Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8759-8762, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02043-6

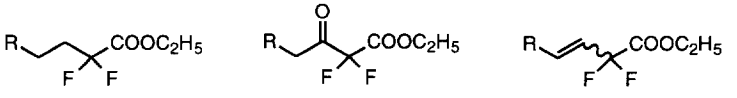
A Novel Synthetic Approach to the Preparation of Various α,α-Difluoroesters

Sylvia Bildstein, Jean-Bernard Ducep* and Detlef Jacobi

Marion Merrell Research Institute, Strasbourg Research Center, 16 rue d'Ankara, 67080 Strasbourg, France

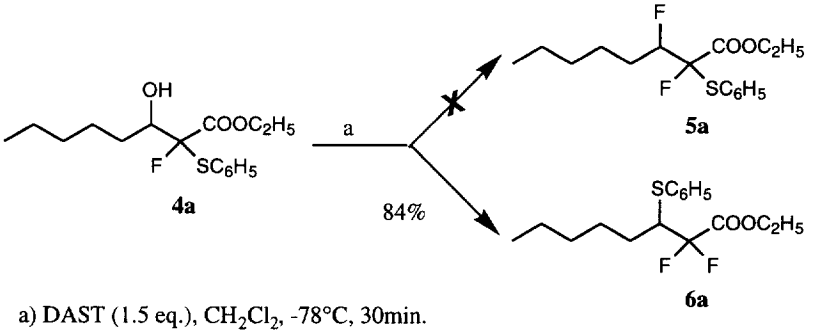
Abstract : Treatment of readily available α-fluoro-β-hydroxy-α-phenylthioesters **4** with DAST afforded α,α-difluoro-β-phenylthioesters **6** which are of interest to synthesize gem-difluorinated derivatives. Copyright © 1996 Elsevier Science Ltd

Gem-difluorinated derivatives have been widely used as enzyme inhibitors or to modify properties of biologically active products[1]. In this publication, we wish to report a synthetic method giving access to α,α-difluoroesters **1**, α,α-difluoro-β-ketoesters **2** or α,α-difluoro-β,γ-unsaturated esters **3**.



1 **2** **3**

These findings originated from an unexpected reaction of ethyl 2-fluoro-3-hydroxy-2-phenylthio hexanoate (**4a**) with diethylaminosulfur trifluoride (DAST). **4a** treated with 1.5 equivalent of DAST in methylene chloride at -78°C during 30 minutes did not give the expected 2,3-difluoro derivative **5a**[2], but yielded ethyl 2,2-difluoro-3-phenylthiohexanoate (**6a**)[12] as the sole product (84 %) (scheme 1).

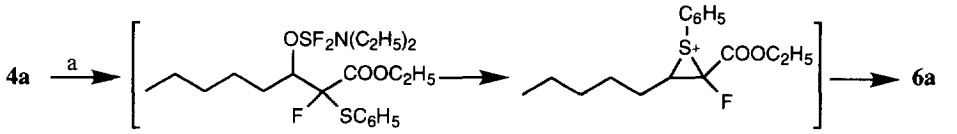


4a **5a** **6a**

a) DAST (1.5 eq.), CH_2Cl_2, -78°C, 30min.

Scheme 1

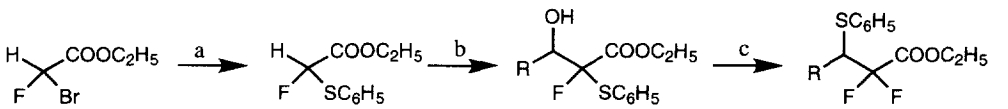
This surprising result can be explained by the participation of the phenylthio group during **4a** reaction with DAST, leading to the episulfonium **8a**[3]. The fluoride ion added preferentially to the carbon α to the ester, yielding **6a**[12] (scheme 2).



a) DAST (1.5 eq.), CH_2Cl_2, -78°C, 30min.

Scheme 2

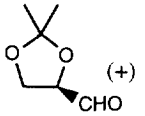
This rearrangement was found to be general for α-fluoro-β-hydroxy-α-phenylthio esters **4** with the exception of ethyl 2-fluoro-3-hydroxy-2-phenylthiohydrocinnamate (**4c**) which gave exclusively the non-rearranged product **5c**[12]. The synthetic sequence for the preparation of **6** is simple and gives good yields from commercially available compounds : ethyl bromofluoroacetate (**9**) and aldehydes **10** (scheme 3-Table 1).



a) C_2H_5ONa, C_2H_5OH, C_6H_5SH; b) LDA (1eq.), THF, -78°C; then RCHO, THF;
c) DAST (1.5eq.), CH_2Cl_2.

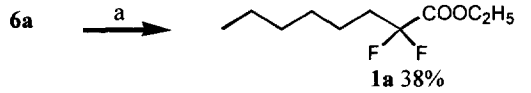
Scheme 3

Table 1

Entry	Aldehyde **10**	Alcohol **4**[c] (yield %)	**6** (conditions and yield %)
a	n-$C_5H_{11}CHO$	86	-78°C, 30 min, (84)
b	CH_3CHO	52	-78°C, 30 min, (94)
c	C_6H_5CHO	71	-78°C, 30 min, (0)[a]
d	$C_6H_5CH_2CHO$	18[b]	-78°C, 60 min, (50)
e	c-$C_6H_{11}CHO$	46	-78°C, 30 min, (81)
f		92	0°C, 180 min, (80)

a) Only ethyl 2,3-difluoro-3-phenyl-2-phenylthiopropanoate (**5c**)[12] was isolated (86%). b) The low yield is due to enolization of the aldehyde **10d** which competed with addition on carbonyl. c) Mixture of diastereomers.

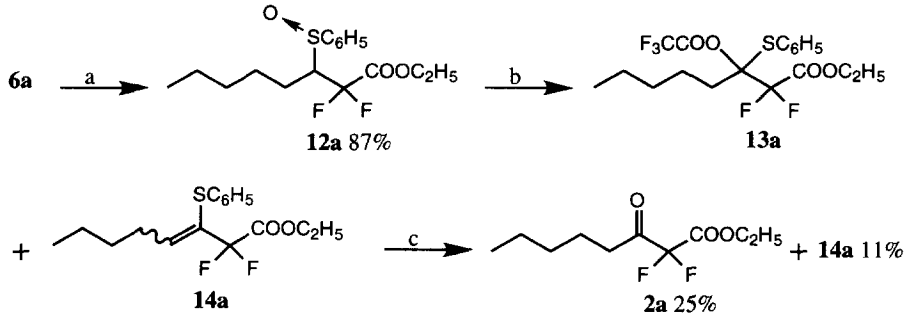
6a desulfurization was carried out using tri-*n*-butyltinhydride in refluxing toluene with a catalytic amount of AIBN[4] to yield **1a**[12] (Scheme 4). Such derivatives are usually obtained by DAST fluorination of α-ketoester or copperdifluoroacetate alkylation[6].



a) n-Bu_3SnH (1.3 eq.), AIBN (cat.), toluene, reflux 24h.

Scheme 4

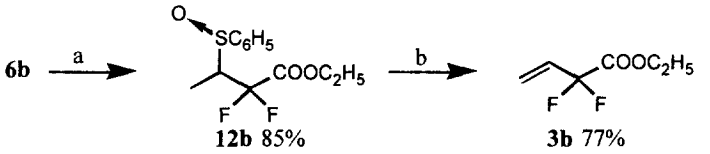
Oxidation of sulfide **6a** with meta-chloroperbenzoic acid[7] gave the sulfoxide **12a**. Pummerer rearrangement on **12a** using trifluoroacetic anhydride with collidine[8] gave the hemithiotrifluoroacetal **13a** along with vinylthioether **14a**. Treatment of the mixture without isolation by mercuric chloride afforded, after purification, ketoester **2a**[12] (25%) and sulfide **14a** (11%) (Scheme 5). Compounds of type **2** are obtained by Reformatsky reaction of ethyl bromodifluoroacetate with a suitable aldehyde, followed by oxidation[9] of the obtained alcohol. Thus, the above method in some cases could be a useful alternative to the Reformatsky-oxidation sequence.



a) m-CPBA (1eq.), CH_2Cl_2; b) $(CF_3CO)_2O$ (2eq.), 2,4,6-collidine (2eq.), 0°C, 12h;
c) $HgCl_2$ (1.4eq.), CH_3CN, 0°C, 3h.

Scheme 5

Sulfoxides of type **12** can give access to α,α-difluoro-α,β-unsaturated esters **3**. Thus, pyrolysis of **12b** in a short path distillation apparatus yielded, after elimination of sulfenic acid[10], **3b**[12] (77%) (Scheme 6). This method is an alternative to the available method using the reaction between ethyl copperdifluoroacetate and a vinylic iodide[6] which requires the use of ethyl difluoroiodoacetate, not readily available[11].



a) m-CPBA (1eq.), CH_2Cl_2; b) Δ 120°C, neat, Kugelrohr distillation.

Scheme 6

REFERENCES AND NOTES

1. Filler, R. *J .Fluorine Chemistry* **1986**, *33*, 361-374; Welch, J.T. *Tetrahedron* **1987**, *43*, 3123-3194; Welch, J.T.; Eswarakrishman, S. *Fluorine in Bioorganic Chemistry*, John Wiley ; New York, 1991.

2. Hudlicky, M. *Organic Reactions* **1988**, *35*, 513-637.

3. Kil'disheva, O.V.; Lin'kova, M.G.; Rasteikiene, L.; Zabelaite, V.; Pociute, N.; Knunyants, I.L. *Dokl Akad. Nauk. SSSR* **1972**, *203*, 1072-1074 ; Brownbridge, P. ; Warren, S. *J.C.S. Perkin I* **1977**, 1131-1141.

4. Gutierrez, C.G. ; Summerhays, L.R. *J. Org. Chem.* **1984**, *49*, 5202-5213.

5. Erni, B.; Khorana, H.G. *J. Am. Chem. Soc.* **1980**, *102*, 3888-3896 ; Gerskenberger, M.C., Haas, A. *Angew Chem. Int. Ed. Engl.* **1981**, *20*, 647-667.

6. Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehava, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103-6106 ; Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Chem. Lett.* **1989**, 389-392.

7. Oae, S. *Organic Sulfur Chemistry : Structure and Mechanism*; Doi, J.T. Ed.; CRC Press Inc.; Boca Raton, **1991**; pp 253-254.

8. Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881; Arnone, A.; Bravo, P.; Frigerio, M.; Salami, G Viani, F. *Tetrahedron* **1994**, *50*, 13485-13492.

9. Peet, N.P.; Burkhart, M.R.; Angelastro, M.R.; Giroux, E.L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394-407.

10. Grieco, P.A.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1181-1183; Reutrakul, V.; Rukachaisirikul, V. *Tetrahedron Lett.*, **1983**, *24*, 725-728.

11. Kumai, S; Samejima, S.; Munekata, S.; Yamabe, M. *Asahi Garasu Kenkyu Hokoku* **1983**, *33*, 127-133; *Syntheses of Fluoroorganic compounds* ; Knunyants, I.L.; Yakobson G.G. Eds.; Springer-Verlag Berlin; **1985**; pp 63-64.

12. All new compounds gave analytical and spectroscopic data in agreement with the assigned structure; **1a** ^{19}F NMR δ (282 MHz, $CDCl_3$, C_6F_6) 55.78 (2F, t, J_{HF}=15Hz); ^{1}H NMR δ (300 MHz, $CDCl_3$, TMS) 0.89 (3H, t, J_{HH}=7Hz, O-C-CH_3), 1.30-1.55 (8H, m, $H_{4,5,6,7}$), 2.00-2.10 (2H, m, H_3), 4.32 (2H, q, J_{HH}=7Hz, O-CH_2-C); MNH_4^+=226. **2a** ^{19}F NMR δ (282 MHz, $CDCl_6$, C_6F_6) 47.88 (2F, s); ^{1}H NMR δ (300 MHz, $CDCl_3$, TMS) 0.88 (3H, t, J_{HH}=7Hz, H_8), 1.25-1.70 (9H, m, $H_{5,6,7}$,O-C-CH_3), 2.71 (2H, t, J_{HH}=7Hz, H_4), 4.34 (2H, q, J_{HH}=7Hz, O-CH_2-C); MNH_4^+ =240; IR ν(C=O)=1750, 1781 cm^{-1}. **3b** ^{19}F NMR δ (282 MHz, $CDCl_3$, C_6F_6) 55.94 (2F, d, J_{HF}=10Hz); ^{1}H NMR δ (300 MHz, $CDCl_3$, TMS) 1.35 (3H, t , J_{HH}=7Hz), 433 (2H, q, J_{HH}=7Hz, O-CH_2-C), 5.55-6.20 (3H, m, $H_{3,4}$); MNH_4^+=168. **5c** ^{19}F NMR δ (282 MHz, $CDCl_3$, C_6F_6)-11.7 (1F, dd, J_{FF}=19Hz, J_{HF}=43Hz, F_3), 8.85 (1F, t , J_{HF}=J_{FF}=19Hz, F_2); ^{1}H NMR δ (300 MHz, $CDCl_3$, TMS) 1.02 (3H, t, J_{HH}=7Hz, O-C-CH_3), 4.00 (2H, q, J_{HH}=7Hz, O-CH_2-C), 6.05 (1H, dd, J_{HF}=19Hz, J_{HF}=43Hz, H_3), 7.20-7.65 (10H, m, H aromatic); MNH_4^+=340. **6a** ^{19}F NMR δ (282 MHz, $CDCl_3$, C_6F_6), 47.64 (1F, dd, J_{FF}=255Hz, J_{HF}=20Hz), 59.84 (1F, dd; J_{FF}=255Hz, J_{HF}=10Hz); ^{1}H NMR δ (300 MHz, $CDCl_3$, TMS) 0.90 (3H, J_{HH}=7Hz, H_8), 1.24 (3H, t, J_{HH}=7Hz, O-C-CH_3), 125-140 (4H, m, $H_{6,7}$), 1.45-1.60 (2H, m, $H_{4a,5a}$), 1.75-1.95 (2H, m, $H_{4b,5b}$), 3.45 (1H, ddt, J_{HF}=20Hz, J_{HF}=10Hz, J_{HH}=10Hz, J_{HH}=3Hz, H_3), 4.05-4.30 (2H, 2m, O-CH_2-C); MNH_4^+=334.

(*Received in France* 9 *September* 1996; *accepted* 16 *October* 1996)