An Expeditious Synthesis of 3-Fluoroacrylic Acid[1]

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Although variously fluorinated esters of acrylic acid have found important application as monomers in the polymer field, the chemistry of β-fluorinated acrylic acids and esters has received little attention.[2] On the other hand, acrylates and related derivatives have proved to be versatile building blocks in organic synthesis, *e.g.*, as dienophiles[3] or as Michael acceptors.[4]

In an attempted route to 6-fluoroshikimic acid we needed 3-fluoroacrylic acid (**1**) as a possible dienophile for a Diels–Alder reaction with furan.[5]

$$\underset{\mathbf{1}}{CHF{=}CHCO_2H}$$

Two routes to either the acid itself or some of its esters were previously reported by our group. The first approach involved a regioselective Baeyer–Villiger oxidation of 2-chloro-2-fluoroethyl isopropyl ketone, followed by a dehydrochlorination step and subsequent cleavage of the ester by trimethylsilyl iodide.[6] The second method, leading to the corresponding ethyl ester, employed a photochemical addition of tribromofluoromethane to ethyl vinyl ether. At the penultimate step, a vinylic bromine reduction was achieved with tributyltin hydride.[7] While only the *E* acid was produced by the first method, the second approach led to a 70:30 *Z*/*E* mixture of esters. More recently, a five-step synthesis of ethyl β-fluoroacrylate and β-fluoromethacrylate, as well as the corresponding nitriles, was described starting from the parent Michael acceptors. A fluoro-Pummerer rearrangement of sulfoxides mediated by (diethylamino)sulfur trifluoride (DAST) was used as the key fluorination step.[8]

We report here a three step synthesis leading *directly* to 3-fluoroacrylic acid (**1**). Introduction of fluorine was realized through regioselective photochemical addition of carbon tetrabromide to vinyl fluoride (**2a**) in pentane, leading in acceptable yield to the 1:1 adduct **3a** as the main fluorinated compound (Scheme I). Bromoform was also formed in the reaction along with the mixture of other byproducts probably deriving from the solvent.[9]

Scheme I

$$\underset{\substack{\mathbf{2a},\ X=H\\ \mathbf{b},\ X=F}}{CFX{=}CH_2} \xrightarrow[h\nu]{CBr_4} \underset{\mathbf{3}}{CFXBrCH_2CBr_3} \xrightarrow{HNO_3} \underset{\mathbf{4}}{CFXBrCH_2CO_2H}$$

Incidentally and as a possible route to 3,3-difluoroacrylic acid (**5**),[10] we also examined the photochemical addition of carbon tetrabromide to 1,1-difluoroethylene (**2b**). As expected, the adduct **3b** was also formed as the major fluorinated product in 25% isolated yield.[9]

The regiochemistry of radical addition to fluoroolefins **2a** and **2b** was in line with literature precedent. Haszeldine first reported the regiospecific addition of trifluoromethyl iodide to fluoroethylene under ultraviolet irradiation, leading to 1,1,1,3-tetrafluoro-3-iodopropane.[11] A similar observation was made by Tarrant *et al.* in the thermal, peroxide-promoted addition of dibromodifluoromethane to fluoroethylene and 1,1-difluoroethylene which proceeded *via* attack of the bromodifluoromethyl radical at the methylene carbon of the olefin. Under the conditions used, significant proportions of 2:1 addition products were also formed.[12]

Owing to the presence of various more volatile byproducts and also of unreacted carbon tetrabromide, thorough purification of the adducts **3a** and **3b** by distillation and then flash column chromatography was required. Subsequent hydrolysis of their tribromomethyl group with fuming nitric acid at 80 °C led to the carboxylic acids **4a** and **4b**, respectively, in good yields, despite rather drastic reaction conditions. Hydrogen bromide was evolved during the reaction. Albeit unusual, such a hydrolysis with nitric acid is precedented with trichloromethyl groups.[13,14] Initially, we studied the radical addition of carbon tetrachloride to vinyl fluoride and 1,1-difluoroethylene, leading to the chlorinated analogs of the adducts **3**. In fact, the trichloromethyl group of these tetrachloroalkanes was found to be resistant to hydrolysis not only in concentrated sulfuric acid[14] or oleum but also in warm

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(2) (a) For a review on various fluoroacrylates (except the β-fluorinated ones) and their polymers, see: Boutevin, B.; Pietrasanta, Y. In *Les acrylates et polyacrylates fluorés, dérivés et applications*; Erec, Ed.; Puteaux: France, 1988; pp 25–246. (b) See also for α-fluoroacrylates the recent review: Boguslavskaya, L. S.; Panteleeva, I. Yu; Morozova, T. V.; Kartashov, A. V.; Chuvatkin, N. N. *Russ. Chem. Rev. (Engl. Transl.)* **1990**, *59*, 906. See also: Gassen, K.-R.; Bielefeldt, D.; Marhold, A.; Andres, P. *J. Fluorine Chem.* **1991**, *55*, 149. Dapperheld, S.; Heumüller, R.; Ulmschneider, D. *J. Fluorine Chem.* **1991**, *54*, 74 (abstract of a paper presented at the 13th International Symposium on Fluorine Chemistry, Bochum, Germany, Sept 2–6, 1991).

(3) See, for example: (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. (b) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299.

(4) For a comprehensive review on conjugate additions to alkenoic acid derivatives, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*: Baldwin, J. E., Magnus, P. D., Eds.; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1992; Vol. 9, pp 199–282.

(5) For a closely related work using ethyl 3,3-difluoroacrylate, see: Leroy, J.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1987**, *52*, 290.

(6) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1984**, *25*, 447.

(7) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1989**, *45*, 155 (abstract of a paper presented at the IXth European Symposium on Fluorine Chemistry, Leicester, U.K., Sept. 4–8, 1989).

(8) Krishnan, G.; Sampson, P. *Tetrahedron Lett.* **1990**, *31*, 5609.

(9) ^{19}F NMR spectrum of the crude product showed an additional signal (ddd) at −134.5 ppm, tentatively assigned to the regioisomer of **3a** (14% by integration of the two signals). However, this compound was neither isolated nor fully identified (see also Experimental Section). Similarly, during the preparation of **3b**, an additional triplet was found at −49.6 ppm in the ^{19}F NMR spectrum of the crude mixture, which was tentatively attributed to the regioisomer of **3b** (25% by integration).

(10) Previous reported synthetic routes to 3,3-difluoroacrylates: (a) Dickey, J. B.; McNally, J. G. U.S. Patent 2,571,687, 1951; *Chem. Abstr.* **1951**, *46*, 4279c. Knunyants, I. L.; Sterlin, R. N.; Bogachev, V. E. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1958**, 425; *Engl. Transl.* **1958**, 407. (c) Archibald, T. G.; Baum, K. *J. Org. Chem.* **1990**, *55*, 3562. See also refs 5 and 6 above. For the preparation of the acid, see: (d) Gillet, J. P.; Sauvêtre, R.; Normant, J. F. *Synthesis* **1982**, 297. For the acid fluoride and the anhydride, see: (e) Brahms, J. C.; Dailey, W. P. *J. Org. Chem.* **1991**, *56*, 900.

(11) Haszeldine, R. N.; Steele, B. R. *J. Chem. Soc.* **1953**, 1199.

(12) Tarrant, P.; Lovelace, A. M.; Lilyquist, M. R. *J. Am. Chem. Soc.* **1955**, *77*, 2783.

(13) Freidlina, R. Kh; Vasile'va, E. I. *Dokl. Akad. Nauk SSSR* **1955**, *100*, 85; *Chem. Abstr.* **1956**, *50*, 1578i.

(14) Nesmeyanov, A. N.; Freidlina, R. Kh.; Zakharkin, L. I.; Vasil'eva, E. I.; Kost, V. N.; Vasil'eva, T. T. *Zh. Obshch. Khim.* **1957**, *27*, 2418; *J. Gen. Chem. USSR (Engl. Transl.)* **1957**, *27*, 2481.

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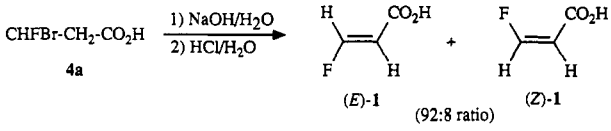
fuming nitric acid. For these reasons, we turned to the more labile tribromomethyl group.

We anticipated that the ultimate step, *i.e.*, dehydrobromination of the acids **4** with a base, could be delicate since it must be conducted rather unconventionally in the presence of a carboxylate moiety. Among the tertiary amines, triethylamine had already proved useful for the clean dehydrochlorination of isopropyl 3-chloro-3-fluoro-[6] and 3-chloro-3,3-difluoropropanoates[10c] as well as for dehydrobromination of ethyl 3-bromo-3,3-difluoropropanoate.[5] The use of triethylamine in dichloromethane to dehydrobrominate the acid **4a** was unsatisfactory as only traces of the expected acid **1** (*E* isomer) were evident by NMR spectral analysis. Although some acid (*E*)-**1** was



laboriously obtained by treating **4a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, best results were finally obtained with simple aqueous sodium hydroxide, allowing the isolation of a 92:8 mixture of acids (*E*)- and (*Z*)-**1** in 49% overall yield. Solid acid (*E*)-**1** was obtained in pure form by simple adsorption of the low-melting mixture on a porous plate.

Unfortunately, an attempted dehydrobromination of acid **4b** using sodium hydroxide led to the loss of fluorine by hydrolysis of the sensitive difluoromethylene moiety. Neither of the two amine bases examined above for the dehydrobromination of **4a** proved effective with **4b**. Although formation of 2,2-difluoroacrylic acid (**5**) could be evidenced by ^{19}F NMR spectral analysis after reaction of **4b** at 0 °C with DBU in dichloromethane, isolation of the sensitive free acid after acidic treatment was difficult. On the other hand, use of triethylamine in dichloromethane led invariably to an inseparable mixture mainly containing the desired acid **5** and 3,3,3-trifluoropropanoic acid (**6**).

$$\underset{\mathbf{4b}}{CF_2BrCH_2CO_2H} \xrightarrow{Et_3N} \underset{\mathbf{5}}{CF_2{=}CHCO_2H} + \underset{\mathbf{6}}{CF_3CH_2CO_2H}$$

The proportion of the acid **6** was found to increase dramatically by prolonging the reaction time. Formation of the trifluoromethylated compound by disproportionation has already been observed in the dehydrochlorination of cyclohexyl 3-chloro-3,3-difluoropropanoate with triethylamine.[6] Despite our failure to prepare satisfactorily 3,3-difluoroacrylic acid by this route, its esters remain easily accessible after prior esterification of the acid **4b** followed by a dehydrobromination step with triethylamine as already described.[5,10c] For example, the acid **4b** was readily esterified with diazomethane and the resulting methyl ester subsequently dehydrobrominated with triethylamine to give methyl 3,3-difluoroacrylate.

In conclusion, the adducts obtained photochemically from carbon tetrabromide and fluoro-substituted ethylenes are valuable precursors of 3-bromo-3-fluoro- and 3-bromo-3,3-difluoropropanoic acids. 3-Fluoroacrylic acid can be reliably prepared from the former acid.

Experimental Section

CAUTION. The photochemical reactions with low-boiling gases should be conducted behind an adequate safety shield. The reactions with fuming nitric acid should also be conducted behind a safety shield and under an efficient hood.

General. ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200.13, 188.3, and 50.3 MHz, respectively. NMR chemical shifts (δ) are reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. Melting points were determined on a Mettler FP-61 apparatus. Irradiations were conducted with a 125-W UV lamp (mercury H.P.K. type, Philips, Holland). Silica gel 60 Merck (230–400 mesh) was used for flash chromatography.

1,1,1,3-Tetrabromo-3-fluoropropane (3a). A *ca.* 170-mL heavy-walled Pyrex vial (*ca.* 16 × 210 mm) equipped with a Teflon stopper and a magnetic stirrer was charged with pentane (30 mL) and carbon tetrabromide (35 g, 0.105 mol). The suspension was cooled at −120 °C, and 1-fluoroethylene gas (6.5 g, 0.141 mol) was condensed in. The vial was securely closed and allowed to warm to room temperture, an the mixture was irradiated for 48 h under stirring. After being cooled at −120 °C, the vial was opened and the solution allowed to degass on warming. Dichloromethane was added (100 mL), and the solution was washed with water (2 × 75 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation under reduced pressure. The residual liquid was distilled. A first fraction, boiling up to 75 °C (15 mmHg), was collected and submitted to a preparative gas chromatographic separation (30% SE-30 column); ^1H NMR spectral analysis of the two main fractions collected revealed, by order of elution, the presence of (substituted) alkane(s) (alkyl chains located at δ *ca.* 0.80–1.85 and multiplets at δ *ca.* 3.3–4.16) then of bromoform (δ 6.75). The second distillation fraction, boiling at 75–120 °C (15 mmHg), was purified by flash chromatography (pentane) affording **3a** as a colorless liquid (19.0 g, 50.3 mmol, 48% from CBr_4, 36% from 1-fluoroethylene), bp 219–221 °C (Siwoloboff's method[15]): ^1H NMR δ 3.96 [ddd (*ABMX*), 1 H, $^3J_{HF}$ = 25.7 Hz, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 2.2 Hz, H-2), 4.26 [ddd (*ABMX*), 1 H, $^2J_{HH}$ = 15.9 Hz, $^3J_{HF}$ = 14.7 Hz, $^3J_{HH}$ = 7.4 Hz, H-2′), 6.89 (ddd, 1H, $^2J_{HF}$ = 50.7 Hz, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 2.2 Hz, H-3); ^{19}F NMR δ −131.16 (ddd). Anal. Calcd for $C_3H_3Br_4F$ (377.671): C, 9.54; H, 0.80; F, 5.03; Br, 84.63. Found: C, 9.84; H, 0.83; F, 4.81; Br, 86.05.

3-Bromo-3-fluoropropanoic Acid (4a). 1,1,1,3-Tetrabromo-3-fluoropropane (**3a**) (19.0 g, 50.3 mmol) was added with stirring to fuming nitric acid (*d* 1.48, 29 mL) at 80 °C with gentle bubbling of argon through the acid. After rapid addition of *ca.* 1.5 mL of **3a**, an exothermic reaction took place and abundant red vapors evolved. Slower dropwise addition was continued. At the end of addition, heating and argon bubbling were maintained for *ca.* 30 min to 1 h until the red solution faded. After cooling, water was added (20 mL) and the mixture was continuously extracted overnight with dichloromethane. After concentration, crude **4a** (probably containing traces of nitric acid) was obtained as a pale yellow liquid (10.42 g) which was purified by distillation. The acid **4a** was obtained as a viscous, pale yellow liquid (6.6 g, 77%), bp 110–113 °C (23 mmHg): ^1H NMR δ 3.25 [ddd (*ABMX*), 1H, $^3J_{HF}$ = 23.8 Hz, $^2J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 4.9 Hz, H-2], 3.42 [ddd (*ABMX*), 1 H, $^2J_{HH}$ = 17.0 Hz, $^3J_{HF}$ = 12.4 Hz, $^3J_{HH}$ = 6.9 Hz, H-2′), 6.72 (ddd, 1 H, $^2J_{HF}$ = 49.5 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HF}$ = 4.9 Hz, H-3); ^{19}F NMR δ −134.89 (ddd); ^{13}C NMR δ 45.55 (d, $^2J_{CF}$ = 23.3 Hz, C-2), 87.99 (d, $^1J_{CF}$ = 251.6 Hz, C-3), 173.96 (d, $^3J_{CF}$ = 6.2 Hz, C-1).

3-Fluoroacrylic Acid (1). 9 M Aqueous sodium hydroxide (8.4 mL, 76 mmol) was added dropwise to the stirred (solid) acid **4a** (7.8 g, 45.6 mmol) cooled at 0 °C. Liquefaction readily occurred. The resulting mixture was stirred for 20 min at 0 °C and was then acidified to pH 2 with 10 M HCl (the pale yellow solution discolored). The two-phase mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over granular calcium chloride. After filtration, several hydroquinone crystals were added and the solvent was distilled off. The residual liquid was distilled through a Vigreux column under reduced pressure (200 mmHg) to give partially crystallized **1** as a 92:8 *E*/*Z* mixture (2.01 g, 22.3 mmol, 49%), bp ~90–95 °C (200 mmHg). Pure acid (*E*)-**1** was obtained as a white microcrystalline powder by crushing the refrigerator-cooled semioily mixture on a porous plate, mp 40.9–41.7 °C (lit.[6] mp 38 °C): ^1H

(15) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of practical organic chemistry*, 5th ed.; Longman Scientific and Technical: Essex, 1989; p 242.

NMR (*E* isomer) δ 5.76 (dd, 1 H, $^3J_{HF}$ = 14.1 Hz, $^3J_{HH}$ = 11.2 Hz, H-2), 7.61 (dd, 1 H, $^2J_{HF}$ = 78.6 Hz, $^3J_{HH}$ = 11.2 Hz, H-3), 11.09 (broad s, 1 H, CO_2H); ^{19}F NMR (*E* isomer) δ −105.89 (dd, $^2J_{FH}$ = 78.6 Hz, $^3J_{FH}$ = 14.1 Hz); ^{13}C NMR (*E* isomer) δ 106.29 (d, $^2J_{CF}$ = 15.3 Hz, C-2), 164.88 (d, $^1J_{CF}$ = 283.8 Hz, C-3), 171.43 (d, $^3J_{CF}$ = 23.9 Hz, C-1); IR (CCl_4) (*E* isomer) ν 3300–2500, 1704, 1653, 1428, 1318, 1295, 1250, 1238 cm^{-1}; ^{1}H NMR (*Z* isomer, not isolated) δ 5.35 (dd, 1 H, $^3J_{HF}$ = 36.6 Hz, $^3J_{HH}$ = 5.4 Hz, H-2), 6.86 (dd, 1 H, $^2J_{HF}$ = 77.0 Hz, $^3J_{HH}$ = 5.4 Hz, H-3), ~11.5 (broad s, CO_2H); ^{19}F NMR (*Z* isomer) δ −96.91 (dd, $^2J_{FH}$ = 77.0 Hz, $^3J_{FH}$ = 36.6 Hz); ^{13}C NMR (*Z* isomer) δ 103.28 (d, $^2J_{CF}$ = 3.8 Hz, C-2), 159.19 (d, $^1J_{CF}$ = 293.1 Hz, C-3), 168.86 (s, C-1). Anal. Calcd for $C_3H_3FO_2$ (*E* isomer) (90.053): C, 40.01; H, 3.36; F, 21.10. Found: C, 39.99; H, 3.08; F, 21.80.

1,1,1,3-Tetrabromo-3,3-difluoropropane (3b). This compound was prepared by the same procedure as for **3a** using the following amounts of materials: carbon tetrabromide (33.5 g, 0.1 mol), pentane (30 mL), and 1,1-difluoroethylene (7.8 g, 0.12 mol). The mixture was irradiated for 3 d and treated as for **3a**. The crude liquid obtained after workup was distilled under reduced pressure through a Vigreux column, and the fraction boiling at 90–92 °C (15 mmHg) was collected. The liquid was purified by flash chromatography (pentane) to provide **3b** as a colorless oil (10 g, 25.2 mmol, 25% from CBr_4, 21% from 1,1-difluoroethylene), bp 209–211 °C (Siwoloboff's method[15]): ^{1}H NMR δ 4.36 (t, $^3J_{HF}$ = 12.8 Hz, C-2); ^{19}F NMR δ −45.97 (t, $^3J_{FH}$ = 12.8 Hz); ^{13}C NMR δ 22.33 (s, C-1), 67.60 (t, $^2J_{HF}$ = 20.6 Hz, C-2), 117.41 (t, $^1J_{CF}$ = 312.2 Hz, C-3). Anal. Calcd for $C_3H_2Br_4F_2$ (396.661): C, 9.11; H, 0.51; Br, 80.78; F, 9.60. Found: C, 9.36; H, 0.39; Br, 78.48; F, 8.95.

3-Bromo-3,3-difluoropropanoic Acid (4b). This acid was obtained by hydrolysis of **3b** (10 g, 25.2 mmol) with fuming nitric acid (14.5 mL) under the same conditions as for **4a**. Continuous extraction of the reaction mixture with CH_2Cl_2 afforded crude **4b** (4.62 g, 97%) as a pale yellow liquid. Redistillation under reduced pressure was accompanied with evolution of red vapors. A main fraction was obtained as an orange liquid, bp ~90–95 °C (17 mmHg): ^{1}H NMR δ 3.53 (t, 1 H, $^3J_{HF}$ = 12.9 Hz, C-2), 114 (broad s, CO_2H); ^{19}F NMR δ −44.25 (t, $^3J_{FH}$ = 12.9 Hz).