Synthesis of 2-fluoro-3-buten-1-ol

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Abstract

The synthesis of the previously unreported alcohol, 2-fluoro-3-buten-1-ol (**1**), was accomplished by the reaction of butadiene monoxide with pyridinium poly(hydrogen fluoride). Alcohol **1** was obtained as a mixture with pyridine after distillation. Direct use of the pyridine/fluoroalcohol mixture for reaction with t-butyldiphenylsilyl (TBDPS) chloride gave the silyl ether which was readily purified by silica gel chromatography. Ozonolysis of the silyl ether gave the corresponding fluoroaldehyde. The procedure described offers a useful route to **1** and its derivatives.

Introduction

The unique biological, chemical and physical properties of organofluorine compounds make methods for synthesizing them of considerable importance. The rapid progress made in the field of organofluorine compounds during the past decade could be attributed to the development and availability of selective fluorinating agents [1–5] that can be handled using standard laboratory apparatus and techniques, and due to the introduction of new fluorinated building blocks that are useful in the tactical placement of fluorine in a molecule [6–9]. However, monofluorinated structures are still difficult to obtain primarily because of the low selectivity during fluorination [10]. Hence monofluorinated building blocks are of great interest both in basic [11, 12] and in biomedicinal chemistry [13, 14]. This communication describes the preparation of 2-fluoro-3-buten-1-ol (**1**) and its further use for the preparation of the *O*-protected fluoroalkene (**2**) and the fluoroaldehyde (**3**) which are potentially useful monofluorinated intermediates.

Results and discussion

The preparation of fluorohydrins is very difficult, in general. Attempts to prepare **1** have been reported previously to be unsuccessful [15]. The methods that were tried are: (a) regioselective ring-opening of butadiene monoxide using either concentrated aqueous HF or HF in ether (50% solution)

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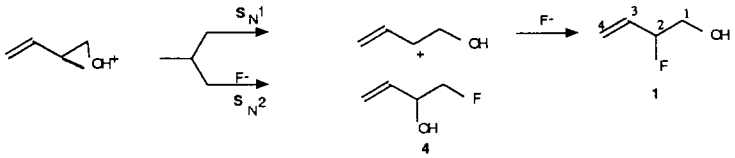
— this approach however, works very well in the synthesis of 2-chloro- and 2-bromo-3-buten-1-ol by reaction of butadiene monoxide with concentrated HCl or HBr [16]; and (b) halogen-exchange reaction using 2-bromo-3-buten-1-ol in a refluxing solution of NaF [17]. After numerous abortive attempts at the synthesis of **1**, we achieved success, albeit in only modest yields of 40%, employing a modified version of the reported synthesis of fluorohydrins from epoxides using pyridinium poly(hydrogen fluoride) [18]. The reaction allows the facile synthesis in gram quantities of the desired alcohol **1** as a mixture with pyridine. This mixture could be used directly for the preparation of the silyl ether **2**. The pyridine/alcohol ratio was determined by ^{1}H NMR spectroscopy from the ratio of the integrals of the pyridine proton at δ 7.6 ppm to that of the alkene proton of the fluoroalcohol at δ 5.85 ppm. Attempts to separate the pyridine from the desired alcohol by distillation were unsuccessful; the alcohol co-distilled with pyridine and appears to decompose during the distillation process. Heating a small amount of the **1**/pyridine mixture at 60 °C resulted in a darkening of the mixture and decomposition of the alcohol, as confirmed by NMR spectroscopy. The only ether that was isolated from reaction of the fluoroalcohol/pyridine mixture with t-butyldiphenylsilyl chloride was **2**, the silyl ether of 2-fluoro-3-buten-1-ol, suggesting that an $S_{N}1$ ring-opening of butadiene monoxide via a stabilized allylic cation is the favored pathway. The silyl ether of the alcohol, 1-fluoro-3-buten-2-ol (**4**), which would be expected from an $S_{N}2$ ring-opening, was not isolated from this reaction mixture.



In an attempt to increase the yield of **1**, several variations of the reaction of butadiene monoxide with the HF/pyridine complex were studied. In these studies, the yield of **1** was found to be dependent on the concentration of the HF/pyridine complex used, the temperature of the reaction during the addition of the HF/pyridine complex and on the addition of a cosolvent to the reaction mixture. The optimum yield was obtained with a 42% w/w solution of HF to pyridine (Table 1). At higher concentrations of HF/pyridine (70% w/w) a significant decrease in yield was observed. Maintaining the temperature of the reaction mixture at −10 °C during the addition of the HF/pyridine solution resulted in increased yields. Further, the use of chloroform as a cosolvent as opposed to neat HF/pyridine solutions also enhanced the yield of **1**. The use of HF/ether or HF/tetrahydrofuran in place of HF/pyridine under similar reaction conditions did not give the desired alcohol.

Experimental

A solution of HF/pyridine (42% w/w, 42 ml) and 50 ml of chloroform was stirred at −10 °C in a polypropylene vessel and under a well-ventilated

TABLE 1

Conditions used for the preparation of **1** from the HF/pyridine complex

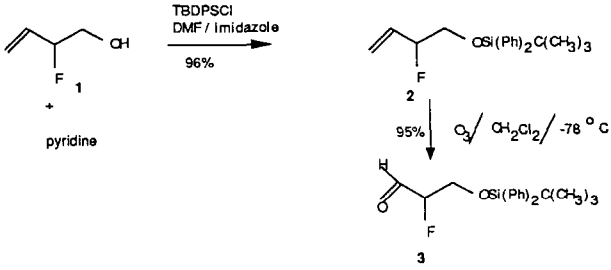
HF/py (% HF)	Reaction time (h)	Reaction temp. (°C)	Products	Yield[a] (%)	Solvent
70	3	−10	2-fluoro-3-buten-1-ol	15	chloroform
42	4	−10	2-fluoro-3-buten-1-ol	40	chloroform
30	4	−10	2-fluoro-3-buten-1-ol	15	chloroform
70	4	r.t.	2-fluoro-3-buten-1-ol	6	chloroform
70	4	0	no product	0	neat

[a] ^{1}H NMR spectroscopy was used to determine the alcohol/pyridine ratio in the mixture; the yield (crude) was calculated from this ratio multiplied by the weight of the mixture.

hood. To this chilled solution was added butadiene monoxide (10 g, 0.143 mol) over a period of 20 min whilst maintaining the reaction temperature at −10 °C. After the addition was complete, the solution was brought to room temperature and stirred for 3–4 h. The reaction mixture was then slowly poured into 200 ml of saturated ice-cold $NaHCO_3$ solution. (Note: if all the bicarbonate dissolved and the pH became acidic; more $NaHCO_3$ was added to the solution until neutral.) The aqueous layer was extracted with 2×200 ml of chloroform. The organic layer was dried over sodium sulfate and concentrated on a rotary evaporator to give 10 g of a light brown oil which was shown by NMR spectroscopy to be an approximately 50/50 mixture of the desired alcohol and pyridine (40% yield of alcohol). The alcohol/pyridine ratio was determined from the integral area of the proton of pyridine at δ 7.6 ppm and the single vinyl proton of the fluoroalcohol at δ 5.85 ppm. ^{1}H NMR ($CDCl_3$/TMS) δ: 8.6 (m, 2H, pyridine; 7.6 (m, 1H, pyridine); 7.2 (m, 2H, pyridine); 5.85 (m, 1H, C_3–H); 5.35 (m, 2H, C_4–H); 4.95 (m, 1H, J_{H-F} = 48.64 Hz, C_2–H); 3.7 (m, 2H, C_1–H) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 133.34 (d, $J_{C,F}$ = 18.93 Hz, C-3); 119.23 (d, $J_{C,F}$ = 11.57 Hz, C-4); 94.42 (d, $J_{C,F}$ = 169.10 Hz, C-2); 65.11 (d, $J_{C,F}$ = 23.35 Hz, C-1) ppm. Exact mass calc. for C_4H_7OF, 90.0481; found, 90.0477.

The ether **2** was prepared as follows: the alcohol/pyridine mixture (2.8 g) containing 1.4 g (15.5 mmol) of alcohol was dissolved in 5 ml DMF followed by the addition of 1.08 g (15.5 mmol) imidazole and 6.47 g (23.3 mmol) of t-butyldiphenylsilyl chloride. The reaction mixture was stirred at room temperature overnight and worked-up by partitioning between 100 ml water and 2×200 ml ethyl acetate. The organic layer was dried over sodium sulfate and the solvent removed on a rotary evaporator. The residue obtained was chromatographed on silica gel (kieselgel-60) eluting with ethyl acetate/hexane (5:95) to give **2** (5.0 g, 96% yield; R_f = 0.65, ethyl acetate/hexane (10:90)) as a colorless oil. ^{1}H NMR ($CDCl_3$/TMS) δ: 7.5 (m, 10 H, phenyl protons); 5.9 (m, 1H, C_3–H); 5.3 (m, 2H, C_4–H); 5.0 (m, 1H, J_{F-H} = 48.6 Hz, C_2–H); 3.8 (m, 2H, C_1–H); 1.1 (s, 9H, t-butyl) ppm. ^{13}C NMR ($CDCl_3$) δ: 136.26 (s, phenyl; 133.96 (d, $J_{C,F}$ = 19.14 Hz, C-3); 130.37 (s, phenyl);

128.33 (s, phenyl); 118.90 (d, $J_{C,F}=11.9$ Hz, C-4); 93.96 (d, $J_{C,F}=172.25$ Hz, C-2); 66.45 (d, $J_{C,F}=24.82$ Hz, C-1); 27.04 (s, $C(CH_3)_3$); 19.54 (s, $C(CH_3)_3$) ppm. The carbon assignments were made using the attached proton test (APT) experiment. Analysis: calc. for $C_{20}H_{25}FOSi$: C, 73.13; H, 7.67; F, 5,78%. Found: C, 73.23; H, 7.87; N, 5.67%.



The silyl aldehyde **3** was prepared by ozonolysis of a solution of **2** in methylene chloride at −78 °C. After the ozonolysis was complete, the ozonide was decomposed using dimethyl sulfide. This procedure gave the aldehyde in 95% yield which did not require further purification. ^{1}H NMR ($CDCl_3$/TMS) δ: 9.7 (d, 1H, $J_{F-H}=6.0$ Hz, C_3–H); 7.5 (m, 10 H, phenyl protons); 4.62 (m, 1H, C_2–H); 4.0 (m, 2H, C_1–H); 1.1 (s, 9H, t-butyl) ppm. ^{13}C NMR ($CDCl_3$) δ: 200.3 (d, $J_{C,F}=35.13$ Hz, C-3); 136.2 (s, phenyl); 130.55 (s, phenyl); 128.35 (s, phenyl); 95.51 (d, $J_{C,F}=172.25$ Hz, C-2); 63.75 (d, $J_{C,F}=20.52$ Hz, C-1); 27.91 (s, C $(CH_3)_3$); 19.47 (s, $C(CH_3)_3$) ppm. Analysis: calc. for $C_{19}H_{23}FO_2Si$: C, 69.06; H, 7.02: F, 5.75%. Found: C, 69.25; H, 7.51; F, 5.55%.

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