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PREPARATION AND SYNTHETIC UTILITY OF DIFLUOROKETENE THIOACETAL. A NOVEL SYNTHETIC ROUTE TO α-MONOFLUOROALKANOIC ACIDS[1)]

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Difluoroketene thioacetal (2) prepared from trifluoroacetaldehyde thioacetal (3) with lithium diisopropylamide or alkyllithiums has been shown to be useful as a building block for the preparation of α-monofluoroalkanoic acids (5), which involves the reaction of 2 with various organometallic compounds followed by hydrolysis of the resulting monofluoroketene thioacetal (4).

Reactions of gem-difluoroolefins with nucleophilic reagents have been extensively studied in organofluorine chemistry and hence may serve as a useful means for carbon-carbon bond formations.[2)] As a part of a research program designed to uncover new applications of organofluorine reagents in organic synthesis,[3)] we have recently reported the reactions of 2,2-difluorovinyl sulfides (1) with various organolithium reagents permitting ready access to a variety of acetylenic thioethers (eq 1).[4]

$$CF_3CH_2\text{-}SR^1 \xrightarrow{R^2Li} [\ CF_2{=}CH\text{-}SR^1\ ] \xrightarrow{R^2Li} R^2\text{-}C{\equiv}C\text{-}SR^1 \qquad (1)$$

1

In a continuation of these studies, we now wish to report the first example of the preparation of difluoroketene thioacetal (2) and to demonstrate the synthetic potentiality of the reagent 2 as a building block which provides a novel synthetic route to α-monofluoroalkanoic acids (5), a class of compounds which have currently received biological interest.[5)] The overall scheme is shown in eq 2.

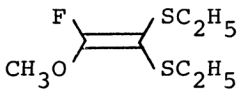
$$CF_3CH(SC_2H_5)_2 \xrightarrow{RLi \text{ or } (i\text{-}Pr)_2NLi} CF_2{=}C(SC_2H_5)_2$$

3 2

$$\xrightarrow[M = Li \text{ or } MgX]{R\text{-}M} \begin{matrix} F \\ R \end{matrix}\!\!>\!C{=}C<\!\!\begin{matrix} SC_2H_5 \\ SC_2H_5 \end{matrix} \xrightarrow{Hydrolysis} R\text{-}\underset{F}{CH}\text{-}CO_2H \qquad (2)$$

4 5

The difluoro-thioacetal 2 was prepared via elimination of hydrogen fluoride from trifluoroacetaldehyde thioacetal (3) which was readily accessible from trifluoroacetaldehyde hydrate and ethanethiol.[6] Treatment of 3 with 1.0 equiv of lithium diisopropylamide in tetrahydrofuran at -78 ~ -40°C for 2.5 h afforded 2 in 62% isolated yield: bp 85-87°C/45mmHg; ^{1}H NMR[7] (CCl_4), δ 1.27(t) and 2.70(q); ^{19}F NMR[7] (CCl_4), δ -5.8(s); IR(neat), 1670 cm^{-1}(C=C). The difluoro-thioacetal 2 thus obtained underwent facile reactions with various nucleophilic reagents. For example, the reaction of 2 with sodium methoxide at room temperature gave the substitution product (6)[8] in 67% yield. The reaction with butyllithium in diethyl ether at room temperature underwent carbon-carbon bond formation giving rise to the monofluoroketene thioacetal (4a) in ca. 90% yield: bp 116-118°C/11mmHg; ^{1}H NMR(CCl_4), δ 0.95(t), 1.20(t), 1.3-1.6(m), 2.63, and 2.67(q); ^{19}F NMR(CCl_4), δ 0.3(t); IR(neat), 1615 cm^{-1}(C=C). The difluoro-thioacetal 2 is also reactive toward Grignard reagents, though the reaction was very sluggish and the product yield was much lower. For instance, the reaction with butylmagnesium bromide in diethyl ether at room temperature for 5 days gave 4a in 39% yield.



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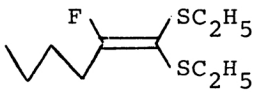

4a

More conveniently, the reagent 2 was generated in situ from 3 with alkyllithium reagents, providing a one-pot procedure for the preparation of 4 from 3. Thus treatment of 3 with 2 equiv of butyllithium at -78°C ~ room temperature afforded 4a in 89% yield. Similar reactions of 3 with other organolithium reagents produced the corresponding monofluoro-thioacetal 4 in good yields (Table I). Unfortunately, however, Grignard reagents were not so reactive enough to react with 3.

Finally, hydrolysis of the monofluoro-thioacetal 4 thus obtained furnished the corresponding α-monofluoroalkanoic acids (5).[9] Thus 4 was hydrolyzed in 90% sulfuric acid at 50°C for 3 hr giving a mixture of the desired acid 5 and its ethyl thioester which was further hydrolyzed in 5% aqueous sodium hydroxide at room temperature followed by acidification, ultimately providing good overall yields of the corresponding α-monofluoroalkanoic acids (5) (Table I).

The following features of the present synthetic method for α-monofluoroalkanoic acids compared with previous ones are noteworthy. While most of previous methods are based on the introduction of the fluorine atom by replacement of an appropriate leaving group (X) on a pre-constructed α-functionalized alkanoic acids (7),[10] the present method involves facile carbon-carbon bond forming reactions between the gem-difluoroolefin and carbon-nucleophiles. Furthermore, the net effect of the present process allows the difluoro-thioacetal 2 to serve as an equivalent of the α-fluorocarbonium

Table 1 Preparations of α-Monofluoroalkanoic Acids (5)

RM	Thioacetal (4)[a,b]		α-Fluoroalkanoic Acid (5)[a]			
	Yield, %[c]	Bp, °C/mmHg	Structure	Yield, %[c]	Mp, °C	^{19}F NMR[d] (CCl_4), δ ppm
$CH_3(CH_2)_3MgBr$	(39)[e]	116-118/11	$CH_3(CH_2)_3\underset{F}{C}HCO_2H$	81	Oil[f]	114.0(d,t)
$CH_3(CH_2)_3Li$	89					
$CH_3(CH_2)_9Li$	62	150-152/0.2	$CH_3(CH_2)_9\underset{F}{C}HCO_2H$	79	73-74	112.5(d,t)
C_6H_5Li	89	143-145/3	$C_6H_5\underset{F}{C}HCO_2H$[g]	52	83-84[h]	103.5(d)
$(EtOCO)_2\underset{CH_3}{C}Na$	46[i]	135-137/0.07	$(EtOCO)_2\underset{H_3C}{C}\text{-}\underset{F}{C}HCO_2H$	54	Oil	117.5(d)

[a] All products exhibited spectral (IR, ^{1}H, and ^{19}F NMR) data in accord with the assigned structures or with the literature values. [b] Unless otherwise noted, the monofluoro-thioacetals (4) were obtained by reactions with 3 with organometallic reagents in diethyl ether at -78°C~room temperature for 3 hr. [c] Based on 3 and 4 for 4 and 5, respectively. [d] See ref. 7. [e] Obtained by the reaction with 2 (see text). [f] Lit.bp, 106-106.5°C/11mmHg: F. L. M. Pattison, et al., ref. 11. [g] Mandelic acid was isolated in 26% yield as a by-product. [h] Lit. mp, 83-85°C: F. L. M. Pattison, et al., ref. 11. [i] The reaction was run in THF at room temerature for 2 days.

ion (8), being in direct contrast to other types of previous methods which rely upon reactions of an equivalent of the α-fluorocarbanion (9) (e.g., α-Fluoromalonates) with carbon-electrophiles.[11] The present method is more advantageous than the latter ones in the points of the overall yields, and the availability and toxicity of the requisite fluorine reagents.

$R\text{-}\underset{X}{C}H\text{-}CO_2H$ (7, X = Br, OTs, OH, NH_2, etc.) $\quad \overset{\oplus}{\underset{F}{C}}H\text{-}CO_2H$ (8) $\quad \overset{\ominus}{\underset{F}{C}}H\text{-}CO_2H$ (9)

In summary, the utilization of the reagent 2 as a building block permits ready access to various α-monofluoroalkanoic acids. Thus this work serves to illustrate an example of the potential applicability of organofluorine reagents in organic synthesis.

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2) For example, M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Ellis Horwood, New York, N. Y., 1976.

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4) K. Tanaka, S. Shiraishi, T. Nakai, and N. Ishikawa, Tetrahedron Lett., 1978, 3103.

5) For biological aspects of carbon-fluorine compounds, consult "Carbon-Fluorine Compounds," (A CIBA Foundation Symposium), Elsevier, Amsterdam, 1972. Also see M. Schlosser, Tetrahedron, 34, 3 (1978).

6) A mixture of ethanethiol and commercially available trifluoroacetaldehyde hydrate was stirred in concentrated sulfuric acid at room temperature for 1.5 hr to give thioacetal 3 in 52% yield: bp 80-82°C/17mmHg; ^{1}H NMR(CCl_4), δ 1.30(t), 2.78(q), and 4.07(q); ^{19}F NMR(CCl_4), δ -9.3(d). A mixture of trifluoroacetaldehyde hydrate and its hemiacetal easily obtained by reduction of methyl trifluoroacetate with lithium aluminum hydride can be used in place of trifluoroacetaldehyde hydrate. For reduction of trifluoroacetate, see O. R. Pierce and T. G. Kane, J. Am. Chem. Soc., 76, 300 (1954).

7) The chemical shifts for ^{1}H and ^{19}F NMR are given in δ ppm downfield from internal tetramethylsilane and upfield from external trifluoroacetic acid, respectively.

8) Bp 125-127°C/25mmHg; ^{1}H NMR(CCl_4), δ 1.23(t), 2.70(q), and 3.87(s); ^{19}F NMR(CCl_4), δ -4.8(s); IR(neat), 1640 cm^{-1}(C=C).

9) Treatment of the monofluoroketene thioacetal (4a) with sodium hydroxide in dimethyl formamide at 80°C for 3 hr resulted in the formation of 1,1-bis(ethylthio)-1,2-hexadiene in 73% yield.

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