A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

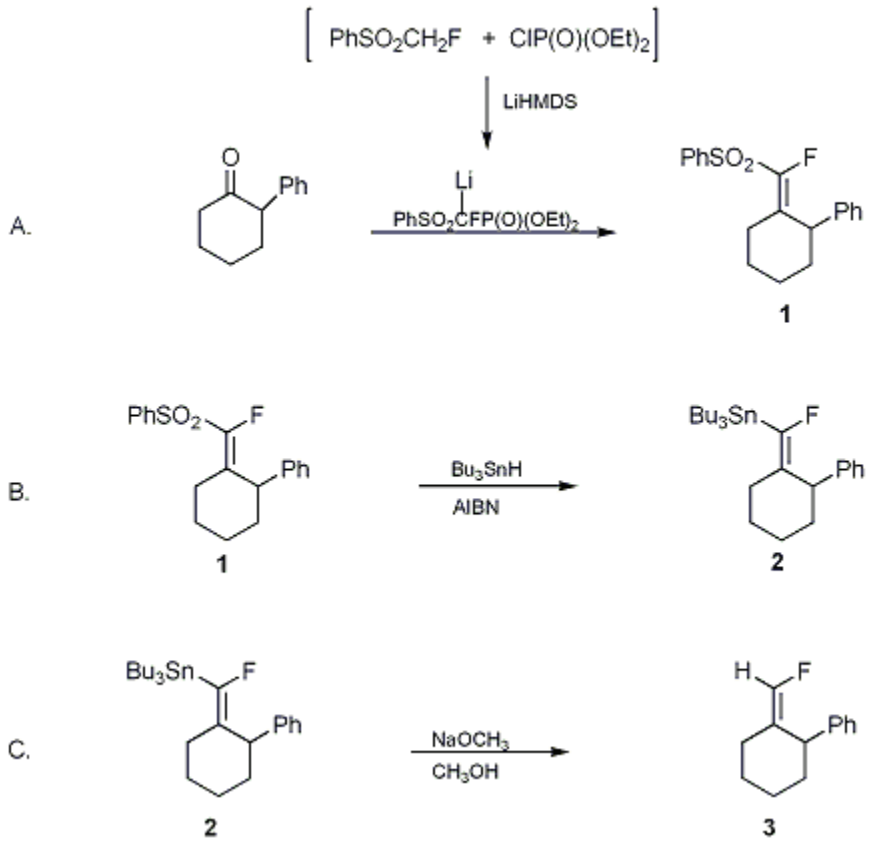
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.072.0216

Organic Syntheses, Coll. Vol. 9, p.442 (1998); Vol. 72, p.216 (1995).

STEREOSELECTIVE SYNTHESIS OF 2,2-DISUBSTITUTED 1-FLUORO-ALKENES: (E)-[[FLUORO(2-PHENYLCYCLOHEXYLIDENE)-METHYL]SULFONYL]BENZENE AND (Z)-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE

[Benzene, [fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]-, (E)-(±)- and Benzene, [2-(fluoromethylene)cyclohexyl]-, (Z)-(±)-]



Submitted by James R. McCarthy, Donald P. Matthews, and John P. Paolini[1].
Checked by Carmen M. Simone and Albert I. Meyers.

1. Procedure

CAUTION! All reactions should be conducted in an efficient fume hood.

A. *(E)-[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene* ***(1)***. To an oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, thermometer, magnetic stirring bar, and a 500-mL addition funnel with side arm and septum, are added 25.0 g (0.14 mol) of fluoromethyl phenyl sulfone (Note 1), diethyl chlorophosphate (24.8 g, 0.14 mol) (Note 2), and anhydrous tetrahydrofuran (THF) (300 mL). The solution is kept under a nitrogen atmosphere and cooled to −70°C with a dry ice-acetone bath. A solution of 1 M lithium bis(trimethylsilyl)amide (LiHMDS) in THF (310 mL, 0.31 mol) (Note 3) is transferred via cannula to the dropping funnel and added over 15 min. After the reaction mixture is stirred for 1 hr at ≤ −70°C (Note 4), the addition funnel is replaced with a septum. 2-Phenylcyclohexanone (17.4 g, 0.10 mol) (Note 5) is dissolved in THF (65 mL) and added via a syringe. The reaction mixture is allowed to warm to ambient temperature. Stirring

is continued for 2 hr at room temperature and, during this time, a white precipitate forms in solution. The reaction mixture is poured into an ice-cold mixture of ethyl acetate (250 mL), saturated aqueous ammonium chloride (250 mL), and concd hydrochloric acid (30 mL). The organic layer is collected and the aqueous layer is extracted with ethyl acetate (250 mL). The combined organic layers are washed with saturated aqueous sodium chloride (100 mL) and dried (magnesium sulfate). The solvent is removed under reduced pressure and the resulting orange-brown oil is purified by flash chromatography[2] (1.25 L of 230–400 mesh silica gel) using ether/hexane (1:10) to provide 23 g of colorless oil (Note 6). The oil is dissolved in hot ethanol (200 mL) and the solution is cooled in the freezer. The shiny white crystals that form are collected by filtration and dried under reduced pressure to afford 19.5–23.1 g (59–70%) of **1**, mp 75–78°C (Note 7).

B. *(E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane* ***(2)***. To a 1-L, round-bottomed flask with reflux condenser, magnetic stirring bar, and nitrogen inlet with gas bubbler are added fluorovinyl sulfone **1** (22.0 g, 0.067 mol), tributyltin hydride (42.0 g, 38.9 mL, 0.14 mol), azobisisobutyronitrile (AIBN) (500 mg) (Note 8) and benzene (700 mL) (Note 9). The solution is refluxed for 3 hr under a nitrogen atmosphere (Note 10), cooled to room temperature, and 125 mL of silica gel (230–400 mesh) is added. The mixture is concentrated on a rotary evaporator to a white powder (Note 11) and applied to the top of a flash silica gel column[2] (1.3 L) packed with hexane. The column is eluted with hexane and fractions containing **2** (Note 12) are combined and concentrated on a rotary evaporator to give 23.4–27.5 g (74–87% yield) of **2** as a colorless oil (Note 13).

C. *(Z)-[2-(Fluoromethylene)cyclohexyl]benzene* ***(3)***. To a solution of (fluorovinyl)stannane **2** (26.0 g, 0.054 mol) in dry THF (150 mL) is added 65 mL of 1 M sodium methoxide in methanol (prepared by the addition of 1.50 g (0.065 g-atom) of sodium to 65 mL of methanol). The solution is refluxed for 18 hr under nitrogen (Note 14), cooled to ambient temperature and concentrated on a rotary evaporator. The residue is partitioned between water (200 mL) and hexane (200 mL). The aqueous layer is separated and extracted with hexane (100 mL). The combined organic layers are dried (magnesium sulfate) and concentrated on a rotary evaporator to give a colorless oil (30 g). Kugelrohr distillation gives 10.0–10.2 g (97–100%) of fluoro olefin **3** (bp 85–90°C, 0.4 mm) as a colorless oil (Note 15).

2. Notes

1. See McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth., Coll. Vol. IX* **1998**, 446.
2. Diethyl chlorophosphate was purchased from Aldrich Chemical Company, Inc., and distilled before use; bp 60°C (2 mm). This reagent is a highly toxic acetylcholinesterase inhibitor and should be handled with care.
3. 1 M Lithium bis(trimethylsilyl)amide in THF was purchased from Aldrich Chemical Company, Inc.
4. Formation of the carbanion of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate is followed by gas chromatography, by quenching a small aliquot of the reaction in ether/saturated aqueous ammonium chloride. The carbanion forms in ca. 85% to 95% yield after 1 hr.
5. 2-Phenylcyclohexanone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
6. Alternatively, the orange-brown oil can be crystallized twice from ethanol (200 mL, 150 mL) (seed crystal) to provide 16.6 g (50%) of off-white crystals of **1**, mp 75–78°C. The checkers observed mp 68–70°C for this material.
7. Spectral and elemental analysis data for **1** are the following: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.3–2.1 (m, 6 H), 2.46 (d, 1 H, J = 14.3), 3.61 (dd, 1 H, J = 3.5, 14.2), 4.22 (s, 1 H), 7.0–8.1 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.76, 23.34, 27.17 (d, $^{3}J_{F,CH2}$ = 2.2), 29.42, 38.45 (d, $^{3}J_{F,CH}$ = 7.5), 126.35, 127.11, 127.96, 128.65, 129.34, 134.07, 134.96 (d, $^{2}J_{F,C}$ = 6.7), 139.46, 139.67, 147.80 (d, $^{1}J_{F,C}$ = 280.1); ^{19}F NMR (282 MHz, $CDCl_3$) δ: −123.4 (s); MS (CI/CH_4) m/z 331 (MH^+). Anal. Calcd for $C_{19}H_{19}FO_2S$: C, 69.06; H, 5.80. Found: C, 68.88; H, 5.86. The structure for **1** was confirmed by X-ray crystallography.[3]
8. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and used as received.
9. *Benzene is a known carcinogen*. Follow manufacturer's recommended procedures for handling, storage, and disposal. Cyclohexane was found to be a suitable alternate solvent for other examples of this reaction.

10. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane) since the time required for completion of the reaction can vary up to 16 hr. An additional 500 mg of AIBN is added to the reaction mixture after 3 hr if starting material is still present.
11. An adapter tube containing a fritted disc prevents loss of silica gel into the condenser of the rotary evaporator. These tubes are available from Aldrich Chemical Company, Inc. Alternatively, the checkers found that the silica gel can be added to the crude mixture after removal of benzene.
12. Fractions containing **2** of ca. ≥90% purity by gas chromatography (flame ionization detector) were combined.
13. In some runs, material (≤5%) with the retention time of tributyltin hydride is present in product **2**. This impurity does not interfere in the last step of the reaction sequence. Spectral and elemental analysis data for **2** are the following: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 9 H, J = 7.0), 1.0–1.1 (m, 6 H), 1.2–2.0 (m, 19 H), 2.41 (d, 1 H, J = 13.9), 4.4 (m, 1 H), 7.2 (m, 1 H), 7.3–7.4 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.44, 13.74, 21.68, 26.75 (d, $^{3}J_{F,CH2}$ = 11.8), 27.23, 28.37 (d, $^{4}J_{F,CH2}$ = 2.7), 29.06, 29.52, 36.31 (d, $^{3}J_{F,CH}$ = 15.0), 125.42, 127.60, 128.21, 135.37, 142.02 (d, $^{2}J_{F,C}$ = 5.2), 163.34 (d, $^{1}J_{F,C}$ = 306.2); ^{19}F NMR (282 MHz, $CDCl_3$) δ: −110.52 (84%, m) (16%, dm, J = 282); MS (CI/CH_4) m/z 461 (MH^+ - HR). Anal. Calcd for $C_{25}H_{41}FSn$: C, 62.65; H, 8.62. Found: C, 62.43; H, 8.61. Proton-fluorine NOE difference spectroscopy ($CDCl_3$) showed an enhancement in the fluorine signal (δ − 110.5) when the benzylic proton (δ 4.4) was irradiated and showed no enhancement when the allylic protons (δ 2.41, equatorial proton and δ 1.77, axial proton) were irradiated. See reference [4] for a discussion of this technique.
14. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane).
15. Spectral and elemental analysis data for **3** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.2–2.0 (m, 7 H), 2.37 (d, 1 H, J = 13.2), 4.2 (m, 1 H), 6.6 (dm, 1 H, J = 87.1), 7.2 (m, 1 H), 7.25–7.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.72, 25.06 (d, $^{3}J_{F,CH2}$ = 6.9), 27.71 (d, $^{4}J_{F,CH2}$ = 2.8), 29.74, 36.13 (d, $^{3}J_{F,CH}$ = 5.2), 123.18 (d, $^{2}J_{F,C}$ = 3.8), 125.73, 127.54, 128.31, 141.55, 142.19 (d, $^{1}J_{F,C}$ = 252.6); ^{1}9F NMR (282 MHz, $CDCl_3$) δ: − 139.64 (dd, J = 3.4, 86.8); MS (CI/CH_4) m/z 191 (MH^+). Anal. Calcd for $C_{13}H_{15}F$: C, 82.07; H, 7.95. Found: C, 82.13; H, 8.15.

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

The procedure described here provides a stereospecific synthesis of (E)- and (Z)-fluoroalkenes from the corresponding (E)- and (Z)-fluorovinyl sulfones. Fluorovinyl sulfones obtained from ketones are, in most cases, readily separable into (E) and (Z) isomers either by crystallization or by chromatography.[5] In the example described, only the (E)-fluorovinyl sulfone **1** is formed (which is converted into the (Z)-fluoroalkene **3** with complete retention of configuration). The reaction sequence has been used for the stereospecific synthesis of fluoroalkene nucleosides[6] as well as for 1-deutero-1-fluoroalkenes. In the case of fluoroalkenes obtained from aldehydes, conversion of the intermediate monosubstituted fluorovinyl sulfones to (fluorovinyl)stannanes does not proceed with retention of configuration.[7] However, subsequent cleavage of the vinyltributyltin group with either sodium methoxide, cesium fluoride or methanolic ammonia does proceed with retention of configuration. Since (E)- and (Z)-vinylstannanes are usually separable, this method also provides a route to stereochemically-pure, terminal, mono-substituted fluoroalkenes.[4] A significant property of the intermediate (fluorovinyl) stannanes is their ability to act as fluorovinyl carbanion equivalents. Thus, treatment of (fluorovinyl) stannanes with acid chlorides in the presence of a palladium(0) catalyst provides α-fluoro-α,β-unsaturated ketones with complete retention of configuration.[4] Iodine reacts with (fluorovinyl)stannanes to give 1-iodo-1-fluoroalkenes with complete retention of configuration.[7,4]

It should be noted that addition of the tributyltin radical to 1-fluoro-1-(phenylsulfonyl)ethene provides phenyl vinyl sulfone as the only isolated product. However, 2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene reacts with tributyltin hydride in the presence of AIBN to provide (E)-2-trimethylsilyl-1-fluoro-1-tributylvinylstannane. The vinylstannane is an equivalent for the synthon

"$H_2C{=}CF^-$" providing a convenient route to 2-fluoro-1-alkenes.[8] The trimethylsilyl group can be removed with potassium fluoride in dimethyl sulfoxide-water or oxalic acid-methanol at the end of the reaction sequence.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 446

[9]

References and Notes

1. Marion Merrell Dow Research Institute, 2110 E. Galbraith Rd., Cincinnati, OH 45215.
2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
3. Dr. John C. Huffman, Indiana University (IU Report 91705).
4. Matthews, D. P.; Huber, E. W.; McCarthy, J. R., unpublished works.
5. McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T. *Tetrahedron Lett.* **1990**, *31*, 5449.
6. McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439.
7. Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360.
8. Matthews, D. P.; Gross, R. S.; McCarthy, J. R., unpublished works.
9. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

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

silica gel

AIBN

Benzene, [fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]-, (E)-(±)-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

sodium methoxide (124-41-4)

sodium (13966-32-0)

palladium(0) (7440-05-3)

magnesium sulfate (7487-88-9)

Tetrahydrofuran,
THF (109-99-9)

potassium fluoride (7789-23-3)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

tributyltin hydride (688-73-3)

2-phenylcyclohexanone (1444-65-1)

diethyl chlorophosphate (814-49-3)

lithium bis(trimethylsilyl)amide (4039-32-1)

cesium fluoride (13400-13-0)

azobisisobutyronitrile (78-67-1)

(E)-[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene,
(E)-[[FLUORO(2-PHENYLCYCLOHEXYLIDENE)-METHYL]SULFONYL]BENZENE (135790-01-1)

(Z)-[2-(Fluoromethylene)cyclohexyl]benzene,
(Z)-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE,
Benzene, [2-(fluoromethylene)cyclohexyl]-, (Z)-(±)- (135790-02-2)

Fluoromethyl phenyl sulfone (20808-12-2)

(E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane (135789-96-7)

diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate

1-fluoro-1-(phenylsulfonyl)ethene

2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene

(E)-2-trimethylsilyl-1-fluoro-1-tributylvinylstannane

oxalic acid-methanol