Tetrahedron Letters, Vol. 33, No. 24, pp. 3491-3494, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

α,α-Difluoroalkanecarboxylic Acids: A General Synthesis via Alkyl Radical Addition to 1,1-Dichloro-2,2-difluoroethylene

Takashi Okano, Nobuyuki Takakura, Yuko Nakano and Shoji Eguchi*

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-01, Japan

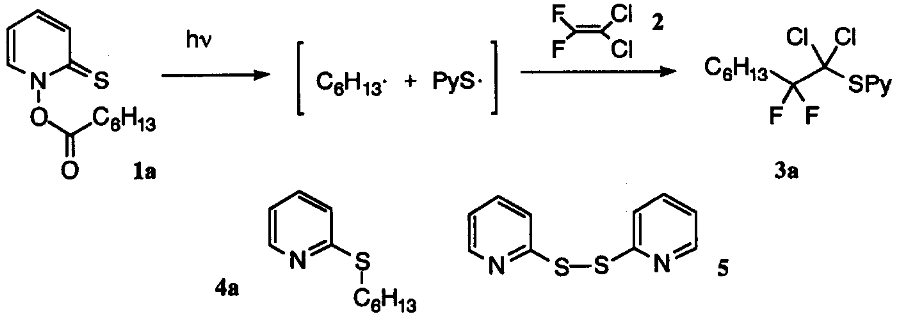
Key Words: fluorinated acid; difluoromethylene; Barton ester; radical addition; fluoroolefin

Abstract: Photodecomposition of alkanoic acid esters of N-hydroxy-2-thiopyridone with 1,1-dichloro-2,2-difuoroethylene gives alkyl-radical-trapped products, which give α, α-difluoroalkanoic acids and their methyl esters on hydrolytic or methanolytic treatment with silver nitrate.

Difluoromethylene-containing compounds are receiving considerable attention because of their potential biological activities.[1] Although α,α-difluoroalkanoic acids are expected to be good building blocks for the construction of such difluoromethylene subunits, there seem to be no simple and general methods to obtain the difluoro acids. We report here a general procedure to access such difluoroalkanoic acids.[2]

Ishikawa *et al.*[3] reported the synthesis of α-fluoroalkanoic acids via alkyl metal addition-elimination reaction on difluoroketene dithioacetal and subsequent hydrolysis. To avoid elimination of fluoride anion, alkyl radicals could be employed as alkylating species. Thiohydroxamic-alkanoic mixed anhydrides (Barton's esters) (**1**)[4] are suitable precursors for the generation of alkyl radicals. Since the difluoroketene dithioacetals had shown no reactivity to radical addition, we used 1,1-dichloro-2,2-difluoroethylene (**2**) as an alternative radical-trapping olefin. Olefin **2** has been successfully used for trapping of hydroxyalkyl radicals by Muramatsu,[5] and the addition of the radicals occurs regioselectively at the CF_2 side, *i.e.*, the formation of the more stable $RCF_2CCl_2\bullet$ radical as intermediates.

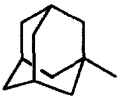
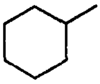
The Barton ester of heptanoic acid **1a**,[6] which generates *n*-hexyl radical, was irradiated with a large excess (over 10 molar) of **2** in a small amount of acetonitrile with a 500W-tungsten lamp at room temperature.[7] Chromatographic separation of the reaction mixture afforded adduct **3a** in 77% yield. The existence of $^{3}J_{^{1}\mathrm{H}-^{19}\mathrm{F}}$ (t,



1a **3a** **4a** **5**

Scheme I

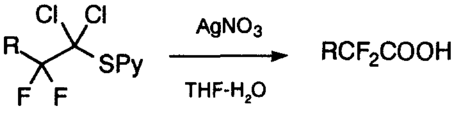
Table I

entry	1	R-	Yields (%)		
			RCF_2CCl_2SPy (**3**)	PySR (**4**)	RCF_2COOH (**6**)
1	**1a**	n-C_6H_{13}-	77	11	89
2	**1b**		62	7	80
3	**1c**		62	18	84
4	**1d**	$(CH_3)_3C$-	52	9	53
5	**1e**	$C_6H_5CH_2CH_2$-	40	36	86
6	**1f**	$C_6H_5CH_2$-	44	28	91
7	**1g**	C_6H_5-	0[a)]	0	—

[a)] Benzoic anhydride was the major product.

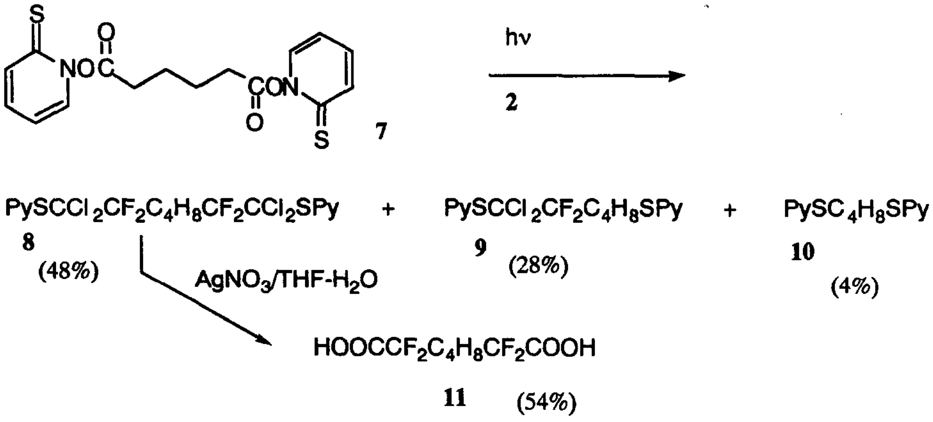
19Hz)[8] in the ^{19}F and ^1H NMR spectra reveals the regioselective formation of the adduct **3a**. Identified side-products were decarboxylative rearrangement product **4a** (11 %) and disulfide **5** (11 %). (Sheme 1)

Hydrolysis of the addition product **3a** was readily performed by refluxing with a 4-molar amount of silver nitrate in THF-H_2O. Almost pure difluorocarboxylic acid **6a** was obtained in 89% yield by simple extraction of the reaction mixture with an aqueous hydrogen carbonate solution followed by acidification with sulfuric acid. No thiol ester was found in the organic layer.



3a R = C_6H_{13} **6a**

This transformation from the Barton esters **1** to the difluoroalkanecarboxylic acids **6** is quite general for alkanecarboxylic anhydrides. In Table I,[8] the yields of the difluoro acids from some Barton esters are summarized. Primary (entries 1 and 5), secondary (entry 3), tertiary (entries 2 and 4), and also benzyl (entry 6) radicals gave dichlorodifluorothioethers **3**, which were convertible into the corresponding difluoroalkanecarboxylic acids **6**. However, phenyl derivative **1g** gave no adduct. In this case, a mixture of benzoic anhydride and benzoic acid was obtained after chromatography. This unreactivity of **1g** is explained by the fact pointed out by Barton *et al.*[9] that the decarboxylation of benzoyloxy radical is slow and the major reaction of the phenyl derivative is an



Scheme II

ionic reaction affording benzoic anhydride.

The addition of an alkyl radical to the polyhaloethylene **2** is competitive with the decarboxylative rearrangement to thiopyridyl derivatives **4** (product ratio (addition / rearrangement) = 1/1 - 7/1). Thus, in the case of bifunctional Barton ester of adipic acid **7** with a 10-equivalent amount of **2**, a nearly statistical mixture of the radical products **8**, **9**, and **10** was obtained (addition / rearrangement = 7/2). The product distribution suggests an independent two-step reaction and no intramolecular addition of the first generated alkyl radical to the thiocarbonyl group. Although this statistical effect reduces the yield of the 1:2 addition product, 2,2,7,7-tetrafluorooctanedioic acid **11** was obtained after hydrolysis of the 1:2 adduct **8**. (Scheme II)

In order to obtain the difluoro-esters directly, methanolysis of the radical adducts **3** was also attempted. The reaction of **3a-c** with a 4-molar amount of silver nitrate in refluxing methanol gave the corresponding methyl ester **12a** (47%), **12b** (77%), and **12c** (74%), respectively.

$$\mathbf{3} \xrightarrow[CH_3OH]{AgNO_3} \underset{\mathbf{12}}{RCF_2COOCH_3}$$

a R = C_6H_{13}
b R = 1-Adamantyl
c R = C_6H_{11}

As described, photodecarboxylative decomposition of Barton esters in the presence of 1,1-dichloro-2,2-difluoroethylene is a useful route to access difluoroalkanecarboxylic acids and esters which are difficult to obtain easily by other methods. Application of this method to other functionalized carboxylic acids is now under way.

Acknowledgements: We thank Professor Derek H. R. Barton for helpful discussions. Finantial support by the Naito Research Grant is acknowledged.

REFERENCES AND NOTES

1. (a) Welch, J. T. *Tetrahdron* **1987**, *43*, 3123. (b) *Biomedical Aspects of Fluorine Chemistry*, Filler, R.; Kobayashi, Y., Ed.; Kodansha Ltd.: Tokyo, 1982. (c) For recent examples of synthesis of biologically active difluoromethylene compounds: Casara, P. J.; Kenny, M. T.; Jund, K. C. *Tetrahedron Lett.*, **1991**, *32*, 3823: Sham, H. L.; Wideburg, N. E.; Spanton, S. G.; Kohlbrenner, W. E.; Betebenner, D. A.; Kempf, D. J.; Norbeck, D. W.; Erickson, J. W. *J. Chem. Soc., Chem. Commun.* **1991**, 110: Bradbury, R. H.; Rivett, J. E. *J. Med. Chem.* **1991**, *34* 151: Sham, H. L.; Rempel, C. A.; Stein, H.; Cohen, J. *J. Chem. Soc., Chem. Commun.* **1990**, 904: Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Terashima, S. *Tetrahedron Lett.* **1989**, *30*, 4259: Dreyer, G.; Metcalf, B. W. *Tetrahedron Lett.* **1988**, *29*, 6885.
2. For the preparation of difluoromethylene carbonyl compounds: Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125 and references cited therein.
3. Tanaka, K.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1979**, 175
4. (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 993. (b) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (d) Boivin, J.; Crepon, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 199. (e) Recently, Barton *et al.* reported the one-carbon extension reaction of carboxylic acids using Barton esters: Barton, D. H. R.; Chern, C.-Y.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1991**, *32*, 3309.
5. Muramatsu, H. *J. Org. Chem.* **1962**, *27*, 2325.
6. Barton esters **1a-g** were prepared from corresponding carboxylic acids and *N*-hydroxy-2-thiopyridone with *N,N*-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 in good yields.
7. At this temperature, the reaction mixture refluxes because of the low boiling point of **2** (b.p. 19°C). A reflux condenser in which coolant (aqueous ethanol, -30°C) circulates is used to avoid loss of **2**. Irradiation time is dependent on the substrate (4 - 7 hr).
8. ^{19}F-NMR spectra: Chemical shifts are reported in ppm relative to $CFCl_3$ as an internal standard (δ) in $CDCl_3$. **3a**: δ -104.12 (t, J = 19 Hz). **3b**: δ -104.21 (s). **3c**: δ -103.06 (d, J = 15 Hz). **3d**: δ -100.60 (s). **3e**: δ -104.12 (t, J = 17 Hz). **3f**: δ -102.24 (t, J = 19 Hz). **6a**: δ -106.90 (t, J = 16 Hz). **6b**: δ -120.47 (s). **6c**: δ -114.34 (d, J = 15 Hz). **6d**: δ -116.19 (s). **6e**: δ -107.43 (t, J = 16 Hz). **3f**: δ -105.76 (t, J = 17 Hz). **8**: δ -103.91 (t, J = 19 Hz). **9**: δ -103.97 (t, J = 19 Hz). **11**: δ -104.68 (in DMSO-d_6, t, J = 16 Hz). **12a**: δ -106.23 (t, J = 16 Hz). **12b**: δ -119.94 (s). **12c**: δ -113.93 (t, J = 15 Hz).
9. Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 4321. Barton, D. H. R.; Blundell, P.; Jaszberenyi, J. Cs. *J. Am. Chem. Soc.* **1991**, *113*, 6937.

(Received in Japan 29 January 1992)