Journal of Fluorine Chemistry 129 (2008) 986–990

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

A convenient AIBN-initiated radical addition of ethyl iododifluoroacetate to alkenes

Leo Leung, Bruno Linclau *

School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK

ARTICLE INFO

Article history:
Received 5 February 2008
Received in revised form 3 March 2008
Accepted 5 March 2008
Available online 13 March 2008

Dedicated to Prof. Dennis Curran on the occasion of receiving the 2008 ACS Award for Creative Work in Fluorine Chemistry.

Keywords:
Addition reaction
Radical addition
Ethyl iododifluoroacetate
Fluorinated building block
2,2-Difluoroester
Iodide reduction

ABSTRACT

The AIBN-initiated addition of ethyl 4-iodo-2,2-difluoroacetate to a variety of alkene substrates is described. The addition generally led to the corresponding addition products in good to excellent yields and various functional groups could be tolerated under the reaction conditions.

1. Introduction

The synthesis of fluorinated compounds is of importance across a number of areas, notably in pharmaceutical, agrochemical, and materials chemistry [1]. An important subset of fluorinated compounds contains a difluoromethylene (CF_2) group [2]. This group can be obtained by direct fluorination of ketones [3], or by a building block approach using appropriately fluorinated synthons [4]. For the syntheses of α,α-difluoroesters **3** (Scheme 1), (m)ethyl bromo and iodo difluoroacetate **1a**,**b** are useful building blocks, with the desired products accessible via a Reformatsky or aldol-type reaction or via a radical-mediated addition to alkenes.

A Reformatsky process is typically performed using **1** [2,5], and leads to adducts **2c**, of which the alcohol group subsequently needs removing to obtain **3**. This is typically achieved by a 2-step Barton-McCombie reduction process [6] via a thiocarbamate [7] or a thiocarbonate [8] derivative. Alternatively, a radical-mediated addition reaction using **1a**,**b** leads to adducts **2a** or **2b**, with subsequent reduction of the halide required to obtain **3**. A range of initiators have been reported, such as copper [9], sodium dithionite [10], and triethylborane [11]. In the majority of cases, **1b** is used as reagent. Subsequent reduction of **2b** to **3** is reported using $NiCl_2{\cdot}6H_2O$ [9c]. In addition, Burton has also reported an addition process of **1b** to alkenes leading directly to products **3** using $NiCl_2{\cdot}6H_2O$/Zn [12], and Taguchi has reported the direct formation of the reduced product **3** when the electron deficient acrylamide was used, with Sn as reagent [9b].

In our hands, addition of **1b** to alkenes using $NiCl_2{\cdot}6H_2O$/Zn appeared to be a rather capricious process, presumably due to the quality of the Zn metal used and/or inadequate Zn-activation. We wish to report a convenient, high-yielding alternative in that radical-mediated addition of **1b** to alkenes was found to proceed by simply using AIBN as initiator. Subsequent iodide reduction to afford difluoroalkane **3** was achieved in high yields using $NiCl_2{\cdot}6H_2O$/Zn or Et_3B/Bu_3SnH.

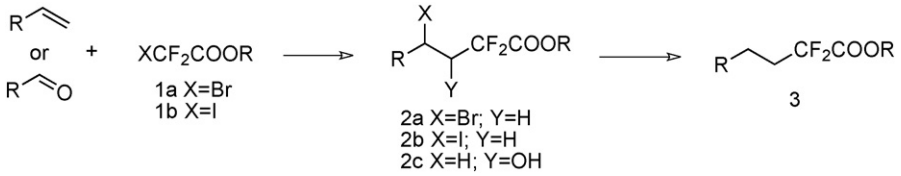
2. Results and discussion

2.1. AIBN-initiated addition of ethyl 4-iodo-2,2-difluoroacetate to alkenes

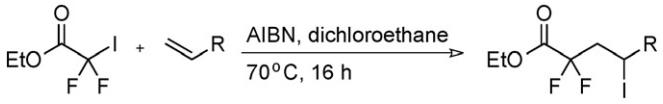
AIBN is a commonly employed radical initiator in organic synthesis. Several examples of AIBN-initiated addition of perfluoroalkyliodides to alkenes have been reported in the literature,

* Corresponding author. Tel.: +44 23 8059 3816; fax: +44 23 8059 6805.
E-mail address: bruno.linclau@soton.ac.uk (B. Linclau).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.03.002



Scheme 1.



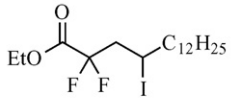
Scheme 2.

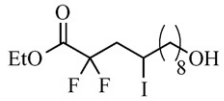
the earliest of which was reported in the 1960s [13]. To the best of our knowledge, this reagent has not yet been applied in radical additions involving iododifluoroacetates such as **1b**, though an AIBN-initiated allylation involving allyltin has been described starting from a 2-bromo-2,2-difluoroacetamide derivative [14].

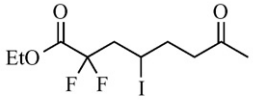
We were thus pleased to find that when difluoroacetate **1b** was reacted with a range of alkene substrates **4**–**10** with AIBN, the addition products **11**–**17** were generally formed in good to excellent yields (Scheme 2 and Table 1). Unfortunately, when ethyl bromodifluoroacetate was submitted under these reaction conditions no reaction was observed.

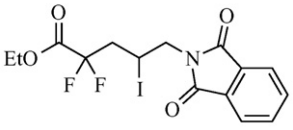
In most cases, a slight excess of difluoroacetate **1b** was required in order to achieve optimum results (Entries 2–8). When 1.5 equivalents of tetradecene **4** and 1.0 equivalent of iododifluoroaceate **1b** were treated with AIBN (10%), a modest 54% yield of product **11** was obtained (Entry 1). On the other hand, using a small

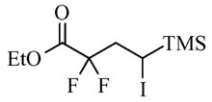
Table 1
AIBN-initiated addition of difluoroacetate **1b** to alkene substrates

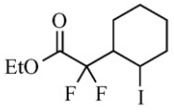


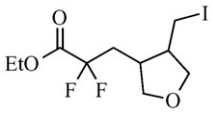












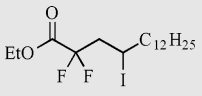
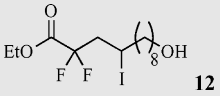
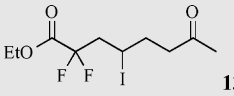
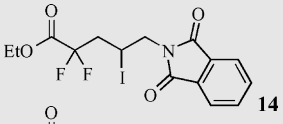
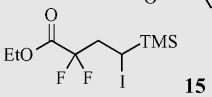
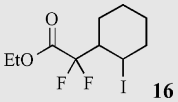
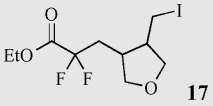
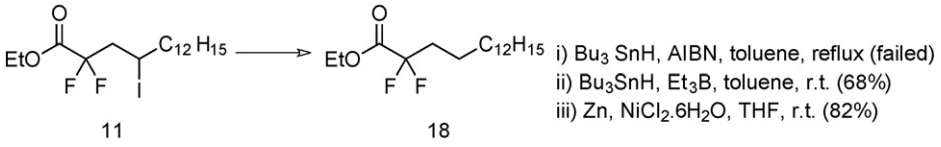
Entry	Alkene	Equiv	AIBN (mol%)	**1b** (equiv)	Product	Yield[a] (%)
1	Tetradecene **4**	1.5	10%	1.0	 **11**	54
2	**4**	1.0	10%	1.5	**11**	77

Table 1 (*Continued*)

Entry	Alkene	Equiv	AIBN (mol%)	**1b** (equiv)	Product	Yield[a] (%)
3	**4**	1.0	20%	1.5	**11**	83
4	**4**	1.0	20%	1.3	**11**	88
5	9-Decen-1-ol **5**	1.0	20%	1.3	 **12**	69
6	Hex-5-en-2-one **6**	1.0	20%	1.3	 **13**	46
7[b]	**6**	1.0	30%	1.3	**13**	62
8	*N*-Allyl phthalimide **7**	1.0	20%	1.3	 **14**	37
9	Trimethyl(vinyl)silane **8**	1.0	10%	1.5	 **15**	66
10	**8**	3.0	10%	1.0	**15**	86
11	Cyclohexene **9**	1.0	10%	1.5	 **16**	33, 1: 2.5 (*cis*:*trans*)
12	**9**	3.0	10%	1.0	**16**	70, 1: 2.0 (*cis*:*trans*)
13	Diallyl ether **10**	3.0	10%	1.0	 **17**	86, 1: 3.1

[a] Isolated yield.
[b] 60 °C instead of 70 °C (significant decomposition of product at 70 °C).



Scheme 3.

excess of difluoroacetate **1b** (1.5 equiv) over tetradecene **4** (1.0 equiv) led to an improved yield of 77% (Entry 2). Increasing the amount of AIBN was found to improve the yield further (Entry 3), and an excellent yield of product **11** could still be obtained when the amount of difluoroacetate **1b** was reduced to 1.3 equiv (Entry 4). Alkanol **12** was obtained in 69% yield from 9-decen-1-ol under similar conditions (Entry 5).

When stirring difluoroacetate **1b** and hex-5-en-2-one **6** at 70 °C for 16 h, a deep brown solution was obtained which, after purification by column chromatography, afforded adduct **13** in 46% yield (Entry 6). The colour of the reaction mixture was significantly less intense when the reaction was performed at 60 °C and an improved yield of 62% was obtained using 30% of AIBN (Entry 7). However, when *N*-allyl phthalimide **7** was employed, the desired product **14** was only obtained in 37% yield (Entry 8).

For volatile substrates such as trimethyl(vinyl)silane **8**, cyclohexene **9** and diallyl ether **10**, an excess (3 equivalents) of the alkene was necessary to deliver good yields of the corresponding adducts **15**–**17** (Entries 10, 12–13). Hence, when iododifluoroacetate **1b** was used in small excess (1.5 equiv), the yield of product **15** was significantly lower than when an excess (3.0 equiv) of the corresponding alkenes **8** was employed (Entries 10 vs. 9). Similarly, when excess cyclohexene **9** was employed (Entry 12), adduct **16** was obtained in 70% yield (mixture of cis/trans, 1:2.5), in contrast to the 33% yield of **16** obtained when using a small excess of iododifluoroacetate **1b** (Entry 11). THF-derivative **17** was also synthesised from diallyl ether **10** (3.0 equiv) in a similar manner (Entry 12).

2.2. Subsequent iodide reduction

Iodide reduction of the addition product **11** was initially attempted using AIBN and Bu_3SnH in refluxing toluene (Scheme 3), but the desired product was not formed. A second product was isolated which likely resulted from the lactonisation of **11** [15]. Fortunately, ambient-temperature initiation of the same reduction using Et_3B instead of AIBN gave difluoroester **18** in 68% yield [16]. Alternatively, iodide reduction could also be achieved using Zn/$NiCl_2{\cdot}6H_2O$ [9c] in wet THF to afford difluoroester **18** in 82% yield (Scheme 3).

3. Conclusion

We have successfully established the AIBN-initiated addition of ethyl 4-iodo-2,2-difluoroacetate to a variety of alkene substrates. Subsequent iodide reduction of the addition products could be achieved using Zn/$NiCl_2{\cdot}6H_2O$ or Et_3B/Bu_3SnH, as demonstrated in the conversion of iodide **11** to difluoroester **18**. The process will

serve as an alternative to existing methods that enables the facile introduction of an α,α-difluoroalkyl fragment.

4. Experimental

4.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Brüker DPX400 or AV300 spectrometer as indicated. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. Low resolution ES mass spectra and EIMS were recorded on a Waters ZMD and Thermoquest TraceMS Quadrapole spectrometer respectively. Infrared spectra were recorded as neat films on a Nicolet Impact 380 ATR spectrometer. Melting points were recorded on a Gallencamp Melting Point Apparatus and are uncorrected.

Column chromatography was performed on 230–400 mesh Matrex silica gel. Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250 mm × 22 mm column eluting at 20 mL min^{-1}, connected to a Kontron 475 refractive index detector. Reactions were monitored by TLC (Merck) with detection by $KMnO_4$ or anisaldehyde stains.

Reaction solvents were dried before use as follows: THF and Et_2O were distilled from sodium/benzophenone; CH_2Cl_2 and Et_3N were distilled from CaH_2; toluene was distilled from sodium. Ethyl iododifluoroacetate (light pink) was purchased from Fluorochem Ltd and in most cases was used without further purification. If the purchased ethyl iododifluoroacetate was deep purple in colour, the reagent was dissolved in Et_2O, washed with sat. $Na_2S_2O_3$ solution and concentrated *in vacuo* to give a light yellow oil. Zinc metal was activated by stirring with 1 M HCl and washed with H_2O followed by anhydrous THF. All reaction vessels were flame dried under vacuum prior to use and all experiments were carried out under a nitrogen atmosphere. All other reagents were purchased from commercial sources and used without further purification.

4.2. Typical procedures for the preparation of 2,2-difluoro-4-iodo esters

AIBN was added to a solution of alkene and iododifluoroacetate **1b** in dichloroethane. The mixture was stirred at 70 °C for 16 h, followed by concentration *in vacuo*. The crude mixture was purified by column chromatography to afford the desired 2,2-difluoro-4-iodo esters.

4.2.1. Ethyl 2,2-difluoro-4-iodohexadecanoate (11)

Ester **11** was prepared from tetradecene **4** (92% purity; 275 μL, 1.0 mmol), difluoroacetate **1b** (374 mg, 1.5 mmol) and AIBN (16.4 mg, 0.1 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 0 → 5%) to afford a colourless oil (395 mg, 88%). IR (cm^{-1}) 2923 vs, 2853 s, 1770 vs, 1466 m, 1432 w, 1374 m, 1338 w, 1299 m, 1183 s, 1071 vs; ^{19}F NMR (282 MHz, $CDCl_3$) −102.3 (d, J = 263.0 Hz), −107.0 (d, J = 264.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 4.35 (2H, q, J = 7.0 Hz), 4.23 (1H, dtd, J = 8.5, 7.0, 4.5 Hz), 2.92 (1H, dtd, J = 18.5, 16.0, 6.5 Hz), 2.74 (1H, dddd, J = 18.0, 16.0, 13.0, 7.5 Hz), 1.87–1.69 (2H, m), 1.59–1.21 (20H, m), 1.38 (3H, t, J = 7.0 Hz), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 163.6 (t, J = 32.0 Hz), 115.4 (t, J = 251.5 Hz), 63.4, 45.6 (t, J = 22.5 Hz), 32.1, 29.79, 29.76, 29.70, 29.66, 29.55, 29.51, 28.7, 23.5 (t, J = 4.0 Hz), 22.9, 14.3, 14.1; ES$^+$ m/z (%) 469 ((M+Na)$^+$, 100); HRMS (ES$^+$) for $C_{18}H_{33}F_2IO_2$ (M+Na)$^+$: Calcd 469.1386; Measured 469.1378.

4.2.2. Ethyl 2,2-difluoro-5-hydroxy-4-iododododecanoate (12) [9c]

Ester **12** was prepared from 9-decen-1-ol (184 μL, 1.0 mmol), difluoroacetate **1b** (324 mg, 1.3 mmol) and AIBN (32.8 mg, 0.2 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 15 → 30%) to afford a colourless oil (282 mg, 69%). ^{19}F NMR (282 MHz, $CDCl_3$) −102.3 (d, J = 262.0 Hz), −107.0 (d, J = 262.0 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 4.36 (2H, q, J = 7.0 Hz), 4.23 (1H, dtd, J = 9.0, 7.0, 4.5 Hz), 3.65 (2H, t, J = 6.5 Hz), 2.92 (1H, dtd, J = 18.5, 15.5, 6.5 Hz), 2.74 (1H, dddd, J = 18.0, 15.5, 12.5, 7.0 Hz), 1.87–1.69 and 1.61–1.29 (15H, m), 1.38 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 163.6 (t, J = 32.5 Hz), 115.3 (t, J = 251.5 Hz), 63.4, 63.1, 45.5 (t, J = 23.0 Hz), 32.9, 29.6, 29.4, 28.6, 25.8, 23.4 (t, J = 3.5 Hz), 14.3.

4.2.3. Ethyl 2,2-difluoro-4-iodo-7-oxooctanoate (13) [9c]

Ester **13** was prepared from hex-5-en-2-one (118 μL, 1.0 mmol), difluoroacetate **1b** (324 mg, 1.3 mmol) and AIBN (49.2 mg, 0.3 mmol) in dichloroethane (3.3 mL) at 60 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford a pink oil (216 mg, 60%) which needed to be stored in the freezer to minimise decomposition. ^{19}F NMR (282 MHz, $CDCl_3$) −102.4 (d, J = 264.5 Hz), −106.6 (d, J = 264.5 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 4.30 (2H, q, J = 7.5 Hz), 4.21 (1H, dtd, J = 10.5, 7.0, 4.0 Hz), 2.89 (1H, dtd, J = 18.0, 15.5, 6.5 Hz), 2.77–2.54 (3H, m), 2.13 (3H, s), 2.05 (1H, dddd, J = 15.0, 8.5, 6.5, 4.0 Hz), 1.94 (1H, m), 1.33 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 206.5, 163.3 (t, J = 32.5 Hz), 115.0 (t, J = 251.5 Hz), 63.3, 45.4 (t, J = 23.0 Hz), 43.5, 34.1, 30.1, 22.2, 13.9.

4.2.4. Ethyl 2,2-difluoro-4-iodo-5-(1,3-dioxoisoindolin-2-yl)pentanoate (14)

Ester **14** was prepared from *N*-allyl phthalimide (187 mg, 1.0 mmol), difluoroacetate **1b** (324 mg, 1.3 mmol) and AIBN (32.8 mg, 0.2 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford a colourless oil (161 mg, 37%). IR (cm^{-1}) 2985 w, 1767 m, 1709 vs, 1614 w, 1468 w, 1430 m, 1392 s; ^{19}F NMR (282 MHz, $CDCl_3$) −102.1 (d, J = 265.0 Hz), −106.2 (d, J = 264.0 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 7.90–7.86 (2H, m), 7.78–7.73 (2H, m), 4.59 (1H, m), 4.34 (2H, q, J = 7.0 Hz), 4.14 (1H, dd, J = 14.5, 8.5 Hz), 3.97 (1H, dd, J = 14.5, 7.5 Hz), 2.94 (1H, dtd, J = 17.5, 16.0, 7.5 Hz), 2.79 (1H, dddd, J = 17.5, 16.0, 13.0, 6.0 Hz), 1.36 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 168.1, 163.5 (t, J = 33.0 Hz), 134.8, 132.1, 124.1, 115.3 (t, J = 252.5 Hz), 63.8, 46.4, 43.2 (t, J = 23.5 Hz), 15.9 (m), 14.3; ES$^+$ m/z (%) 460 ((M+Na)$^+$, 90), 492 ((M+Na+MeOH)$^+$, 100); HRMS (ES$^+$) for $C_{15}H_{14}F_2INO_2$ (M+H)$^+$: Calcd 438.0008; Measured 438.0002.

4.2.5. Ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanoate (15) [9c]

Ester **15** was prepared from vinyltrimethylsilane (440 μL, 3.0 mmol), difluoroacetate **1b** (249 mg, 1.0 mmol) and AIBN (16.4 mg, 0.1 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 0 → 5%) to afford a colourless oil (302 mg, 86%). ^{19}F NMR (282 MHz, $CDCl_3$) −102.5 (d, J = 260.0 Hz), −108.0 (d, J = 260.0 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 4.36 (2H, q, J = 7.0 Hz), 3.11 (1H, m), 2.68–2.58 (2H, m), 1.38 (3H, t, J = 7.0 Hz), 0.19 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 163.9 (t, J = 32.5 Hz), 115.8 (t, J = 249.0 Hz), 63.3, 39.2 (t, J = 24.0 Hz), 14.0, 4.5, −2.3.

4.2.6. Ethyl 2,2-difluoro-2-(2-iodocyclohexyl)acetate (16) [9c,10a]

Ester **16** was prepared from cyclohexene (304 μL, 3.0 mmol), difluoroacetate **1b** (249 mg, 1.0 mmol) and AIBN (16.4 mg, 0.1 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 5 → 20%) to afford a colourless oil (234 mg, 70%, cis/trans 1.0:2.1).

^{19}F NMR (282 MHz, $CDCl_3$) −106.1 (*trans*; d, J = 264.5 Hz), −110.0 (*cis*; d, J = 262.0 Hz), −111.8 (*cis* + *trans*; d, J = 262.0 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) 4.66 – 4.29 ($3H_{cis+trans}$, m), 2.73 – 2.61 ($1H_{cis+trans}$, m), 2.34 – 1.37 ($8H_{cis+trans}$, m), 1.343 ($3H_{trans}$, t, J = 7.0 Hz), 1.340 ($1H_{cis}$, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 163.8 (t, J = 32.5 Hz), 163.7 (t, J = 32.5 Hz), 116.4 (t, J = 251.5 Hz), 115.3 (t, J = 253.5 Hz), 63.1, 48.1 (t, J = 21.0 Hz), 47.0 (t, J = 22.0 Hz), 39.1, 37.3, 28.8 (t, J = 4.0 Hz), 26.4, 25.3 (t, J = 3.0 Hz), 25.1, 24.4 (m), 23.4, 22.3 (t, J = 2.5 Hz), 22.2, 13.92, 13.90.

4.2.7. Ethyl 2,2-difluoro-3-(tetrahydro-4-(iodomethyl)furan-3-yl)propanoate (17) [9c]

Ester **17** was prepared from allyl ether (367 μL, 3.0 mmol), difluoroacetate **1b** (249 mg, 1.0 mmol) and AIBN (32.8 mg, 0.2 mmol) in dichloroethane (3.3 mL) at 70 °C for 16 h. The crude was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford a colourless oil (mixture of isomers, 1:3.1; 300 mg, 86%). ^{19}F NMR (282 MHz, $CDCl_3$) −104.3 (minor; d, J = 262.0 Hz), −104.4 (major; d, J = 262.0 Hz), −106.3 (minor; d, J = 262.0 Hz), −106.6 (d, J = 258.0 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) 4.34 ($2H_{min+maj}$, q, J = 7.0 Hz,), 4.13 ($1H_{min}$, m), 4.00–3.92 ($1H_{min}$ + $2H_{maj}$, m), 3.72 ($2H_{maj}$, dd, J = 9.0, 4.5 Hz), 3.62 – 3.47 ($1H_{maj}$ + $2H_{min}$, m) 3.30 ($1H_{min}$, dd, J = 10.0, 5.0 Hz), 3.22 ($1H_{maj}$, ddd, J = 9.5, 5.0, 1.0 Hz), 3.14 ($1H_{min}$, dd, J = 10.0, 8.5 Hz), 3.04 ($1H_{maj}$, dd, J = 11.0, 9.5 Hz), 2.74 ($1H_{maj}$, m), 2.55 ($1H_{maj}$, m), 2.42 – 1.96 ($4H_{min}$ + $2H_{maj}$, m), 1.35 ($3H_{maj+min}$, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 163.6 (t, J = 32.5 Hz), 115.6 (t, J = 249.5 Hz), 115.4 (t, J = 32.5 Hz), 73.9, 73.7, 73.4, 71.5, 63.1, 47.6, 45.1, 40.0, 37.1 (t, J = 22.5 Hz), 36.6, 31.8 (t, J = 23.0 Hz), 25.0, 13.9, 7.3, 3.7.

4.3. Ethyl 2,2-difluorohexadecanoate (18) [12]

(a) $NiCl_2 \cdot 6H_2O$ procedure: A drop of water was added to a mixture of iodide **11** (180 mg, 0.404 mmol), Zn (52.8 mg, 0.808 mmol) and $NiCl_2 \cdot 6H_2O$ (9.6 mg, 0.0808 mmol) in THF (1.1 mL) and it was stirred at r.t. for 16 h. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (petroleum ether) to afford a colourless oil (106 mg, 82%). ^{19}F NMR (282 MHz, $CDCl_3$) −106.2; ^{1}H NMR (400 MHz, $CDCl_3$) 4.33 (2H, q, J = 7.0 Hz), 2.11–1.99 (2H, m), 1.50–1.40 (2H, m), 1.38–1.22 (22H, m), 1.36 (3H, t, J = 7.0 Hz), 0.89 (3H, t, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 164.6 (t, J = 33.0 Hz), 116.6 (t, J = 248.0 Hz), 62.8, 34.7 (t, J = 23.0 Hz), 32.1, 29.82, 29.79, 29.73, 29.55, 29.52, 29.4, 29.2, 22.9, 21.6 (t, J = 4.5 Hz), 14.3, 14.1.

(b) Et_3B procedure: Et_3B (1 M solution in hexane; 46.5 μL, 46.5 μmol) was added to a solution of iodide **11** (199 mg, 0.465 mmol) and Bu_3SnH (193 μL, 0.696 mmol) in toluene (2.3 mL) and the mixture was stirred at r.t. for 16 h. The reaction mixture was then filtered through K_2CO_3, concentrated *in vacuo* and purified by column chromatography (petroleum ether) to afford a colourless oil (96.6 mg, 68%).

Acknowledgement

We thank Cancer Research Technology for funding.

References

[1] Reviews
(a) K.L. Kirk, J. Fluorine Chem. 127 (2006) 1013–1029;
(b) J.-P. Bégué, D. Bonnet-Delpon, J. Fluorine Chem. 127 (2006) 992–1012;
(c) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, ChemBioChem 5 (2004) 637–643;
(d) P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2004;
(e) F.M.D. Ismail, J. Fluorine Chem. 118 (2002) 27–33;
(f) P. Vierling, C. Santaella, J. Greiner, J. Fluorine Chem. 107 (2001) 337–354;
(g) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, 2000.
[2] M.J. Tozer, T.F. Herpin, Tetrahedron 52 (1996) 8619–8683.
[3] R.P. Singh, J.M. Schreeve, Synthesis (2002) 2561–2578.
[4] J.M. Percy, Top. Curr. Chem. 193 (1997) 131–195.
[5] (a) E.A. Hallinan, J. Fried, Tetrahedron Lett. 25 (1984) 2301–2304;
Reviews
(b) A. Fürstner, Synthesis (1989) 571–590;
(c) R. Ocampo, W.R. Dolbier Jr., Tetrahedron 60 (2004) 9325–9374.
[6] D.H.R. Barton, S.W. McCombie, J. Chem. Soc. Perkin I (1975) 1574–1585.
[7] Examples:
(a) E.A. Hallinan, S.W. Kramer, S.C. Houdek, W.M. Moore, G.M. Jerome, D.P. Spangler, A.M. Stevens, H.S. Shieh, P.T. Manning, B.S. Pitzele, Org. Biomol. Chem. 1 (2003) 3527–3534;
(b) P. Meffre, R.H. Dave, J. Leroy, B. Badet, Tetrahedron Lett. 42 (2001) 8625–8627;
(c) H.S. Gill, J.M. Londowski, R.A. Corradino, A.R. Zinsmeister, R. Kumar, J. Med. Chem. 33 (1990) 480–490;
(d) E.A. Hallinan, T.J. Hagen, R.K. Husa, S. Tsymbalov, S.N. Rao, J.-P. vanHoeck, M.F. Rafferty, A. Stapelfeld, M.A. Savage, M. Reichman, J. Med. Chem. 36 (1993) 3293–3299.
[8] Examples:
(a) G.H. Posner, H.J. Kim, M. Kahraman, H.B. Jeon, B.C. Suh, H. Li, P. Dolan, T.W. Kensler, Bioorg. Med. Chem. 13 (2005) 5569–5580;
(b) Y. Ding, J. Wang, K.A. Abboud, Y. Xu, W.R. Dolbier Jr., N.G.J. Richards, J. Org. Chem. 66 (2001) 6381–6388.
[9] (a) Z.-Y. Yang, D.J. Burton, J. Fluorine Chem. 45 (1989) 435–439;
(b) O. Kitagawa, A. Miura, Y. Kobayashi, T. Taguchi, Chem. Lett. (1990) 1011–1014;
(c) Z.-Y. Yang, D.J. Burton, J. Org. Chem. 56 (1991) 5125–5132;
(d) K. Sato, M. Omote, A. Ando, I. Kumadaki, J. Fluorine Chem. 125 (2004) 509–515.
[10] (a) F. Xiao, F. Wu, Y. Shen, L. Zhou, J. Fluorine Chem. 126 (2005) 63–67;
(b) F. Wu, F. Xiao, X. Yang, Y. Shen, T. Pan, Tetrahedron 62 (2006) 10091–10099.
[11] B. Moreno, C. Quehen, M. Rose-Hélène, E. Leclerc, J.-C. Quirion, Org. Lett. 9 (2007) 2477–2480.
[12] (a) Z.-Y. Yang, D.J. Burton, J. Chem. Soc., Chem. Commun. (1992) 233–234;
(b) Z.-Y. Yang, D.J. Burton, J. Org. Chem. 57 (1992) 5144–5149.
[13] (a) N.O. Brace, J. Org. Chem. 27 (1962) 4491–4498;
Reviews
(b) N.O. Brace, J. Fluorine Chem. 108 (2001) 147–175;
(c) N.O. Brace, J. Fluorine Chem. 96 (1999) 101–127;
(d) N.O. Brace, J. Fluorine Chem. 93 (1999) 1–25;
(e) W.R. Dolbier Jr., Top. Curr. Chem. 192 (1997) 97–163;
(f) W.R. Dolbier Jr., Chem. Rev. 96 (1996) 1557–1584.
[14] J.L. Roberts, J. Borgese, C. Chan, D.K. Keith, C.-C. Wei, Heterocycles 35 (1993) 115–120.
[15] The IR of the crude reaction mixture (still contaminated with alkyl tin residues) shows a strong absorption band at 1811 cm^{-1}, which is characteristic for 2,2-difluoro-γ-lactones (Ref. [10a]). In addition, ES MS analysis shows the $(M+H)^+$ peak and $(M+H+MeOH)^+$, and the ^{1}H NMR of the crude reaction mixture shows characteristic signals at 4.61, 2.81, and 2.30 ppm (Ref. [10a]). Lactonisation of such adducts is reported under basic conditions—see Ref. [10a].
[16] K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, Bull. Chem. Soc. Jpn. 62 (1989) 143–147.