Large Scale Synthesis of 2-Fluoroacrolein

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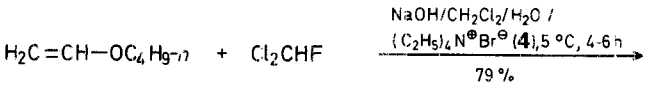
A large scale preparation of 2-fluoroacrolein (1) is achieved by refluxing the cyclopropyl ether (5), prepared by the addition of chlorofluorocarbene (3) to *n*-butyl vinyl ether (2), in *n*-butanol/pyridine mixture and subsequently hydrolysing the acetal 7 formed.

2-Fluoroacrolein (1) is used as a precursor for the preparation of alkyl or aryl 2-fluoroacrylates[1]. A one-pot synthesis of this aldehyde has been reported[2] and the method applied to the preparation of 2-fluorovinyl ketones[3]. In this procedure, a mixture of fluorodichloromethane, the appropriate enol ether, and oxirane is heated in an autoclave at 110 °C in the presence of a quaternary ammonium salt. The method is satisfactory for the preparation of small quantities of 2-fluoroacrolein (1). However on a multimolar scale the pressure in the autoclave increases suddenly from 20 to 300 bars[4] and this procedure becomes too dangerous to be used.

Halocyclopropyl ethers are known to undergo solvolysis to give α-fluoro-α,β-unsaturated carbonyl compounds[5,6]. They are usually prepared in a two phase system with crown ethers as catalyst. We have now developed a modified, economically attractive method for the synthesis of 2-fluoroacrolein (1). Chlorofluorocarbene, generated *in situ* from dichlorofluoromethane (3) under phase transfer conditions with sodium hydroxide as base and tetraethylammonium bromide (4) as catalyst, is condensed with *n*-butyl vinyl ether (2). A mixture of the *cis*- and *trans*-isomers of the cyclopropyl *n*-butyl ether 5 is obtained in 79% yield (*cis*/*trans* ratio = 58/42).



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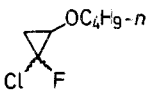

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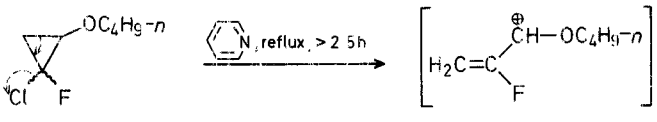
Solvolysis of the isomeric mixture 5 using sodium dodecyl sulfate[5] was incomplete[7]. The *trans*-isomer underwent complete ring opening while the *cis*-isomer was recovered unchanged. We have converted the mixture 5 to the acetal 7 by heating 5 in a mixture of *n*-butanol and pyridine (80% yield of 7). Regioselective opening of the cyclopropane ring of 5 gives the allylic cation 6 which reacts immediately with *n*-butanol to give the acetal 7. Acetal 7 is then hydrolysed by dilute hydrochloric acid to give 2-fluoroacrolein (1) in 83% yield (53% overall yield based on 2).



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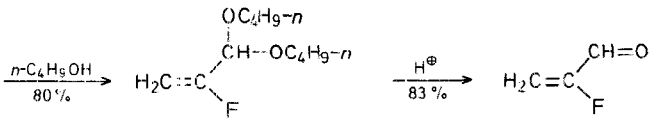

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The explosions observed in the autoclave when the method of Ref.[4] is performed on a large scale are probably caused by insufficient dissipation of heat resulting from ring opening of the excess oxirane or ring opening of the cyclopropane. Our method is safer as the cyclopropyl ether **5** is gradually added to a mixture of *n*-butanol and pyridine and it can be safely performed on a large scale[8].

The synthesis can be performed also with other vinyl ethers (ethyl, isobutyl) and under other phase transfer conditions (potassium hydroxide, triethylbenzylammonium chloride).

^{1}H-N.M.R. spectra (60 MHz, TMS) and ^{19}F.N.M.R. spectra (56.4 MHz, $CFCl_3$) were recorded on a Varian EM360L spectrometer. I.R. spectra were obtained on a Perkin-Elmer 167 instrument.

***cis*- and *trans*-2-*n*-Butoxy-*r*-1-chloro-1-fluorocyclopropane (5):**
Dichlorofluoromethane (**3**; Freon-21; 824 g, 8 mol) is bubbled into a vigorously stirred mixture of *n*-butyl vinyl ether (**2**; 700 g, 7 mol), dichloromethane (1.3 l), tetraethylammonium bromide (**4**; 21 g, 0.1 mol), and aqueous sodium hydroxide (1.9 l, 50% in weight, 37.5 mol) at 5–10 °C. Stirring at 5 °C is continued until the end of the reaction, as controlled by ^{1}H-N.M.R. (no signal for the vinyl protons; between 4 and 6 h). Water (6.5 l) is then added, the two layers are separated, and the aqueous layer is extracted with dichloromethane (2 × 1000 ml). The organic phase is washed with brine (500 ml) and the solvent distilled off. The residue is dried by azeotropic distillation with 1,2-dichloroethane (200 ml) and distilled to give **5** as a mixture of the two isomers *cis* (58%) and *trans* (42%); yield: 926 g (79%); b.p. 55 °C/16 torr.

$C_7H_{12}ClFO$	calc.	C 50.46	H 7.26
(166.6)	found	50.49	7.26

I.R. ($CHCl_3$): ν = 2910, 2860, 1440, 1380, 1350 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.7–2.0 (m, 9 H); 3.4–3.95 ppm (m, 3 H).

^{19}F-N.M.R. ($CDCl_3$): δ = −138 ppm (*cis*-isomer, 8 lines, $^3J_{FH}$ = 7.5, 13 and 18.8 Hz); −160 ppm (*trans*-isomer, 5 lines).

1,1-Di-*n*-butoxy-2-fluoro-2-propene (7):
Compound **5** (666 g, 4 mol) is added to a refluxing mixture of *n*-butanol (888 g, 12 mol) and pyridine (347 g, 4.4 mol). The reflux is kept for at least 2.5 h until the end of the reaction, controlled by ^{19}F-N.M.R. (no signal for the fluorocyclopropyl group). The mixture is cooled and water (500 ml) is added until dissolution of the salt. The two layers are separated and the organic phase is washed with brine (2 × 300 ml), dried with magnesium sulfate, and *n*-butanol is distilled off. Distillation of the residue gives 1,1-di-*n*-butoxy-2-fluoro-2-propene (**7**); yield: 653 g (80%); b.p. 64–67 °C/4 torr.

$C_{11}H_{21}FO_2$	calc.	C 64.67	H 10.36
(204.3)	found	64.94	10.01

I.R. ($CHCl_3$): ν = 2960, 2880, 1685, 1475, 1390, 1370 cm^{-1}

^{1}H-N.M.R. ($CDCl_3$): δ = 0.7–1.8 (m, 14 H); 3.4–3.8 (m, 4 H); 4.4–5.3 ppm (8 lines, 3 H).

^{19}F-N.M.R. ($CDCl_3$): δ = −113 ppm (8 lines, $^3J_{FH}$ = 3, 16.5 and 49 Hz).

2-Fluoroacrolein (1):
A mixture of 1,1-di-*n*-butoxy-2-fluoro-2-propene (**7**; 408 g, 2 mol) and 1 normal hydrochloric acid (750 ml) is refluxed in a still with a total condensation variable take off type head. When the temperature is stabilized at 77–78 °C, distillation is started and continued until the temperature reaches 93 °C (*n*-butanol/water azeotrope). The distillate is dried with calcium chloride and distilled from bulb to bulb at 20 torr (The receiver is cooled at −78 °C). This experimental part is repeated. The condensate is distilled to give 2-fluoroacrolein (**1**); yield: 123 g (83%); b.p. 71–72 °C (Lit.[2], b.p. 71 °C; Lit.[4], b.p. 71–72 °C; Lit.[7], b.p. 80 °C).

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[7] 2-Fluoroacrolein (**1**) was recently obtained in 38% by this method: Camps, F., Coll, J., Fabrias, G., Guerrero, A. *Tetrahedron* **1984**, *40*, 2871.
[8] We thank Lampin, J.P., Nonat, A., Vignal, G., IRCHA, for having performed the reaction on a multimolar scale (up to 200 mol).