CONVENIENT PREPARATION OF 2-PHENYLETHYL 3,3-DIFLUORO-2-METHYLPROPIONATE

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Dedicated to the memory of Professor Miloš Hudlický.

The slow inverse addition of an LDA solution at –78 °C to an ester of 2-(trifluoromethyl)acrylic acid enabled efficient dehydrofluorination. Hydrogenation of the resulting difluoromethylacrylate furnished the target ester of 3,3-difluoro-2-methylpropionic acid in good overall yield.

Keywords: Fluorine; Hydrogenations; Dehydrofluorination; α,β-Unsaturated esters; Fluorinated compounds; *Ab initio* calculations.

Fluorine-containing materials have attracted significant attention of synthetic organic chemists due to their unique physical properties which cannot be usually attained by the presence of any other atoms. However, their application in various fields has been sometimes hampered by limited methods available for the synthesis of specific fluorine-containing structures.

2-Phenylethyl 3,3-difluoro-2-methylpropionate (**5**), recently required for our purpose[1], was actually the case, and there have been only a few preceding instances for obtaining this target compound. One of the most straightforward pathways would be the alkylation of appropriate enolates with $CHClF_2$ [2], but severe global restriction has been imposed on the employment of this CFC responsible for ozone depletion. On the other hand, our previous experience[3] with convenient ultrasonic-assisted hydrogenation led us to the idea that transformation of 3,3-difluoroacrylates could be regarded as an alternative solution for obtaining the desired α-difluoromethylated esters.

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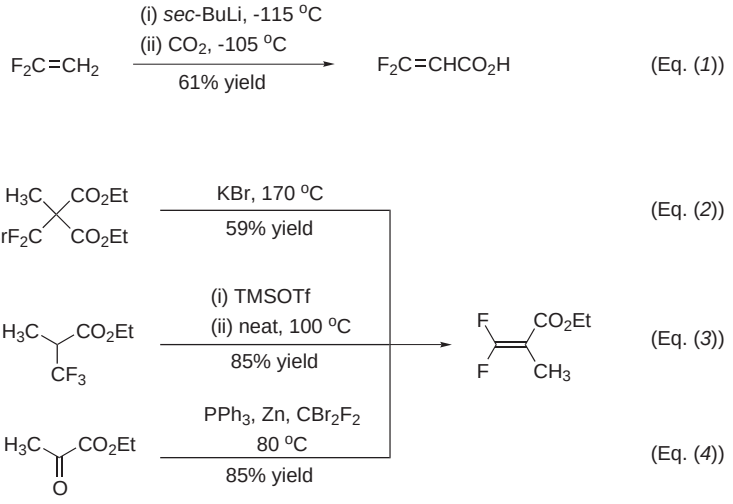
In Scheme 1 are collected the three representative methods which afford 3,3-difluoroacrylates or -methacrylates. Equation (*1*) was reported by the Normant's group two decades ago[4] on *sec*-BuLi-promoted lithiation of 1,1-difluoroethene and trapping of the intermediate with CO_2. Bromodifluoromethylated malonate[5], readily prepared in 76% yield by the reaction of CBr_2F_2 and sodium salt of diethyl methylmalonate[6], was successfully decarboxylated under heating to furnish difluorinated methacrylate (Eq. (*2*)). Recent publication by Botteghi and his coworkers[7] deals with dehydrofluorination of trifluorinated isobutyrate (Eq. (*3*)) as well as Wittig difluoromethylenation of pyruvate (Eq. (*4*)) with reasonably good chemical yields in both instances.

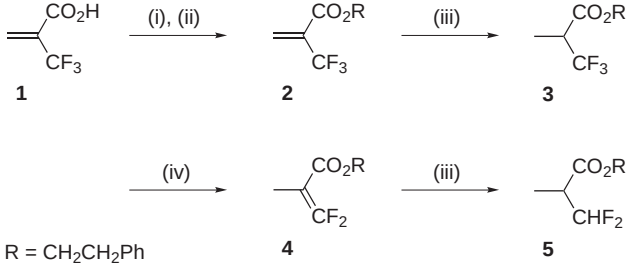


SCHEME 1

In the course of the above literature search, the absence of one of the most direct pathways, the elimination of HF from α-trifluoromethylated carbonyl compounds, made us quite curious[8]. Considering that recent exploitation[9] allowed their facile formation *via* Et_3B-mediated reaction of ketene silyl acetals with ozone-nondestructive CF_3I, success in this dehydrofluorination process would open a new route to variously substituted α-difluoromethylated carbonyl compounds. Based on this concept, we report here the convenient preparation of 3,3-difluoro-2-methylpropionate from the corresponding 3,3,3-trifluorinated analog by the HF elimination-hydrogenation procedure.

RESULTS AND DISCUSSION

We have selected the commercially available α,β-unsaturated acid **1** as the starting material and converted it first to the 2-phenylethyl ester **2** for facile handling and UV detection (Scheme 2). Hydrogenation of **2** was realized in a quite smooth manner by the action of a catalytic amount (0.5 mole %) of 10% Pd/C under atmospheric pressure of hydrogen. This easy conversion might be attributed to the appreciably low LUMO energy level of ester **2** due to direct attachment of the strongly electron-withdrawing CF_3 and carbonyl groups[10] to the C=C system.



(i) phthaloyl dichloride; (ii) ROH, pyridine; (iii) 10% Pd/Cl, H_2; (iv) base

SCHEME 2

This saturated CF_3 ester **3** in hand, we started to study the action of strong but weakly nucleophilic bases as LDA or LHMDS (Table I). As expected, addition of ester **3** to solutions containing these bases at 0 °C seemed to abstract the activated α-proton to the carbonyl group, but only

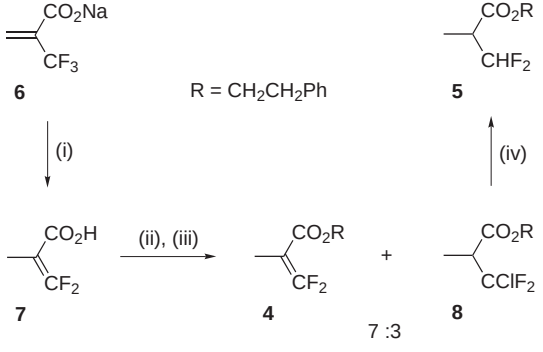
TABLE I
Brief examination of the deprotonation conditions

Base	Equivalent	Method[a]	Temperature, °C	^{19}F NMR yield, %	
				4	**3**
LDA	(1.05)	A	0	11	39
LHMDS	(1.05)	A	0	0	40
LDA	(1.05)	A	–78	25	26
LDA	(2.00)	A	–78	2	0
LDA	(1.05)	B	–78	65	15
LDA	(1.30)	B	–78	79	1
LDA	(1.50)	B	–78	86[b]	0

[a] A: **3** was added to a solution of a base, B: a base solution was added to a solution of **3**. [b]Isolated yield.

complex mixture was formed. Lowering the temperature slightly increased the yield of ester **4**, but this was apparently far from the required level. This protocol allowed **3** to contact an excess amount of the base especially at the early stage of the reaction, and highly electrophilic nature of ester **4** [11] could be considered to be the major reason for its unfavorable decomposition. For verifying this hypothesis, we changed the conditions and a THF solution of LDA was slowly introduced to a cooled solution of **3**. This alteration clearly affected the reaction and significantly improved the yield to 65%. The judicious adjustment of the equivalent of the base finally attained the isolated yield as high as 86%. Hydrogenation of difluorinated methacrylate **4** thus obtained was the last step. A larger amount (13 mole %) of Pd/C was required and this process was found to proceed at higher rate under positive pressure of hydrogen rather than under previous ultrasonic treatment. Following this procedure, our target material **5** was eventually obtained in 48% overall yield in five steps. Reduction of a Pd/C amount to 0.5 mole % as in the case of the transformation of ester **2** to **3** did not lead to the complete conversion, and approximately 30% of ester **4** remained intact even after 40 h stirring.

Our initial synthetic plan of compound **5** is shown in Scheme 3. As was also pointed out by Botteghi and his coworkers[7], transformation of sodium salt **6** to acid **7** following the Fuchikami's protocol[12] did not give any clean product. Moreover, esterification of this crude mixture containing difluorinated methacrylic acid **7** led to the formation of methacrylate **4** along with the unexpected chlorinated ester **8** [13] in a ratio of *ca* 7 : 3 in less than 30% total yield from ester **6** as was confirmed by ^{19}F NMR spectroscopy.



(i) $LiAlH_4$; (ii) phthaloyl dichloride; (iii) ROH, pyridine; (iv) Bu_3SnH

SCHEME 3

While ester **8**, probably obtained by the HCl addition to **4** from the *in situ* generated pyridinium hydrochloride, was almost quantitatively transformed into **5** by the action of Bu_3SnH, difficult separation of chlorinated ester **8** from methacrylate **4** as well as the low efficiency of transformation of acid **7** to ester **5** made us to abandon this initial plan and select the above procedure.

As demonstrated above, we have succeeded in the synthesis of 2-difluoromethylated ester **5** from the corresponding trifluoromethylated precursor **3** in good overall yields using common and facile techniques. We believe that this method is applicable to a wide range of esters as one of the promising routes to synthesize such target compounds by way of α-trifluoromethylation.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Anhydrous ether, THF and CH_2Cl_2 were purchased and were used without further purification.

^1H and ^{13}C NMR spectra were recorded with a Varian Gemini-200 (200 MHz) or a Varian VXR-500 (500 MHz) in $CDCl_3$ unless otherwise noted and chemical shifts (δ) were reported in ppm downfield from internal standard, tetramethylsilane. ^{19}F NMR spectra were recorded with a Varian VXR-500 (470 MHz) in $CDCl_3$ unless otherwise noted and chemical shifts (δ) were reported in ppm downfield from internal standard, hexafluorobenzene (C_6F_6). NMR data were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of nuclei, coupling constants *J* (in Hz). Infrared spectra were obtained on a JASCO FT/IR-5000 spectrometer as thin films on NaCl plates, and were reported using wavenumbers ν (in cm^{-1}). Column chromatography was performed with silica gel (BW-200) by using mixtures of hexanes and ethyl acetate (v/v).

2-Phenylethyl 2-(Trifluoromethyl)acrylate (**2**)

The round-bottom flask containing 2-(trifluoromethyl)acrylic acid (**1**; 54.6 g, 390 mmol) and phthaloyl dichloride (84.3 ml, 580 mmol) was connected to the Claisen distillation head, and the mixture was heated to 150 °C with collecting the resulting acid chloride. The temperature was raised finally to 190 °C to furnish 86.5 g (545 mmol) of the desired acid chloride in 94% yield.

To a CH_2Cl_2 (200 ml) solution containing this acid chloride (54.4 g, 343 mmol) and 2-phenylethanol (52.1 ml, 411 mmol) was slowly added pyridine (37.8 ml, 446 mmol) at –20 °C for 2 h and the mixture was further stirred at that temperature for 2 h. The usual work-up and chromatographic purification afforded 77.1 g (316 mmol) of the target ester **2** in 92% yield as a colorless oil. R_F 0.43 (AcOEt–hexane 1 : 10). ^1H NMR: 7.35–7.25 (5 H, m); 6.68 (1 H, q, $^4J_{HF}$ = 1.7); 6.42 (1 H, q, $^4J_{HF}$ = 1.1); 4.46 (2 H, t, $^3J_{HH}$ = 7.1); 3.02 (2 H, t, $^3J_{HH}$ = 6.9). ^{13}C NMR: 160.96, 137.23, 132.68 (q, $^3J_{CF}$ = 5.0); 131.17 (q, $^2J_{CF}$ = 32.1); 128.79, 128.40, 126.57, 121.23 (q, $^1J_{CF}$ = 272.5); 66.12, 34.69. ^{19}F NMR: 96.06 (s). IR (neat): 3 030,

2 361, 1 736, 1 456, 1 398, 1 352, 1 247, 1 146, 1 097, 989, 810, 748, 696. For $C_{12}H_{11}F_3O_2$ (244.2) calculated: 59.02% C, 4.54% H; found: 58.75% C, 4.49% H.

2-Phenylethyl 3,3,3-Trifluoro-2-methylpropionate (**3**)

Unsaturated ester **2** (29.8 g, 122 mmol) in MeOH (100 ml) was hydrogenated with 10% Pd/C (0.647 g, 0.61 mmol) under atmospheric pressure of hydrogen at room temperature over 12 h. Removal of the catalyst by filtration and chromatographic purification yielded the corresponding saturated ester **3** (27.6 g, 112 mmol) in 92% yield as a colorless oil. R_F 0.49 (AcOEt–hexane 1 : 10). ^{1}H NMR: 7.33–7.20 (5 H, m); 4.42–4.35 (2 H, m); 3.18 (1 H, qq, $^3J_{HF}$ = 8.3, $^3J_{HH}$ = 7.3); 2.97 (2 H, t, $^3J_{HH}$ = 7.1); 1.36 (3 H, d, $^3J_{HH}$ = 7.3). ^{13}C NMR: 167.59 (q, $^3J_{CF}$ = 2.9); 137.18, 128.72, 128.34, 126.50, 124.88 (q, $^1J_{CF}$ = 279.3); 65.84, 44.32 (q, $^2J_{CF}$ = 28.4); 34.62, 10.60 (q, $^3J_{CF}$ = 2.7). ^{19}F NMR: 91.76 (d, $^3J_{FH}$ = 7.6). IR (neat): 2 959, 2 364, 1 748, 1 603, 1 461, 1 335, 1 268, 1 204, 1 124, 1 079, 1 008, 748, 699. For $C_{12}H_{13}F_3O_2$ (246.2) calculated: 58.54% C, 5.32% H; found: 58.18% C, 5.00% H.

2-Phenylethyl 3,3-Difluoro-2-methylacrylate (**4**)

To a THF solution (150 ml) containing ester **3** (25.6 g, 104 mmol) was slowly added LDA at –78 °C, prepared from diisopropylamine (21.8 g, 156 mmol) and BuLi (97.5 ml, 156 mmol; 1.6 mol/l in hexanes) in 100 ml of THF at 0 °C , and the mixture was stirred at the same temperature for 1 h. The usual work-up and chromatographic purification afforded 20.4 g (89.4 mmol) of the desired terminally difluorinated α,β-unsaturated ester **4** in 86% yield as a colorless oil. R_F 0.50 (AcOEt–hexane 1 : 10). ^{1}H NMR: 7.33–7.23 (5 H, m); 4.38 (2 H, t, $^3J_{HH}$ = 7.1); 2.98 (2 H, t, $^3J_{HH}$ = 6.8); 1.78 (3 H, t, $^4J_{HF}$ = 3.2). ^{13}C NMR: 164.23 (dd, $^3J_{CF}$ = 7.7, 5.4); 158.91 (dd, $^1J_{CF}$ = 307.8, 293.7); 137.33, 128.48, 127.99, 126.11, 83.92 (dd, $^2J_{CF}$ = 24.1, 7.7); 65.32, 34.75, 9.18 (d, $^3J_{CF}$ = 1.7). ^{19}F NMR: 92.52 (1 F, q, $^4J_{FH}$ = 3.1); 88.41 (1 F, q, $^4J_{FH}$ = 3.1). IR (neat): 3 030, 2 959, 2 364, 2 343, 1 750, 1 722, 1 498, 1 395, 1 332, 1 159, 1 128, 764, 750, 700. For $C_{12}H_{12}F_2O_2$ (226.2) calculated: 63.71% C, 5.35% H; found: 63.88% C, 5.70 H.

2-Phenylethyl 3,3-Difluoro-2-methylpropionate (**5**)

To a MeOH (10 ml) solution of ester **4** (0.68 g, 3.0 mmol) was added 0.41 g (0. 39 mmol) of 10% Pd/C and the mixture was stirred under hydrogen at 490 kPa pressure for 3 h. Removal of the catalyst by filtration and chromatographic purification yielded saturated ester **5** (0.48 g, 2.1 mmol) in 70% yield as a colorless oil. R_F 0.48 (AcOEt–hexane 1 : 10). ^{1}H NMR: 7.38–7.20 (5 H, m); 5.98 (1 H, td, $^2J_{HF}$ = 55.0, $^3J_{HH}$ = 4.7); 4.37 (2 H, t, $^3J_{HH}$ = 6.9); 2.96 (2 H, t, $^3J_{HH}$ = 6.9); 2.95–2.80 (1 H, m); 1.25 (3 H, d, $^3J_{HH}$ = 7.4). ^{13}C NMR: 165.52 (t, $^3J_{CF}$ = 7.2); 132.70, 124.17, 123.85, 121.99, 111.22 (t, $^1J_{CF}$ = 241.9); 61.02, 39.63 (t, $^2J_{CF}$ = 22.9); 30.39, 5.12 (t, $^3J_{CF}$ = 5.2). ^{19}F NMR: 42.26 (1 F, ddd, $^1J_{FF}$ = 282.7, $^2J_{FH}$ = 56.0, $^3J_{FH}$ = 8.6); 35.17 (1 F, ddd, $^1J_{FF}$ = 283.5, $^2J_{FH}$ = 56.0, $^3J_{FH}$ = 17.2). IR (neat): 2 959, 2 361, 1 740, 1 461, 1 396, 1 323, 1 258, 1 192, 1 155, 1 075, 993, 749, 700. For $C_{12}H_{14}F_2O_2$ (228.2) calculated: 63.15% C, 6.18% H; found: 63.26% C, 6.02% H.

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