



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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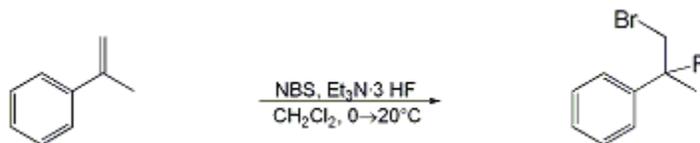
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 10, p.128 (2004); Vol. 76, p.159 (1999).

BROMOFLUORINATION OF ALKENES: 1-BROMO-2-FLUORO-2-PHENYLPROPANE

[Benzene, (2-bromo-1-fluoro-1-methylethyl)]



Submitted by Günter Haufe¹, Gerard Alvernhe², André Laurent², Thomas Ernet¹, Olav Goj¹, Stefan Kröger¹, and Andreas Sattler¹.

Checked by Dudley W. Smith and Stephen F. Martin.

1. Procedure

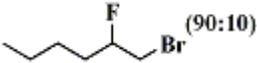
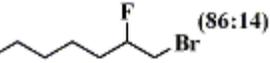
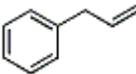
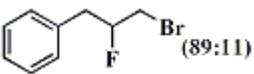
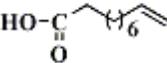
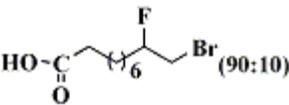
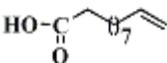
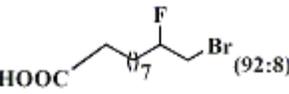
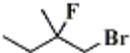
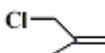
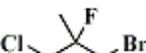
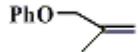
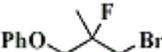
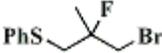
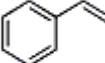
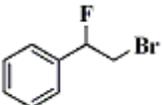
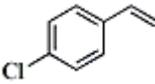
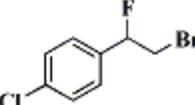
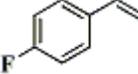
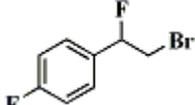
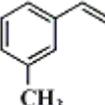
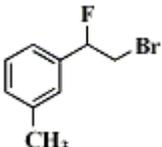
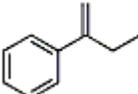
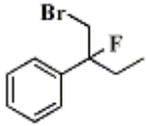
1-Bromo-2-fluoro-2-phenylpropane (Note 1). A magnetically stirred mixture of *α*-methylstyrene (7.1 g, 60 mmol) (Note 2), triethylamine trihydrofluoride (Note 3) and (Note 4) (14.7 mL, 90 mmol) and dichloromethane (Note 5) (60 mL) contained in a 250 mL, single-necked, round-bottomed flask is treated with *N*-bromosuccinimide (11.8 g, 66 mmol) (Note 6) at 0°C. After 15 min, the bath is removed, and stirring is continued at room temperature for 5 hr (Note 7). The reaction mixture is poured into ice water (1000 mL), made slightly basic with aqueous 28% ammonia (Note 8), and extracted with dichloromethane (4 × 150 mL). The combined extracts are washed with 0.1 N hydrochloric acid (2 × 150 mL) and 5% sodium hydrogen carbonate solution (2 × 150 mL) and then dried over magnesium sulfate. After removal of the solvent by rotary evaporation, the crude product is distilled (Note 9) to give the product: 11.6 g (89%); bp 50-52°C (0.15 mm), n_D^{20} 1.5370 (Note 10).

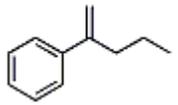
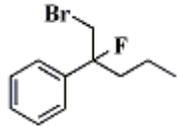
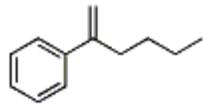
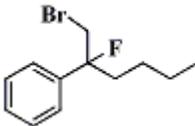
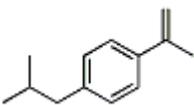
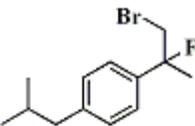
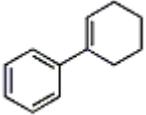
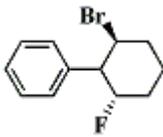
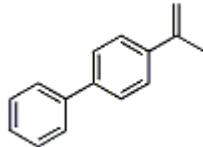
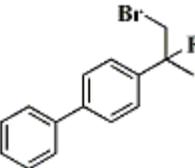
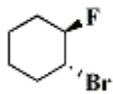
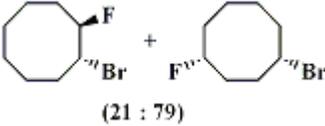
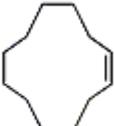
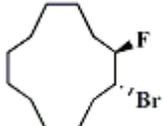
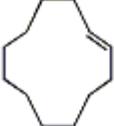
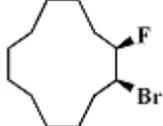
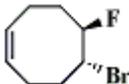
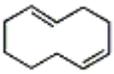
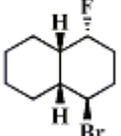
2. Notes

1. Other 1-bromo-2-fluoro compounds that may be prepared following this procedure are listed in the Table.

TABLE
BROMOFLUORINATION OF ALKENES WITH THE REAGENT
COMBINATION *N*-BROMOSUCCINIMIDE/TRIETHYLAMINE
TRISHYDROFLUORIDE

Substrate	Product (ratio of regioisomers) ¹	Reaction time	Temperature	B.p. (mm)	Isolated yield (%)
	(94:6)	15 hr	-78°C	72°C	70
	(94:6)	15 hr	-20°C	75-77°C	73
	(92:8)	15 hr	r.t.	50°C (18)	78
	(80:20)	15 hr	r.t.	42°C (18)	60
		15 hr	r.t.	55°C	66

					(18)	
						
		15 hr	r.t.	70°C (18)	65	
		5 hr	r.t.	69-70°C (0.8)	83	
		5 hr	r.t.	M.p. 49°C	91	
		5 hr	r.t.	M.p. 59°C	95	
		15 hr	r.t.	101- 102°C	53	
		15 hr	r.t.	90°C (18)	68	
		18 hr	r.t.	57°C (12)	92	
		12 hr	r.t.	n.d. ²	88(crude)	
		12 hr	r.t.	n.d. ²	61	
		5 hr	r.t.	n.d. ²	85	
		18 hr	r.t.	n.d. ²	63	
		18 hr	r.t.	n.d. ²	63	
		5 hr	r.t.	n.d. ²	81	
		14 hr	r.t.	n.d. ²	94	

		14 hr	r.t.	M.p. 22°C	93
		14 hr	r.t.	n.d. ²	93
		14 hr	r.t.	n.d. ²	80
		15 hr	r.t.	M.p. 66°C	44
		14 hr	r.t.	M.p. 52°C	90
		5 hr	r.t.	76-77° C (18)	88
		5 hr	r.t.	49°C (0.09)	13 and 42 ²
		5 hr	r.t.	79-80° C (0.1)	95
		5 hr	r.t.	82-83° C (0.1)	91
		5 hr	r.t.	43°C (0.06)	71 ⁴
		5 hr	r.t.	65-66° C (0.15)	78 (GC) ⁴

¹Determined by ¹⁹F NMR; other regioisomers 2-bromo-1-fluoroalkanes.

²Isolated by column chromatography. Chromatography was done in a 20-cm glass column of 2-cm diameter with 25 silica gel (70-260 mesh, Merck) per g of the bromofluoride using about 500 mL of the cyclohexane/ethyl acetate (9:1).

³In addition 18% of 5-bromocyclooctene was isolated.

⁴In addition two isomeric 2-bromo-6-fluoro-cis-bicyclo[3.3.0]octanes were formed (together 8%)

⁵Plus additional isomers (Ref. ³).

2. The submitters have scaled this procedure up to 100 mmol for several alkenes in the Table and to a 400-mmol scale for 1-pentene.

3. Triethylamine trihydrofluoride is less corrosive than Olah's reagent^{5,6} or anhydrous hydrogen fluoride itself, but all contact with the skin must still be avoided. The reagent has been tested for laboratory use only. The experiments should be done under an efficient hood.

4. Triethylamine trihydrofluoride⁷ is an oily liquid that does not attack borosilicate glassware. The checkers purchased it from Aldrich Chemical Company, Inc., but it is also available from Fluka Chemical Corp. and other suppliers.

5. Dichloromethane was dried over calcium hydride and distilled.

6. N-Bromosuccinimide was purchased from Aldrich Chemical Company, Inc., and used without purification; the purity of the compound is about 90%.

7. The reaction times for other olefins are given in the Table.

8. About 25-30 mL of aqueous 28% ammonia is necessary to make the solution slightly basic. If the aqueous layer is not made basic (pH 9-10), decomposition of the product is observed during distillation.

9. The distillation was performed using a 5-cm Vigreux column; there was no forerun. The product is somewhat sensitive to light and temperature.

10. Spectral data for the product were: ¹H NMR (300 MHz, CDCl₃) δ: 1.74 (3 H, d, ³J_{HF} = 21.9, CH₃), 3.57 (1 H, ²J_{AB} = 11.4, ³J_{HF} = 22.8, CH₂Br), 3.61 (1 H, ²J_{AB} = 11.4, ³J_{HF} = 15.8, CH₂Br), 7.27 (m, 5 H, arom. H); ¹³C NMR (75.5 MHz, CDCl₃) δ: 25.3 (d, ²J_{CF} = 24.3, CH₃), 40.3 (d, ²J_{CF} = 28.3, CH₂Br), 94.3 (d, ¹J_{CF} = 178.7, CF), 124.1 (d, ³J_{CF} = 9.2, o-C), 128.0 (p-C), 128.3 (d, ⁴J_{CF} = 1.1, m-C), 141.3 (d, ²J_{CF} = 21.6, ipso-C); ¹⁹F NMR (188 MHz, CDCl₃, CFCl₃) δ: -147.5 (m); (GC-MS (70 eV): m/z (%): 216/218 (9) [M⁺], 196/198 (1) [M⁺-HF], 123 (100) [M⁺-CH₂Br]; HRMS, 217.0039 (Calcd for C₉H₁₀BrF, 217.0028).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Fluorinated organic compounds are receiving increased interest because of their biological activity. One of the most useful methods for introducing single fluorine substituents into a molecule is by the halofluorination of unsaturated substrates. Although a number of reagents are available for effecting the bromofluorination of alkenes,^{5,6} each suffers some disadvantage(s). The combination of N-bromosuccinimide, which is a source of electropositive bromine, and Et₃N·3HF is a very convenient reagent for effecting the efficient bromofluorinations of various alkenes.⁴

The formal electrophilic addition of "BrF" to a double bond proceeds stereospecifically in an anti-sense as evidenced by the formation in high yields of trans-1-bromo-2-fluorocycloalkanes from cis-cycloalkenes or of cis-1-bromo-2-fluorocyclododecane from trans-cyclododecene, respectively.⁴ The addition is regioselective with the observed regiochemistry being in accordance with the Markovnikov rule. For example, the bromofluorinations of α-substituted styrenes give the 1-bromo-2-fluoro-2-phenylalkanes with virtually complete regioselectivity; only traces (<1%) of the regioisomeric adducts were detectable by ¹⁹F NMR spectroscopy of the crude reaction mixtures. In the bromofluorinations of other simple α-olefins such as 1-alkenes or allylbenzene, the Markovnikov products also predominate (9:1 to 19:1) over the corresponding anti-Markovnikov compounds. Very high regioselectivity has also been found for the bromofluorination of methallyl chloride and methallylphenyl ether,⁸ whereas with methallylphenylthio ether and ω-unsaturated fatty acids,⁹ the selectivity is about 9:1 favoring the

Markovnikov product.

In unsaturated hydrocarbon systems where Wagner-Meerwein-type rearrangements, transannular hydrogen shifts or transannular π -participations are possible, such reactions do occur.³⁻¹⁰ Moreover, in the bromofluorination of 9-oxabicyclo[6.1.0]non-4-ene, a transannular reaction involving oxygen participation has been observed.¹¹

This method for bromofluorination of ethylenic compounds has been extended by others to symmetrical alkenes,¹² terminal allylic alcohols,¹³ vinyl oxiranes,¹⁴ enol esters,¹⁵ and vinyl fluorides.¹⁶

Bromofluoro compounds are themselves useful starting materials for the preparation of monofluorinated compounds. For example, reduction of 1-bromo-2-fluorocyclododecanes with tributyltin hydride gives fluorocyclododecane, while other methods to produce this compound have been unsuccessful.¹⁷ The elimination of hydrogen bromide from vicinal bromofluorides also gives vinyl fluorides in good yields,^{12,18} as is illustrated by the recent synthesis of several substituted α -fluorostyrenes for studies related to [4+2]-cycloadditions.¹⁹

In other applications, the cyclizations of ω -bromo-(ω -1)-fluorocarboxylic acids by the intramolecular nucleophilic displacement of bromide ion by a carboxylate may be used for the syntheses of monofluorinated, medium-sized and large ring lactones.⁹ 1-Acetoxy-2-fluoro-2-phenylalkanes, which were prepared by treating several of the 1-bromo-2-fluoro-2-phenylalkanes shown in the Table with acetate, have been used to prepare 2-fluoro-2-phenylalkanoic acids,²⁰ including several 2-fluorinated analogs of the "profen-family" of anti-inflammatory drugs.²¹ Finally, several γ -fluoro- α -amino acids have been prepared in racemic²² or optically active²³ form using 1-bromo-2-fluoroalkanes as alkylating agents.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

1-Bromo-2-fluoro-2-phenylpropane:
Benzene, (2-bromo-1-fluoro-1-methylethyl)- (9); (59974-27-5)

α -Methylstyrene:
Styrene, α -methyl- (8);
Benzene, (1-methylethenyl)- (9); (98-83-9)

Triethylamine trihydrofluoride:
Ethanamine, N,N-diethyl-, trishydrofluoride (10); (73602-61-6)

N-Bromosuccinimide:
Succinimide, N-bromo- (8);
2,5-Pyrrolidinedione, 1-bromo- (9); (128-08-5)