), 1.4 (2 H, m), 1.3 (10 H, m, narrow), 0.88 (3 H, t, *J* 6.9). - Analysis : calc. for $C_{16}H_{25}FOS$ (284.43) C 67.56, H 8.86; found C 67.81, H 8.92%.

2,2-Difluorodecyl phenyl sulfoxide (2b) : 97%; mp 51 - 52 °C (from hexane). - ^{1}H-NMR ($CDCl_3$) : 7.7 (2 H, m), 7.6 (3 H, m), 3.35 (1 H, dt, *J* 19.0, 13.8), 3.19 (1 H, td, *J* 14.5, 11.7), 2.09 (2 H, symm. m), 1.5 (2 H, m), 1.3 (10 H, m, narrow), 0.89 (3 H, t, *J* 7.0). - ^{1}H-NMR (C_6D_6) : 7.4 (2 H, m), 7.0 (3 H, m), 2.97 (1 H, ddd, *J* 23.5, 11.3, 9.8), 2.80 (1 H, q, *J* 12.8), 2.05 (2 H, symm. m), 1.5 (2 H, m), 1.3 (10 H, m), 0.90 (3 H, t, *J* 6.9). - Analysis : calc. for $C_{16}H_{24}F_2OS$ (302.24) C 63.55, H 8.00; found C 63.83, H 7.83%.

2,2-Difluoro-2-phenylethyl phenyl sulfoxide (2c) : 88%; mp -40 to -38 °C; bp 235 - 240 °C/5 mmHg; n_D^{20} 1.5731. - ^{1}H-NMR ($CDCl_3$) : 7.7 (2 H, m), 7.5 (8 H, m), 3.66 (1 H, ddd, *J* 18.1, 14.5, 12.8), 3.48 (1 H, dt, 17.5, 14.1). - Analysis : calc. for $C_{14}H_{12}F_2OS$ (266.31) C 63.14, H 4.54; found C 63.00, H 4.80%.

Oxidation with 30% aqueous hydrogen peroxide gave **2,2-difluoro-2-phenylethyl phenyl sulfone** as white crystals; mp 126 - 128 °C. - ^{1}H-NMR ($CDCl_3$) : 7.86 (2 H, dt, *J* 8.2, 1.9), 7.65 (1 H, tm, *J* 7.6), 7.52 (2 H, tm, *J* 7.6), 7.40 (5 H, m, s-like), 3.98 (t, *J* 13.9).

3. 2-Fluoro- and 2,2-Difluoro-1-(phenylthio)alkyl acetates

General procedure : Under nitrogen atmosphere, a solution of 2-fluoro- or 2,2-difluoroalkyl phenyl sulfide (25 mmol) and sodiumacetate (8.2 g, 100 mmol) in acetic anhydride (50 mL) was heated 3 h to 130 °C. After evaporation of excess anhydride the residue was absorbed on silica gel (20 g) which was poured on top of a column filled with fresh silica gel (50 g) and eluted with a 10 : 1 mixture of hexane and ethyl acetate.

2-Fluoro-1-(phenylthio)decyl acetate (3a) : 71%; n_D^{20} 1.4987. - A 2 : 1 diastereomeric mixture was obtained . - ^{1}H-NMR ($CDCl_3$) : 7.6 (2 H, m), 7.3 (3 H, m), 6.20 (0.3 × 1 H, dd, *J* 16.4, 3.8), 6.16 (0.7 × 1 H, dd, *J* 14.5, 6.3), 4.64 (0.3 × 1 H, d of symm. m, J_{HF} 48.3), 4.57 (0.7 × 1 H, d of symm. m, J_{HF} 48.3), 2.11 (0.7 × 3 H, s), 2.10 (0.3 × 3 H, s), 1.7 (2 H, m), 1.4 (2 H, m), 1.3 (10 H, s-like m), 0.89 (3 H, t, *J* 7.0). - Analysis : calc. for $C_{18}H_{27}FO_2S$ (326.47) C 66.22, H 8.34; found C 66.35, H 8.19%.

2,2-Difluoro-1-(phenylthio)decyl acetate (3b) : 91%; n_D^{20} 1.4870. - ^{1}H-NMR ($CDCl_3$) : 7.6 (2 H, m), 7.4 (3 H, m), 6.23 (1 H, t, *J* 10.4), 2.12 (3 H, s), 2.03 (2 H, symm. m), 1.51 (2 H, symm. m), 1.3 (10 H, m), 0.89 (3 H, t, *J* 6.9). - Analysis : calc. for $C_{18}H_{26}F_2O_2S$ (344.46) C 62.76, H 7.61; found C 62.54, H 7.78%.

2,2-Difluoro-2-phenyl-1-(phenylthio)ethyl acetate (3c) : 90%; mp -67 to -65 °C; n_D^{20} 1.5430. - ^{1}H-NMR ($CDCl_3$): 7.6 (2 H, m), 7.4 (5 H, m), 7.2 (3 H, m), 6.40 (1 H, t, *J* 10.7), 2.05 (3 H, s). - Analysis : calc. for $C_{16}H_{14}F_2O_2S$ (308.35) C 62.32, H 4.58; found C 62.00, H 5.08%.

4. 2-Fluoro- and 2,2-Difluoroalkanals

2-Fluorodecanal (4a) : A precooled solution of 2-fluoro-1-(phenylthio)decyl acetate (3a; 3.3 g, 10 mmol) in toluene (50 mL) was added to diisobutylaluminum hydride (15 mmol) in toluene (12.5 mL) and kept 2 h at -75 °C. The mixture was concentrated and absorbed on silica gel (10 g). Elution from a column filled with fresh silica gel (20 g) with a 10 : 1 mixture of hexane and ethyl acetate afforded, after evaporation of the solvents, a colorless oil. Immediate distillation under reduced pressure gave **4a**; 1.6 g (92%); bp 92 - 95 °C/15 mmHg; n_D^{20} 1.4439. - ^{1}H-NMR ($CDCl_3$) : 9.78 (~ 1 H, d, *J* 6.5), 4.80 (0.1 H, d, *J* 47.8), 4.76 (~ 1 H, d of symm. m, J_{HF} 49.0), 1.8 (2 H, m), 1.5 (2 H, m), 1.3 (10 H, m, narrow), 0.89 (3 H, t, *J* 7.0). - The signal at 4.80 ppm may be caused by a small equilibrium concentration of the enol. - ^{19}F-NMR ($CDCl_3$) : - 135.8 (dtd, *J* 48, 24, 6). - IR : 1735 (s, ν[C=C]).

2,2-Difluorodecanal (4b) : 2,2-Difluoro-1-phenylthio-1-decanol (**5b**, see Section below; 3.0 g, 10 mmol) was absorbed on wet silica gel (40 g). With a 10 : 1 mixture of hexane and ethyl acetate the hydrate of the aldehyde was eluted (as evidenced by nmr spectroscopy : δ 5.05, symm. m). After evaporation of the solvents, the residue was taken up in toluene (20 mL) and heated in a Dean-Stark trap. Bulb-to-bulb distillation afforded pure **4b**; 1.7 g (85%); bp 71 - 74 °C/5 mmHg. - ^{1}H-NMR* ($CDCl_3$) : 8.89 (1 H, t, *J* ~ 1), 1.58 (2 H, symm. m), 1.2

(10 H, m), 1.0 (2 H, m, narrow), 0.90 (3 H, t, *J* 7.0). - ^{19}F-NMR ($CDCl_3$) : - 47.5 (t, *J* 12.3). - IR : 1760 (s, ν[C=O]).

2,2-Difluoro-2-phenylacetaldehyde (4c) : 2,2-Difluoro-2-phenyl-1-(phenylthio)ethanol (**5c**, see section below; 2.7 g, 10 mmol) was converted in the same way, as described in the preceding paragraph to the hydrate and to the aldehyde **4c**; 1.2 g (78%); bp 66 - 69 °C/5 mmHg. - ^{1}H-NMR* ($CDCl_3$) : 9.56 (1 H, t, *J* 3.2), 7.5 (5 H, m). - ^{19}F-NMR ($CDCl_3$) : - 48.0 (d, *J* 3.0).

5. 2,2-Difluoro-1-phenylthio-1-alkanols

2,2-Difluoro-1-phenylthio-1-decanol (5b) : A precooled solution of 2,2-difluoro-1-(phenylthio)decyl acetate (**3b**; 4.9 g, 15 mmol) in toluene (50 mL) was added to diisobutylaluminum hydride (20 mmol) in toluene (25 mL) at -75 °C. After 2 h, the organic layer was thoroughly washed with ice-cold 10% hydrochloric acid (2 x 20 mL) and saturated aqueous sodium hydrogen carbonate (2 x 15 mL). A solid residue was obtained; 4.2 g (93%); mp 39 - 41 °C (after recrystallization from hexane). - ^{1}H-NMR* ($CDCl_3$) : 7.5 (2 H, m), 7.3 (3 H, m), 5.05 (1 H, dd, *J* 12.0, 9.3), 2.53 (1 H, s, broad), 2.04 (2 H, symm. m), 1.5 (2 H, m), 1.3 (10 H, m, narrow), 0.88 (3 H, t, *J* 7.0). - ^{19}F-NMR ($CDCl_3$) : - 44.1 (td, *J* 17.5, 9.0), - 44.9 (td, *J* 16.7, 5.9). - IR (CH_2Cl_2) : 3560 (s, ν[O-H]). - Analysis: calc. for $C_{16}H_{24}F_2OS$ (302.43) C 63.54, H 8.00; found C 63.45, H 8.11%.

2,2-Difluoro-2-phenyl-1-(phenylthio)ethanol (5c) : In the same way as described for **3b**, 2,2-difluoro-2-phenyl-1-(phenylthio)ethyl acetate (**3c**; 4.6 g, 15 mmol) was converted to **5c** which was obtained as a colorless oil; 3.6 g (90%). - ^{1}H-NMR* ($CDCl_3$) : 7.5 (10 H, m), 5.28 (1 H, t, *J* 9.5), 2.3 (1 H, s, broad). - ^{19}F-NMR ($CDCl_3$) : - 41.1 (d, *J* 9.6), - 41.3 (d, *J* 9.2).

6. 2,2-Difluoro-1-alkanols

2,2-Difluoro-1-decanol (6b) : 2,2-Difluoro-1-(phenylthio)decyl acetate (**3b**; 3.4 g, 10 mmol) was added to a suspension of lithium aluminum hydride (0.46 g, 12 mmol) in diethyl ether (25 mL). After 1 h of stirring at 0 °C, the mixture was poured on ice. The organic solution was filtered, washed with brine (15 mL), dried and concentrated. Upon distillation under reduced pressure a colorless liquid was collected which solidified in the cold; 1.9 g (98%); mp 15 - 16 °C; bp 100 - 104 °C/5 mmHg. - ^{1}H-NMR ($CDCl_3$) : 3.72 (2 H, t, *J* 12.8), 2.49 (1 H, s), 1.90 (2 H, symm. m), 1.5 (2 H, m), 1.3 (10 H, m, narrow), 0.89 (3 H, t, *J* 6.8). - Analysis : calc. for $C_{10}H_{20}F_2O$ (194.27) C 61.83, H 10.38; found C 61.91, H 10.36%.

2,2-Difluoro-2-phenylethanol (6c) : In the same way as described for **3b**, 2,2-difluoro-2-phenyl-1-(phenylthio)-ethyl acetate (**3c**) was reduced to the corresponding alcohol **6c**; 86%. - ^{1}H-NMR ($CDCl_3$) : 7.5 (2 H, m), 7.4 (3 H, m), 3.89 (2 H, t, *J* 13.7), 2.91 (1 H, s).

REFERENCES

[1] F.G. Bordwell, W.T. Brannen, *J. Am. Chem. Soc.* **86** (1964), 4645.

[2] E.T. McBee, R.D. Battershell, H.P. Braendlin, *J. Am. Chem. Soc.* **84** (1962), 3157. - Extrapolation from 35 °C to 75 °C by assuming a 2.5 rate increase per 10 °C temperature raise.

[3] N. Mongelli, F. Animati, R. D'Alessio, L. Zuliani, C. Gandolfi, *Synthesis* **1988**, 310.

[4] H. Suga, T. Hamatani, Y. Guggisberg, M. Schlosser, *Tetrahedron* **45** (1989), preceding article.

[5] S.W. Schneller, *Int. J. Sulfur Chem.* **8** (1976), 579; *Chem. Abstr.* **86** (1977), 42'526g; S. Wolfe, P.M. Kazmaier, *Can. J. Chem.* **57** (1979), 2397; O. Itoh, T. Numata, T. Yoshimura, S. Oae, *Bull. Chem. Soc. Japan* **56** (1983), 266.

[6] *E.g.*, F.G. Bordwell, B.M. Pitt, *J. Am. Chem. Soc.* **77** (1955), 572; H.D. Becker, G.J. Mikol, G.E. Russel, *J. Am. Chem. Soc.* **85** (1963), 3410; S. Oae, T. Kitao, S. Kawamura, *Tetrahedron* **19** (1963), 1783; H. Krauch, W. Kunz, *Reaktionen der organischen Chemie*, Hüthig Verlag, Heidelberg, 1966, page 480.

[7] *E.g.*, E.T. McBee, M.J. Keogh, R.P. Levek, E.P. Wesseler, *J. Org. Chem.* **38** (1973), 632; R.B. Greenwald, D.H. Evans, *J. Org. Chem.* **41** (1976), 1470; W.A. Szarek, G.W. Hay, M.M. Perlmutter, *J. Chem. Soc., Chem. Commun.* **1982**, 1253; V. Dědek, I. Vesely, *Collect. Czech. Chem. Commun.* **50**(1985), 1948; T. Yamazaki, T. Yamamoto, T. Kitazume, *J. Org. Chem.* **54** (1989), 83.

[8] Mono- and difluorinated aldehydes can also be quite conveniently obtained by Swern oxidation of the corresponding alcohols (H. Suga, M. Schlosser, unpublished results, 1988).

[9] Reviews : M. Schlosser, *Tetrahedron* **34** (1978), 3; R.H. Abeles, in : *Enzyme-Activated Irreversible Inhibitors* (editors : N. Seiler, M.J. Jung, J. Koch-Weser), Elsevier/North-Holland Biomedical Press, Amsterdam, 1978; R. Filler, Y. Kobayashi (editors), *Biomedical Aspects of Fluorine Chemistry*, Kodansha Ltd., Tokyo, and Elsevier Biomedical Press, Amsterdam, 1982; C. Walsh, *Tetrahedron* **38** (1982), 871; J.T. Welch, *Tetrahedron* **43** (1987), 3123; J. Mann, *Chem. Soc. Rev.* **16** (1987), 381.

[10] H. Suga, T. Hamatani, M. Schlosser, *Tetrahedron* **45** (1989), first article out of this series of three.