Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5061–5064

TETRAHEDRON LETTERS

Fluorination of α,α-dichlorosulfides: access to *gem*-difluorothioethers as useful building blocks

Sonia Gouault, Cécile Guérin, Laurent Lemoucheux, Thierry Lequeux* and Jean-Claude Pommelet*

Laboratoire de Chimie Moléculaire et Thioorganique, Université de Caen-ENSICaen, UMR CNRS 6507, 6 Boulevard du Maréchal Juin 14050 Caen cedex, France

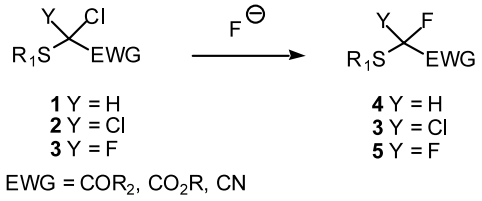
Received 9 April 2003; revised 5 May 2003; accepted 5 May 2003

Abstract—The synthesis of alkylsulfanyldifluoro-acetate and ketones by the Halex reaction is described. The remarkable reactivity of thiodifluoroacetate derivatives opened rapid access for the preparation of useful building blocks such as *gem*-difluoroketones and amides.

α-Fluoro alkyl- or aryl-sulfanyl groups are very versatile building blocks useful for the introduction of mono-, di- or trifluoro functionalized moieties into complex molecules. Since the synthesis of aryl fluoromethyl sulfoxides, prepared for the first time via a halogen exchange reaction,[1] several methods for the preparation of fluorinated sulfoxides,[2] or sulfones,[3] were reported. Attention is always paid to the synthesis of such compounds.[4] Alkylsulfanyl groups, under different oxidation states, can be removed to introduce a carbon–carbon double bond,[5] or to transfer a free radical,[6] or a carbanion.[7] For example, fluoroalkenes can be prepared from fluorosulfoxides by sulfenic acid elimination,[8a] and also by sulfur dioxide extrusion.[8b,c] Other important applications include the introduction of a difluoromethylene group from alkenes and fluorosulfides by trapping fluoroalkyl radical.[6] The α,α-difluoromethylketones are of great interest for the synthesis of peptide isosters,[9] and modified aminoacids.[10,11] In this field, we have been interested by the synthesis of fluorosulfides bearing an electron withdrawing group, as starting material for the preparation of *gem*-difluoroketones and amides. We have already described the preparation of α-monofluoro alkylsulfanyl esters or ketones.[12] Herein we report the extension of this methodology to prepare *gem*-difluoro alkylsulfanyl carbonyl compounds and their use in fluorinated building block synthesis.

The straightforward strategy for the preparation of difluoroalkylsulfanyl esters or amides involves displacement of a bromine atom with thiolates.[3,4] This method allows to obtain fluorosulfides in moderate to good yields,[13] but is limited by the cost of the commercially available bromofluoroacetate derivatives. Another strategy suggested in our previous studies, was based upon a halogen exchange reaction from the *gem*-α,α-dichloroalkylsulfanyl carbonyl compounds.[12] The replacement of a chlorine or bromine atom by a fluorine atom into organic molecules depends on their reactivity, i.e. upon the position of the halogen in the molecule and on the corresponding bond energy. The substitution of halogen atoms by fluorine atoms on non-activated positions of a saturated aliphatic chain is sometimes difficult, but relatively easy in the case of α-alkylsulfanyl esters or ketones **1** or **2** (Scheme 1).

Moreover, the ability to remove the halogen oriented the choice of the fluorinating reagent. We showed that the potassium fluoride-18-crown-6 ether mixture can convert α-chloro into α-fluorothioethers, but 3HF–Et_3N complex[14] (the HF-base reagent most easy to handle) was successfully employed to carry out the same transformation at lower temperatures.[12] The modulation of the reactivity of this reagent can be con-



Scheme 1.

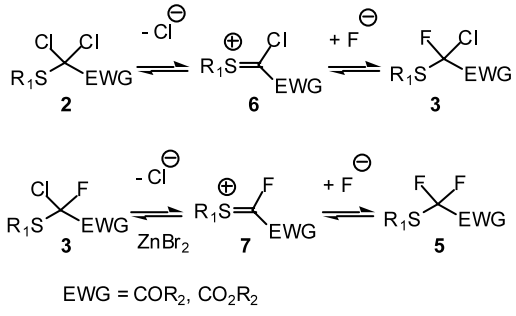
* Corresponding authors. Tel.: +33-231452853; fax: +33-231452877; e-mail: pommelet@ismra.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01134-1

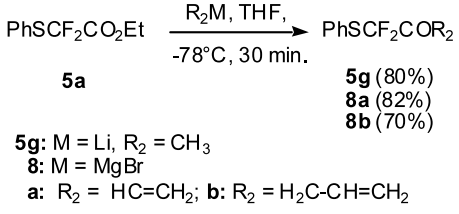
trolled, for example, by modifying the proportion of HF and NEt_3, by adding a co-reagent as IF_5, or by performing fluorination under electrochemical oxidative conditions.[15] Here are reported the preparations of *gem*-α,α-difluoro thioethers from the corresponding dichlorosulfides performed with 3HF–NEt_3 in the presence of mild Lewis acid.

α,α-Dichloroalklylsulfanyl esters or ketones **2** were obtained in two steps and in good overall yields: addition of the corresponding thiolate onto chloro- (or bromo-)acetates or ketones followed by the treatment of the resulting thioethers with two equivalents of sulfuryl chloride or *N*-chlorosuccinimide. Our initial attempts of fluorination carried out with Et_3N–3HF showed that the exchange of the first chlorine atom by the fluorine atom was rapidly performed. The *gem*-fluorochlorosulfides **3a–c** and **3e–f** were the only products obtained over 1 or 2 h in refluxing acetonitrile (Table 1). These were isolated in 65–75% yields. The phenylsulfanyl ester **2a** reacted more slowly, and the *gem*-chlorofluoro ester **3a** was isolated in 52% yield after 8 h in the presence of 4 equiv. of 3HF–NEt_3. When the same reactions were performed in the presence of one equivalent of Lewis acid ($ZnBr_2$) and four equivalents of 3HF–Et_3N, the second chlorine atom was displaced and the total conversions of dichlorothioethers **2a–c** and **2e–f** into difluorosulfides **5a–c** and **5e–f** were observed. Resulting difluorosulfides were isolated in fair to good yields (52–75%, Table 1). This methodology was also generalized to the synthesis of phenylsulfanyl ketones **5g–h**, which were isolated in 54–68% yields. The benzyl and phenylketone derivatives reacted more slowly, and the fluorination was complete after 14–48 h under refluxed solvent (entries 6–8). From the acetylated β-hydroxysulfides, **2d**, the corresponding *gem*-difluoroester **5d**[16] was isolated in 80% yield (Table 1: entry 4). As indicated in Table 1, the rate of the halogen-exchange strongly depends on the nature of the alkylsulfanyl moiety and also on the electron-withdrawing group. It decreased from ethyl- to arylsulfanyl substituents, as shown for the ketones **2e** and **2h**, and from esters to ketones (entries 1 and 8). These results suggest a significant electronic effect of these substituents on the stability of the sulfenium intermediate **6** or **7** (Scheme 2). In addition, in the second step leading to difluorinated sulfides **5** the formation of the sulfenium **7** appeared to be more difficult due to the presence of the first fluorine atom. The use of Lewis acid showed to be sufficient and necessary to displace the equilibrium in favor of **7**. Due to the ionic character of these intermediates, the reaction must be performed in rigorously anhydrous conditions, in order to avoid the formation of α,β-dicarbonyl sulfides as by-products. The sulfenium ions **6** or **7** were easily hydrolyzed on exposure to moisture.

Another strategy was also explored to prepare α,α-difluoroalkylsulfanyl ketones from the easily available ester **5a**. Recently, the synthesis of antifungal key intermediates was reported from difluorothioacetate and aryllithium reagents.[13] We investigated the synthesis of ketones by using alkyllithium or alkylmagnesium reagents. Treatment of the ethyl difluorophenylsulfanyl acetate **5a** by methyl lithium in THF at −78°C afforded the difluoroketone **5g** in 80% yield (Scheme 3). The addition of vinyl- or allylmagnesium bromide on the ester **5a** was attempted in the same conditions. In these



Scheme 2.



Scheme 3.

Table 1. Mono- and difluorination of dichlorosulfides **2** via Scheme 1

Entry	Dichlorosulfide **2**	R_1	EWG	Et_3N–3HF (equiv.), time (h)	Sulfide **3**, (%)[a,b]	$ZnBr_2$ (equiv.)	Time (h)	Sulfide **5**, %[a,b]
1	**2a**	Ph	CO_2Et	4, 8	**3a**, 52	1	5	**5a**,[13] 70
2	**2b**	Bz	CO_2Me	2, 2	**3b**, 70	1	4	**5b**, 52
3	**2c**	MeO_2CCH_2	CO_2Me	2, 2.5	**3c**, 75	1	5.5	**5c**, 75
4	**2d**	$AcO(CH_2)_2$	CO_2Me	–	–	1	2	**5d**, 80
5	**2e**	Et	COPh	2, 2	**3e**, 70	1	3	**5e**, 61
6	**2f**	Bz	COMe	2, 2	**3f**, 65	1	14	**5f**, 72
7	**2g**	Ph	COMe	–	–	1	14	**5g**, 68
8	**2h**	Ph	COPh	–	–	2	48	**5h**,[4] 54

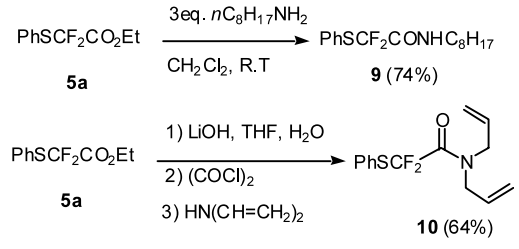
[a] Isolated yield.
[b] All new compounds gave satisfactory analytical data.[19]

cases, vinylic and allylic ketones **8a**,**b**, were isolated in 70 and 82% yields, respectively. At higher temperature or after a long reaction time (>2 h), tertiary alcohols were formed as by-products. By contrast with the Halex reaction, by this way ketone **5g** was easily prepared in good yield.

Due to the current interest for the synthesis of fluoroamides as building blocks for the preparation of lactams or peptide isosters, the chlorination and the halogen-exchange reactions were also investigated to prepare amide **9** or **10** (Scheme 4). However, this functional group was sensitive and a major degradation of products occurred during the chlorination and the fluorination stages. The difluoroester **5a** was used as starting material for the direct synthesis of amides. By addition of *n*-octylamine at room temperature to a solution of **5a**, the corresponding amide was obtained after 30 min of stirring. When a stoichiometric amount of amine was used the phenylsulfanyldifluoroacetamide **9** was isolated in 52% yield, and in the presence of excess of amine (3 equiv.) in 74% yield.

However, using a secondary amine such as morpholine, only a 10–15% of addition product was detected in the crude, and no addition product was observed from diallylamine. The contrasted reactivity between secondary and primary amines toward halogenoesters was previously reported. A competitive formation of amide and urea could be observed.[17] On the other hand, the synthesis of secondary amidosulfides was achieved in three steps from the difluoroester **5a** through the corresponding acyl chloride.[18] The diallylamide **10** was isolated in 64% overall yield (Scheme 4).

In summary, we reported a convenient preparation of α,α-difluoro alkylsufanyl or arylsulfanyl carbonyl compounds as useful building blocks for the synthesis of *gem*-difluoro ketones, esters and amides. The *gem*-difluoro ketones can be obtained by two different ways: by treatment of the corresponding *gem*-dichlorocarbonyl compounds with Et_3N–3HF, $ZnBr_2$ mixture as fluorinating reagent, or by addition of organolithium or Grignard reagents onto the ethyl α,α-difluorophenylsulfanyl acetate **5a** at low temperature. The second route afforded a range of saturated or unsaturated difluoroketones. The difluorosulfide **5a** can be used also as starting material for the synthesis of difluoroamides, by its direct addition to primary amine or by using the corresponding acyl chloride. The Halex reaction can be easily performed on a scale of several grams, permitting to handle large amounts of difluorinated material, especially in the case of the ester **5a**. The use of these fluorinated sulfides in the synthesis of lactams and aminoacid analogues is under investigation.



Scheme 4.

Acknowledgements

We are grateful to the 'Ministère de la Recherche' for it financial support and to C. Lebargy for his contribution.

References

1. More, K. M.; Wemple, J. *Synthesis* **1977**, 791–792.
2. Burton, D. J.; Yang, Z. Y.; Qui, W. *Chem. Rev*. **1996**, *96*, 1641–1715 and references cited therein.
3. Yang, Z. Y.; Burton, D. J. *Heteroatom Chem*. **1992**, *3*, 261–270 and references cited therein.
4. (a) Yagupolskii, L. M.; Matsnev, A. V.; Kondratenko, N. *J. Fluor. Chem*. **2002**, *119*, 59–62; (b) Billard, T.; Langlois, B.; Médebielle, M. *Tetrahedron Lett*. **2001**, *42*, 3463–3465; (c) Burkholder, C.; Dolbier, W. R.; Médebielle, M.; Ait-Mohand, S. *Tetrahedron Lett*. **2001**, *42*, 3459–3462; (d) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett*. **2000**, *41*, 4463–4466; (e) Motherwell, W. B.; Greaney, M. F.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2809–2815; (f) Konno, A.; Fuchigami, T. *J. Org. Chem*. **1997**, *62*, 8579–8581.
5. Pommelet, J. C.; Nyns, C.; Lahousse, F.; Merenyi, R.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 585–586.
6. (a) Motherwell, W. B.; Ross, B.; Tozer, M. J. *Synlett* **1989**, *1*, 68–70; (b) Herpin, T. F.; Motherwell, W. B.; Weibel, J. M. *J. Chem. Soc., Chem. Comm*. **1997**, 923–924; (c) Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. *Org. Lett*. **2001**, *3*, 185–188.
7. Krief, A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp. 85–192.
8. (a) Kim, K.; McCarthy, J. R. *Tetrahedron Lett*. **1996**, *37*, 3223–3226; (b) Chevrie, D.; Lequeux, T.; Pommelet, J. C. *Org. Lett*. **1999**, *1*, 1539–1541; (c) Chevrie, D.; Lequeux, T.; Pommelet, J. C. *Tetrahedron* **2002**, *58*, 4759–4767.
9. (a) Wolfe, M. S.; Citron, M.; Diehl, T. S.; Xia, W.; Donkor, I. O.; Selkoe, D. J. *J. Med. Chem*. **1998**, *41*, 6–9; (b) Schirlin, D.; Baltzer, S.; Altenburger, J.; Tarnus, C.; Remy, J. M. *Tetrahedron* **1996**, *52*, 305–318.
10. Konas, D. W.; Coward, J. K. *Org. Lett*. **1999**, *1*, 2105–2107.
11. Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E.; Meyer, E. F.; Trainor, D. A. *J. Am. Chem. Soc*. **1989**, *111*, 3368–3374.
12. (a) Jouen, C.; Lasne, M. C.; Pommelet, J. C. *Tetrahedron Lett*. **1996**, *37*, 2413–2416; (b) Jouen, C.; Pommelet, J. C. *Tetrahedron* **1997**, *53*, 12565–12574; (c) Jouen, C.; Lemaître, S.; Lequeux, T.; Pommelet, J. C. *Tetrahedron* **1998**, *54*, 10801–10810.
13. Eto, H.; Kaneko, Y.; Takeda, S.; Tokizawa, M.; Sato, S.; Yoshida, K.; Namiki, S.; Ogawa, M.; Maebashi, K.; Ishida, K.; Matsumoto, M.; Asaoka, T. *Chem. Pharm. Bull*. **2001**, *49*, 173–182.

14. McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.
15. (a) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett*. **1990**, *31*, 6527–6530; (b) Ayuba, S.; Yoneda, N.; Fukurhara, T.; Hara, S. *Bull. Chem. Soc. Jpn* **2002**, *75*, 1597–1603; (c) Yoneda, N.; Tsuyoshi, F. *Chem. Lett*. **2001**, 222–223; (d) Brigaud, T.; Laurent, E. *Tetrahedron Lett*. **1990**, *31*, 2287–2290; (e) Fuchigami, T.; Shimojo, M.; Akinori, K. *J. Org. Chem*. **1995**, *60*, 3459–3464.
16. Gouault, S.; Pommelet, J. C.; Lequeux, T. *Synlett* **2002**, 996–998.
17. Joullié, M. M. *J. Org. Chem*. **1955**, *77*, 6662–6663.
18. Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. G.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
19. **Typical procedure**: **Ethyl phenylsulfanyldifluoroacetate 5a**. Sulfuryl chloride (6.98 mL, 86 mmol) was added slowly to a cooled (0°C) solution of ethyl phenylsulfanylacetate (8.4 g, 42.8 mmol) in dichloromethane (100 mL). After 2 h of stirring at room temperature, the solvent was evaporated and the crude oil (10.4 g) was used in the next step without purification. ^{1}H NMR ($CDCl_3$) $\delta=1.24$ (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3), 4.23 (q, $^3J_{HH}=7.1$ Hz, 2H, CH_2), 7.38–7.68 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) $\delta=13.7$ (CH_3), 64.5 (CH_2), 88.0 (CHCl), 128.9, 129.0, 131.1, 137.2 (Ph), 163.8 (CO). Crude ethyl phenylsulfanyldichloroacetate (10.4 g, 39.2 mmol) was added at room temperature under nitrogen to a suspension of freshly dried zinc bromide (8.85 g, 40 mmol) in anhydrous acetonitrile (100 mL). Neat 3HF–NEt_3 complex (26 mL, 157 mmol) was then added to the yellow solution, and the mixture was heated to reflux under nitrogen over 5 h. The solution was cooled down to room temperature and poured into saturated aqueous solution of NH_4Cl (50 mL). The organic layer was extracted with dichloromethane (100 mL), and then washed with a saturated aqueous solution of $NaHCO_3$ and brine until neutral pH, and dried over $MgSO_4$. The resulting crude oil (12.5 g) obtained after concentration under vacuum was purified by distillation (125°C/3×10^{-2} mmHg), leading to ethyl phenylsulfanyldifluoroacetate **5a** (6.4 g, 27.6 mmol, 70%) as colorless oil. ^{1}H NMR ($CDCl_3$) $\delta=1.23$ (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3), 4.22 (q, $^3J_{HH}=7.1$ Hz, 2H, CH_2), 7.30–7.62 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) $\delta=13.7$ (CH_3), 63.6 (CH_2), 120.8 (t, $^1J_{CF}=287.2$ Hz, CF_2), 124.8, 129.2, 130.6, 136.7 (Ph), 161.6 (t, $^2J_{CF}=37.7$ Hz, CO); ^{19}F NMR ($CFCl_3$, $CDCl_3$) $\delta=-82,6$ (s, CF_2); MS (EI) m/z (%) 232 (100), 159 (82), 109 (15), 77 (19), 65 (10); IR (film) ν 1746 cm^{-1}; HMRS calcd for $C_{10}H_{10}F_2O_2S$ 232.0370, found 232.0352. ***N*-Octyl-2,2-difluoro-2-phenylsulfanyl acetamide 9**. Freshly distilled *n*-octylamine (0.63 mL, 3.87 mmol) was added dropwise at room temperature to a solution of ethyl phenylsulfanyldifluoroacetate **5a** (0.3 g, 1.29 mmol) in dichloromethane (5 mL). After 30 min of stirring the solution was washed with HCl (1N) and brine, then dried over $MgSO_4$. The crude product was recrystallized in pentane leading to amide **9** (0.3 g, 74%) as white solid (mp = 54–56°C). ^{1}H NMR ($CDCl_3$) $\delta=0.90$ (t, $^3J_{HH}=6.8$ Hz, 3H, CH_3), 1.10–1.40 (m, 12H, CH_2), 3.12 (dt, $^3J_{HH}=6.8$ Hz, 2H, NCH_2), 6.40 (s br, 1H, NH), 7.30–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) $\delta=14.8$ (s, CH_3), 23.4, 27.4, 29.7, 29.9, 32.5 (s, $(CH_2)_6$), 40.7 (s, CH_2N), 123.3 (t, $^1J_{CF}=289$ Hz, CF_2), 125.9, 130.0, 131.2, 137.4 (s, Ph), 162.4 (t, $^2J_{CF}=28$ Hz, CO); ^{19}F NMR ($CFCl_3$, $CDCl_3$) $\delta=-82.8$ (s, CF_2). MS (EI) m/z (%) 315 (5), 206 (29), 156 (100), 77 (15), 71 (37), 57 (30); Anal. calcd for $C_{16}H_{23}F_2NOS$: C, 60.92, H, 7.35, N, 4.44, S, 10.17, Found: C, 60.77, H, 7.45, N, 4.42, S, 10.13. **1,1-Difluoro-1-phenylsulfanyl-4-pentenone 8b**. A solution of vinylmagnesium bromide (4.5 mL, 1 M in Et_2O, 4.5 mmol) was added dropwise over 5 min to a solution of ethyl phenylsulfanylacetate **5a** (1 g, 4.31 mmol) in anhydrous THF (10 mL) at −78°C. The mixture was stirred for 30 min and then hydrolyzed by addition of an aqueous 1N solution of HCl (3 mL). The mixture was warmed up to room temperature and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuums. The crude oil was purified by bulb-to-bulb distillation (80–85°C/7×10^{-2} mmHg) to afford ketone **8b** (0.68 g, 70%) as a yellow oil. ^{1}H NMR ($CDCl_3$) $\delta=3.33$ (d, $^3J_{HH}=6.8$ Hz, 2H, CH_2), 5.05 (dd, $^3J_{HH}=17.2$ Hz, $^2J_{HH}=1.5$ Hz, 1H, CH), 5.14 (dd, $^3J_{HH}=10.2$ Hz, $^2J_{HH}=1.5$ Hz, 1H, CH), 5.85 (ddd, $^3J_{HH}=17.2$ Hz, $^3J_{HH}=10.2$ Hz, $^3J_{HH}=6.8$ Hz, 1H, CH), 7.23–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) $\delta=40.6$ (s, CH_2), 120.5, 129.8 (Csp^2), 124.8 (t, $^3J_{CF}=2.8$ Hz, Ph), 122.9 (t, $^1J_{CF}=291.1$ Hz, CF_2), 128.4, 131.0, 137.0 (s, Ph), 194.2 (t, $^2J_{CF}=29$ Hz, CO); ^{19}F NMR ($CFCl_3$, $CDCl_3$) $\delta=-85.8$ (s, CF_2); MS (EI) m/z (%) 228 (15), 159 (49), 109 (28), 77(43), 69 (100), 65 (24), 51 (18), 41 (68); HMRS calcd for $C_{11}H_{10}F_2OS$ 228.0420, found 228.0395.