Preparative Flow Techniques; 1. Low-Temperature Organometallic Reactions: Synthesis of Ethyl 2,2-Difluoro-4-pentenoate

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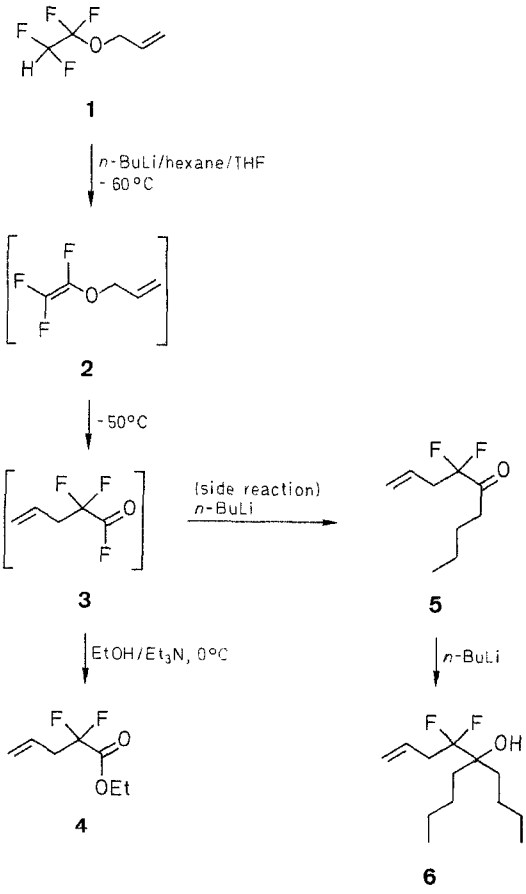
A convenient preparation of the synthetically useful ethyl 2,2-difluoro-4-pentenoate using the low-temperature flow technique is described. The method is suitable for small-scale as well as for large-scale application.

Due to the scarcity of readily available functionalized starting materials, the synthesis of more complex *gem*-difluoro compounds normally implies a fluorine-introducing step in the reaction scheme.[1,2] This usually gives rise to a variety of inconveniences. Problems with the toxicity, corrosiveness, and stability of the reagents employed along with the hazards involved in their handling are encountered. These drawbacks make a convenient starting material already possessing the desired fluorine substitution pattern highly desirable. We report here the preparation of such a starting material, ethyl 2,2-difluoro-4-pentenoate (**4**), on an essentially unlimited scale.

Title compound **4** is synthetically useful for the preparation of a variety of functionalized *gem*-difluoro compounds, such as difluoro ketones, β-difluoro amines, -alcohols, -ethers etc., α- as well as β-difluoro carboxylic acids and derivatives thereof. The synthesis of compound **4** starting from allyl 1,1,2,2-tetrafluoroethyl ether (2*H*-perfluoroethyl allyl ether, **1**; now commercially available[3]) can be carried out using essentially the conditions described for the synthesis of the corresponding acid[4] (Scheme).

The tetrafluoroethyl ether **1** is dehydrofluorinated with butyllithium at −60 °C. Claisen rearrangement of the resultant trifluorovinyl ether **2** to the acid fluoride **3**, reported to occur at −50 °C,[4] followed by quenching at low temperature with absolute ethanol affords ethyl 2,2-difluoro-4-pentenoate (**4**). This procedure gives yields of ~70% on a laboratory scale (10–30 mmol). With scaling up the preparation, the yield of **4** decreases continuously. Apparently, the rate of the Claisen rearrangement **2** → **3** is significant even at temperatures as low as −70 °C. Therefore, with increasing reaction time, butyllithium will react with the intermediate acid fluoride **3** to give the ketone **5** and further the tertiary alcohol **6**. This side reaction not only diminishes the amount of butyllthium available for the dehydrofluorination but also the amount of acid fluoride available for subsequent reaction with ethanol. In our hands, the yield of ester **4** dropped to 20% already on performing the preparation on a 150 mmol scale. This problem was overcome by conducting the dehydrofluorination in a continuous manner with a short residence time in a flow system als depicted in Figure 1. The precooled reagents are pumped into a 50 mL reaction vessel, cooled by immersion in a dry-ice bath; the outlet tube then delivers the reaction mixture to an ice-cold solution of triethylamine in absolute ethanol. The commercially available 1.6 M solution of butyllithium in hexane is used; allyl 2*H*-perfluoroethyl ether (**1**) is diluted with tetrahydrofuran to give a 0.8 M solution. Details of the reaction vessel are given in Figure 2.



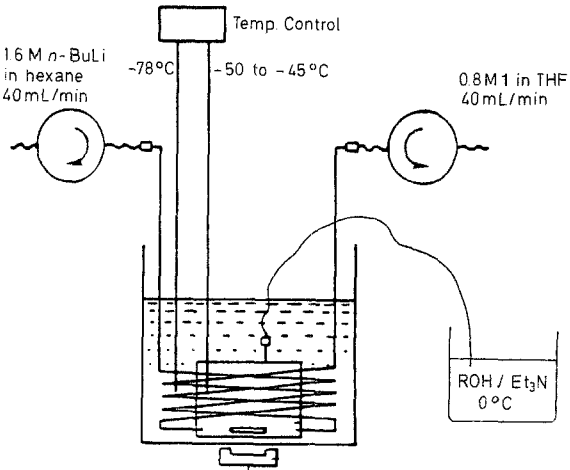


Figure 1. Flow-System Device for the Continuous Dehydrofluorination of Allyl 1,1,2,2-Tetrafluoroethyl Ether (**1**)

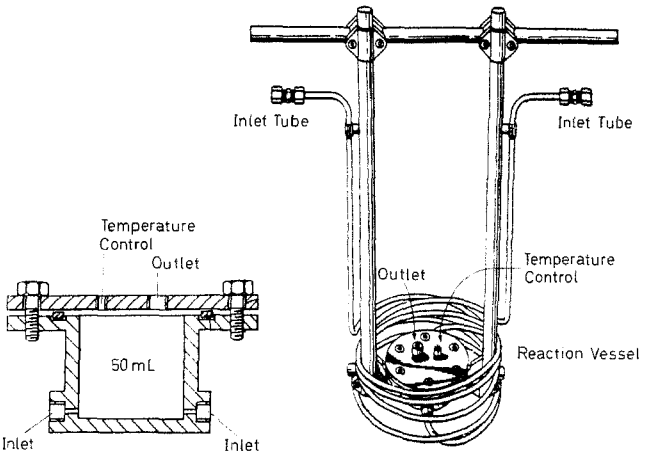


Figure 2. Reactor and Tubing of the Flow-System Apparatus

This simple setup allows the reaction to be performed at a rate of 30 mmol/min, which corresponds to a residence time of ~50 sec for the reagents in the reactor. Details of the pumps used,

the flow system, and the pumping rates of the reagents are given in the experimental section. With dry-ice cooling, the inside temperature under these conditions does not exceed −45 °C.

The overall yield of ester **4** is 50–70%. The use of other quenching reagents allows the preparation of the methyl or isopropyl ester (methanol or isopropanol), the acid (water), or the amide (ammonia in tetrahydrofuran), at comparable rates and in comparable yields.

The use of low-temperature flow techniques is not restricted to the case described here. There is a broad range of reactions for which flow techniques provide advantages of convenience (higher reaction temperatures than for conventional procedures), safety (toxic or explosive reagents or intermediates; closed system, small reaction volume), or in cases where scale-up involves problems of kinetics (instability of intermediates, side reactions of intermediates). Thus, this technique has been used in our laboratory and pilot plant successfully for the synthesis of α-amino α-fluoromethyl nitriles and α-fluoromethyl amines from (toxic) fluoroacetonitrile and Grignard reagents on a scale exceeding 100 mol,[5] and for large-scale (kg quantities) ozonizations.[6]

Conditions of GLC analyses: Girdel 3000; 100 °C, column OV 17 3%. The microanalysis of **4** was performed on a Perkin-Elmer 240 CHN analyzer. IR spectra were recorded on a Perkin-Elmer IR 577 spectrometer. ^{1}H and ^{19}F NMR spectra were obtained with a Varian EM-390 (^{19}F: 84.6 MHz; reported in Φ downfield from $CFCl_3$).

All reagents and solvents were used as obtained from the chemical supplier. 2*H*-perfluoroethyl allyl ether **(1)** was bought from Hoechst.[3] butyllithium in hexane from Metallgesellschaft (both in Frankfurt, West Germany).

Elektronically controlled, short-stroke electromagnet, piston diaphragm dosing pumps ProMinent of the types B 25001 S and E 1002 S, purchased from Chemie und Filter GmbH (Heidelberg, West Germany), were used for the controlled introduction of the reagents into the flow reactor.

Flow Reactor (Figure 2):
A cylindrical reactor (brass, 50 mL) is equipped with a stirring bar. 2 copper tubes (length 1.2 m, 6 mm ∅) connected to the bottom inlets and coiled around the reactor, a teflon tubing (6 mm ∅) at the lid outlet, and a thermocouple, introduced through the lid into the reactor. Tightness of the system is achieved by teflon seal gaskets for the lid, the in- and the outlet openings towards the reactor side, and by pressure screw/ferule joints towards the tubing. The inlet copper tubes are connected by teflon tubing (6 mm ∅, pressure screw/ferule connection) to the pumps, the pump inlets via teflon tubes (6 mm ∅) to either the 2*H*-perfluoroethyl allyl ether **(1)** solution in THF (0.8 M) or to the *n*-BuLi solution (1.6 M in hexane), respectively. Positive N_2 pressure protects all the organolithium containing equipment.

Before the system is started, its integrity is checked by pumping hexane via both inlets. The whole flow reactor with the encoiled copper inlet tubing is immersed in a dry-ice/acetone bath (−78 °C; Figure 1).

Ethyl 2,2-Difluoro-4-pentenoate (4); Typical Procedure:
Allyl 1,1,2,2-tetrafluoroethyl ether (**1**; 2.1 kg, 13.3 mol) in THF (16.6 L) and *n*-BuLi in hexane (8.8 L, 1.6 M) are pumped at a rate of 40 mL/min and 20 mL/min, respectively, into the cooled flow-reactor system (−78 °C, dry-ice/acetone). Stirring is started. The onset of the reaction in the reactor is marked by a rise in the inside temperature from −74 °C to −45 °C. During the 7 h reaction period, the inside temperature varies around −50 °C (±5 °C). The cold outflow is run into an ice-cooled stirred solution of Et_3N (2.1 L, 15 mol) in absolute EtOH (1.6 L, 27.3 mol). For reasons of convenience, the mixture is quenched in 7 separate batches (of ~3.6 L each) with Et_3N (300 mL per batch)/EtOH (230 mL per batch). Then, each batch (~4.1 L) is diluted with pentane (1 L), the pH is adjusted to 6–7 by addition of 6 N aqueous HCl, and H_2O (1 L) is added. The organic layer is separated and the aqueous phase extracted with pentane (2 × 1 L). The combined organic layers are washed with H_2O (2 × 1.5 L) and dried (Na_2SO_4). The organic layers of the seven batches are combined and flash-evaporated (~45 L; rotary evaporator, 45 °C, 200–300 Torr) to a volume of ~2.3 L. Hydroquinone (2 g) is added and the mixture is flash-distilled by dropwise addition into a preheated flask (150 °C, oil-bath temperature; 20 Torr). The crude ester **4** (1.66 kg, 52% pure by GLC) is collected in a cooled (−78 °C) receiver. A second crop of ester is recovered from the distillate (~40 L) of the solvent flash evaporation. This distillate is carefully concentrated, first to a volume of ~15 L (rotary evaporator, 40 °C/500 Torr) and then further (1 m Vigreux column, 20–25 °C/20 Torr) to give more crude ester **4** (~500 g, 82% pure by GLC). The combined crude material is fractionally distilled at 24–25 °C/1 Torr (1 m Vigreux column, vacuum jacketed; condenser cooled to −30 °C; receiver cooled to −78 °C) to give ester **4**; yield: 1.1 kg (50%); purity: >95% (GLC); bp 69–71 °C/35 Torr.

$C_7H_{10}F_2O_2$	calc.	C 51.22	H 6.14
(164.2)	found	51.46	6.31.

IR ($CHCl_3$): ν = 1770 (C=O); 1645 (C=C) cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.35 (t, 3 H, J = 7.5 Hz, CH_3); 2.83 (dt, 2 H, J = 7, 17 Hz, CH_2CF_2); 4.33 (q, 2 H, J = 7.5 Hz, OCH_2); 5.37, 5.17 (br s, br d, 2 H, 2:1, $=CH_2$); 6.0–5.5 (m, 1 H, =CH–).

^{19}F-NMR ($CDCl_3/C_6F_6$): Φ = −106.7 (t, J = 17 Hz, CF_2).

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(1) For a recent review on syntheses of fluorinated starting materials, see: Knunyants, I.L., Yakobson, G.G. *Syntheses of Fluoroorganic Compounds*, Springer-Verlag, Berlin, 1985; 500 examples are given, 30 of these referring to compounds with less than three fluorine atoms; and only *one* (!), a difluorocyclopropane derivative, comprises a C–CF_2–C synthon.
(2) For some recent examples see: Martos Alcaniz, M.L., Patino, N., Condom, R., Ayi, A.I., Guedj, R. *J. Fluorine Chem.* **1987**, *35*, 70.
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(3) Hoechst AG, D-6000 Frankfurt/Main, West Germany.
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(5) Gerhart, F., Kolb, M., Leborgne, J.-F., Merrell Dow Research Institute, Strasbourg Center, 1987, to be published.
(6) Frieben, W., Gerhart, F., Kolb, M., Guillamot, G., Merrell Dow Research Institute, Strasbourg Center, 1987, to be published.