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Working with Hazardous Chemicals

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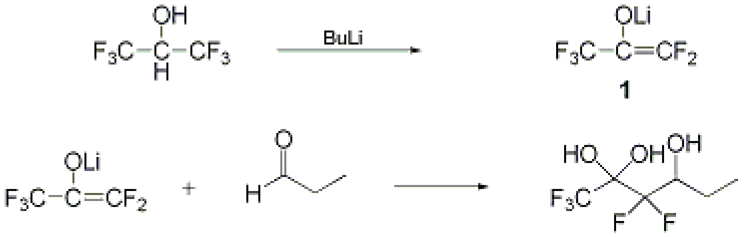
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.076.0151

Organic Syntheses, Coll. Vol. 10, p.460 (2004); Vol. 76, p.151 (1999).

GENERATION AND USE OF LITHIUM PENTAFLUOROPROPEN-2-OLATE: 4-HYDROXY-1,1,1,3,3-PENTAFLUORO-2-HEXANONE HYDRATE

[2,2,4-Hexanetriol, 1,1,1,3,3-pentafluoro- from 1-Propen-2-ol, 1,1,3,3,3-pentafluoro-, lithium salt]



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Checked by Christine Kim, Peter Belica, and Steven Wolff.

1. Procedure

An oven-dried (Note 1), 300-mL, three-necked, round-bottomed flask containing a magnetic stirring bar, and fitted with a rubber septum inlet, a thermometer and a balloon full of nitrogen is charged with 100 mL of dry tetrahydrofuran (Note 2) and 6.3 mL (60 mmol) of hexafluoroisopropyl alcohol (Note 3). The flask and its contents are cooled to −70°C with a dry ice/acetone bath. After the apparatus has cooled, 76.9 mL of a 1.6 M hexane solution of butyllithium (123 mmol) is added dropwise using a 100-mL syringe over a period of 15 min. The reaction temperature is kept below −40°C (Note 4). After the addition is complete, the reaction mixture is further stirred for 10 min at −70°C and warmed to 0°C with an ice bath for 1 hr to afford lithium pentafluoropropen-2-olate , **1**, (Note 5). To the pale yellow solution is added dropwise 4.8 mL (66 mmol) of propionaldehyde (Note 6) via a syringe over 30 min, and the reaction mixture is stirred for 1 hr at 0°C. The flask is opened to the atmosphere, and about 65 mL of 1.0 M hydrochloric acid is added for neutralization. The quenched reaction solution is stirred for 10 min at room temperature and then transferred to a 500-mL separatory funnel. The aqueous layer is separated. The organic layer is diluted with 100 mL of ethyl acetate and washed with 150 mL of saturated brine . The combined aqueous material is extracted with two 75-mL portions of ethyl acetate . The organic extracts are combined, dried over anhydrous magnesium sulfate , filtered and evaporated. The yellow oily residue is further dried under reduced pressure at room temperature for several hours until crude crystals (about 12-14 g) are formed (Note 7). To the crude crystals is added 20 mL of hexane , and the resulting material is left at 5°C overnight. After the supernatant liquid is decanted, the wet crystals are washed further with two 20-mL portions of hexane followed by decantation and dried under reduced pressure to give a first crop of pure crystalline product. The hexane washings are concentrated and treated as described for the oily residue, giving a second crop of pure crystalline product (Note 8). The total yield is 8.64 g (64%) of 4-hydroxy-1,1,1,3,3-pentafluoro-2-hexanone hydrate (mp 74-78°C) (Note 9).

2. Notes

1. All the glassware was washed with acetone and oven-dried for a least 4 hr at 80°C, assembled hot, and allowed to cool under a nitrogen atmosphere.
2. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium/benzophenone prior to use.
3. Hexafluoroisopropyl alcohol was obtained from Central Glass Company, Ltd. , and used without additional purification. It is advisable to keep this reagent under a nitrogen atmosphere because it is highly hygroscopic.
4. During the addition of butyllithium, a temperature higher than −40°C must be avoided to prevent the

formation of a by-product arising from further reaction of the lithium perfluoroenolate with butyllithium.

5. This perfluoro enolate displays the following spectroscopic data: ^{19}F NMR (56.45 MHz, THF, $CFCl_3$) δ: −68.5 (dd, 3 F, J = 28.6, 9.4, CF_3), −109.8 (br d, 1 F, J = 84.7, CF_2), −117.8 (br d, 1 F, J = 84.7, CF_2) .

6. Propionaldehyde was distilled prior to use.

7. Crystals are difficult to form unless the solvent is removed as completely as possible.

8. The ratio of the first and second crops, and the total amount of crystallized product depend mainly on whether the ethyl acetate is removed completely. If necessary, the second hexane washings can be treated again to give a third crop of product.

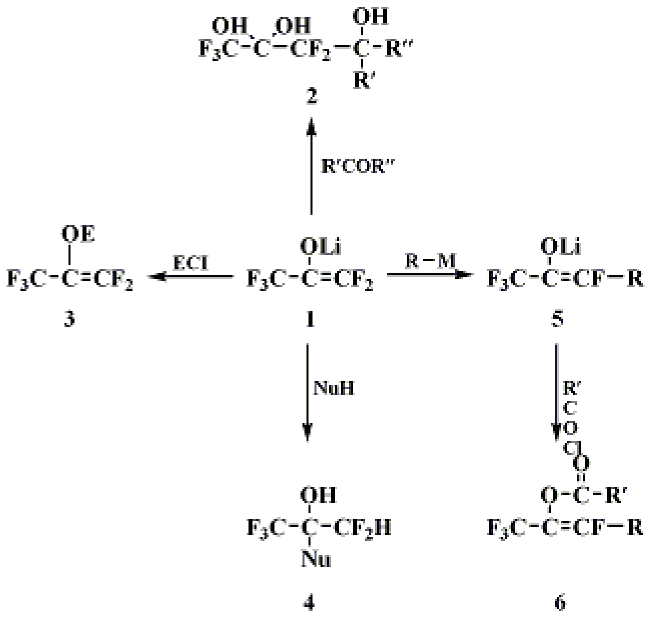
9. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.94 (t, 3 H, J = 7.5, CH_3), 1.45 (ddq, 1 H, J = 14.0, 9.9, 7.2, CH_2), 1.76 (dddq, 1 H, J = 14.0, 2.7, 2.3, 7.6, CH_2), 3.85-4.05 (m, 1 H, HOCH), 5.96 (d, 1 H, J = 6.5, HOCH), 7.54 [s, 1 H, $C(OH)_2$], 7.92 [s, 1 H, $C(OH)_2$] ; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, 3 H, J = 7.4, CH_3), 1.60-1.80 (m, 1 H, CH_2), 1.80-2.05 (m, 1 H, CH_2), 2.2-2.9 (br s, 1 H, OH), 3.8-4.4 (br s, 1 H, OH), 4.27 (dddd, 1 H, J = 21.7, 9.9, 3.1, 1.4, HOCH), 5.4-6.3 (br s, 1 H, OH) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.9 (CH_3), 22.4 (CH_2), 71.0 (dd, J = 27.7, 22.7, HOCH), 92.6 [m, $C(OH)_2$], 118.5 (t, J = 256.5, CF_2), 122.6 (q, J = 289.3, CF_3) ; ^{19}F NMR (56.45 MHz, AcOEt, $CFCl_3$) δ: −80.0 (dd, 3 F, J = 13.5, 11.7, CF_3), −120.0 (ddq, 1 F, JF_A-F_B = 275.3, JF_A-H = 2.0, JF_A-CF_3 = 13.5, CF_AF_B), −132.0 (ddq, 1 F, JF_B-F_A = 275.3, JF_B-H = 21.9, JF_B-CF_3 = 11.7, CF_AF_B) ; IR (neat film/NaCl plate) cm^{-1}: 3400, 2980, 1440, 1200, 1100, 1070, 980, 920, 850, 770, 750 . Anal. Cacld for $C_6H_9F_5O_3$: C, 32.15; H, 4.05; F, 42.38. Found: C, 32.09; H, 3.96; F. 42.04.

Waste Disposal Information

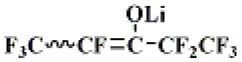
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

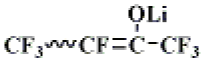
The present procedure describes an extremely convenient preparation of lithium perfluoropropenolate (**1**) and illustrates its use in organofluorine synthesis. The following scheme shows the wide spectrum of reactivity observed with lithium F-enolate **1**.[2,3,4] Several features of the F-enolate reactivity have been demonstrated: (a) The F-enolate exhibits the usual enolate reactivities, i.e., O- and C-nucleophilicity, to afford various classes of polyfluorinated compounds of types **2**–**4** that are otherwise difficult to obtain. (b) The F-enolate is capable of undergoing aldol reactions with various carbonyl compounds to afford adducts as hydrates **2**. (c) In reactions with reagents bearing an active hydrogen, the initial protonation occurs at the β-carbon, not at the oxygen, to yield products of type **4**. (d) Most significantly, the F-enolate exhibits a rather unusual electrophilic reactivity toward organometallic reagents to generate a geometric mixture of the β-alkyl F-enolates **5** via an addition-elimination process. This means that the F-enolate behaves as a kind of perfluoroolefin that is well-known to undergo a similar type of substitution reaction. Some examples of these reactions are shown in Tables I and II.



Finally, it should be noted that the present procedure is applicable to preparations of various lithium F-enolates such as **7** and **8** that exhibit different reactivity from that of **1**.[3,4]

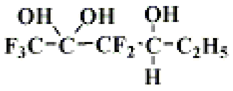
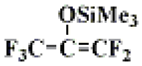
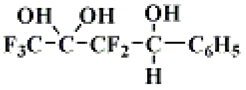
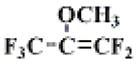
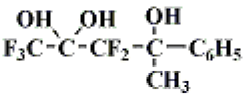
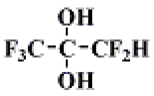
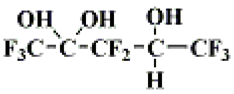
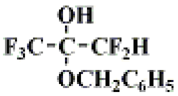

$F_3C\sim CF=C(OLi)-CF_2CF_3$

7


$CF_3\sim CF=C(OLi)-CF_3$

8

TABLE I
REACTION OF LITHIUM PENTAFLUOROPROPEN-2-OLATE WITH ELECTROPHILES

Electrophile	Product (% Yield)	Electrophile	Product (% Yield)
EtCHO	 $F_3C-C(OH)_2-CF_2-CH(OH)-C_2H_5$ (71)	Me_3SiCl	 $F_3C-C(OSiMe_3)=CF_2$ (80)
PhCHO	 $F_3C-C(OH)_2-CF_2-CH(OH)-C_6H_5$ 72	$(MeO)_2SO_2$	 $F_3C-C(OCH_3)=CF_2$ (72)
PhCOMe	 $F_3C-C(OH)_2-CF_2-C(OH)(CH_3)-C_6H_5$ (82)	H_2O	 $F_3C-C(OH)_2-CF_2H$ (86)
CF_3CHO	 $F_3C-C(OH)_2-CF_2-CH(OH)-CF_3$ (87)	$PhCH_2OH$	 $F_3C-C(OH)(OCH_2C_6H_5)-CF_2H$ (71)
$(C_2F_5)_2CO$		$PhCONH_2$	

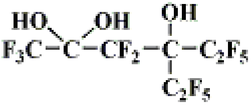
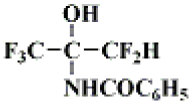
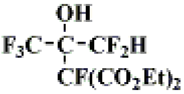
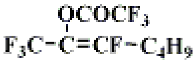
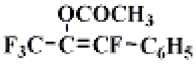
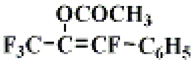
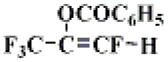
	 $F_3C-\overset{HO\ \ OH}{C}-CF_2-\underset{C_2F_5}{\overset{OH}{C}}-C_2F_5$		 $F_3C-\underset{NHCOC_6H_5}{\overset{OH}{C}}-CF_2H$ (74)
PhCOCl	 $F_3C-\overset{OCOC_6H_5}{C}=CF_2$	$CHF(CO_2Et)_2$	 $F_3C-\underset{CF(CO_2Et)_2}{\overset{OH}{C}}-CF_2H$ (61)

TABLE II
REACTION OF LITHIUM PENTAFLUOROPROPEN-2-OLATE WITH NUCLEOPHILES

Nucleophile	Product[a]	Yield (%)
BuLi	 $F_3C-\overset{OCOCF_3}{C}=CF-C_4H_9$ (E/Z = 72/28)	71
PhLi	 $F_3C-\overset{OCOCH_3}{C}=CF-C_6H_5$ (E/Z = 77/23)	64
PhMgBr	 $F_3C-\overset{OCOCH_3}{C}=CF-C_6H_5$ (E/Z = 83/17)	48
Red-Al	 $F_3C-\overset{OCOC_6H_5}{C}=CF-H$ (E/Z = 43/57)	55

[a] Metal enolates **5** thus formed were isolated after acylation with an acyl chloride.

References and Notes

1. Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo, Japan.
2. Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 4119.
3. Qian, C.-P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602.
4. Qian, C.-P.; Nakai, T. In "Selective Fluorination in Organic and Bioorganic Chemistry"; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; ACS Symposium Series 456; p. 82.

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

Lithium pentafluoropropen-2-olate:
1-Propen-2-ol, 1,1,3,3,3-pentafluoro-, lithium salt (12); (116019-90-0)

4-Hydroxy-1,1,1,3,3-pentafluoro-2-hexanone hydrate:
2,2,4-Hexanetriol, 1,1,1,3,3-pentafluoro- (12); (119333-90-3)

Hexafluoroisopropanol alcohol:
2-Propanol, 1,1,1,3,3,3-hexafluoro- (8,9); (920-66-1)
Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Propionaldehyde (8);
Propanal (9); (123-38-6)