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A CONVENIENT SYNTHESIS OF 2,2-DIFLUORO ENOL SILYL ETHERS FROM CHLORODIFLUOROMETHYL KETONES

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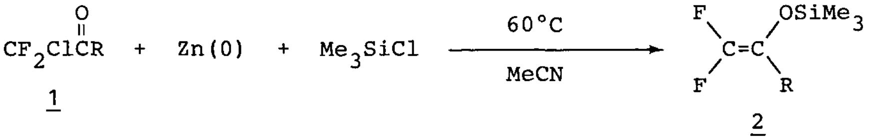
Abstract: Various chlorodifluoromethyl ketones can be converted to the corresponding 2,2-difluoro enol silyl ethers in good yields, by the action of zinc dust and chlorotrimethylsilane in dry acetonitrile at 60°C.

Since the findings of improved methods for the preparation of enol silyl ethers,[1] it has well been recognized that these derivatives from aldehydes and ketones can serve as useful synthetic intermediates in many organic transformations.[2] In contrast to the data accumulated on fluorine-free enol silyl ethers, however, there exist no reports on the preparation of fluorinated enol silyl ethers or their use in organic synthesis. In view of the remarkable enhancement of the specific physiological activity caused by introducing halogen atom(s) into organic molecules,[3] it is of much interest to prepare such a new class of compounds.

This communication is the first paper that describes a method generally applicable for preparing one of such fluorinated enol silyl ethers, i.e., 2,2-difluoro enol silyl ethers (2).



$$CF_2Cl\overset{O}{\overset{\|}{C}}R + Zn(0) + Me_3SiCl \xrightarrow[MeCN]{60°C} F_2C{=}C(OSiMe_3)R$$

In the preliminary experiments on the reaction of chlorodifluoromethyl ketones (1)[4] with a variety of metals,[6] these ketones were found to be reduced by zinc and methanol in tetrahydrofuran (THF) to give difluoromethyl ketones in reasonable yields. This observation, suggesting the existence of intermediary zinc enolate in the reaction, prompted us to examine the effectiveness of zinc metal[7] for the preparation of difluoro enol silyl ethers. Chlorodifluoromethyl ketones smoothly reacted with zinc dust in the presence of chlorotrimethylsilane to produce good yields of the desired enol silyl ethers (2). Commercially available zinc dust could be used without any activation. Both acetonitrile and THF could be employed as solvent for this reaction, but the former gave better yields of the products than the latter. The results of the reaction are summarized in Table I, along with the boiling points of the products.

Table I. Preparation of 2,2-Difluoro Enol Silyl Ethers (2)

R	Enol silyl ether 2	Time[a] h	Yield of 2[b] %	Bp of 2 °C (mmHg)
$CH_3(CH_2)_4CH_2$	2a	20	68	80 (16)
$CH_3(CH_2)_6CH_2$	2b	20	74	95 (7)
$(CH_3)_2CHCH_2CH_2$	2c	20	35	53 (32)
cyclo-C_6H_{11}	2d	20	58	91 (20)
$PhCH_2$	2e	3	52	104 (20)
Ph	2f	3	64	88 (17)

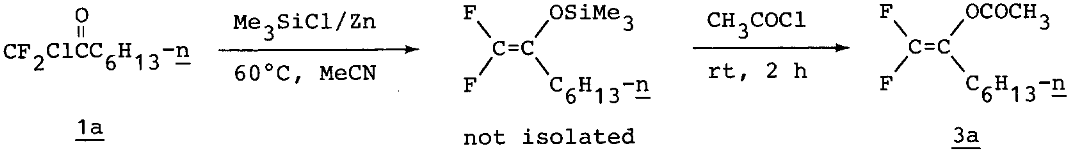
[a] Reaction temperature, 60°C. [b] Isolated yields.

The general procedure is as follows. To a mixture of zinc dust (25 mmol) and chlorotrimethylsilane (25 mmol) in dry acetonitrile was added dropwise a chlorodifluoromethyl ketone (1) (20 mmol) at room temperature under an argon atmosphere. The whole mixture was gradually heated to 60°C with stirring. After a specified period, the reaction mixture was quickly filtered and the precipitates were washed with dry hexane (20 ml × 2). The combined filtrates were distilled under reduced pressure to give pure 1,1-difluoro-2-trimethylsiloxy-1-alkene (2).[8] Among these fluorinated enol silyl ethers, phenyl-substituted ones 2e and 2f could be stored in a refrigerator only for a few days. Other enol silyl ethers were considerably stable even at room temperature and could be kept unchanged for several months.

The conventional procedures of House, et al.[1e,f] using difluoromethyl ketones[9] were found to be ineffective for preparing 2,2-difluoro enol silyl ethers. Thus, the treatment of difluoromethyl octyl ketone with triethylamine and chlorotrimethylsilane at 80°C for 20 h gave 1,1-difluoro-2-trimethylsiloxy-2-decene in 93% yield, but no trace of 1,1-difluoro-2-trimethylsiloxy-1-decene (2b) was detected in the reaction mixture. The treatment of difluoromethyl octyl ketone with lithium diisopropylamide followed by addition of chlorotrimethylsilane gave unidentified products, not containing the desired enol silyl ether.

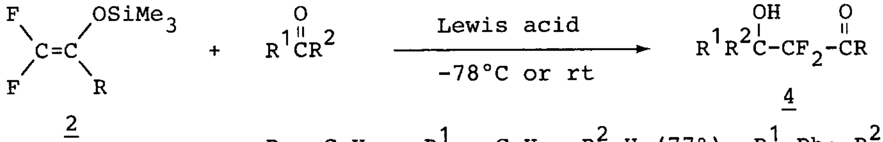
These results show that the reaction of chlorodifluoromethyl ketones (1) with zinc dust and chlorotrimethylsilane provides a most convenient method for the preparation of 2,2-difluoro enol silyl ethers (2).

It has also been found that 2,2-difluoro enol acetates can directly be obtained from chlorodifluoromethyl ketones (1) by this method: After chlorodifluoromethyl hexyl ketone (1a) was allowed to react with zinc dust and chlorotrimethylsilane in dry acetonitrile under the above-described conditions, the mixture was treated with acetyl chloride (2 equiv) at room temperature for 2 h. Evaporation, filtration, and column chromatography on silica gel gave 2-acetoxy-1,1-di-



fluoro-1-octene (3a)[10] in 85% yield.

It was found that the 2,2-difluoro enol silyl ethers obtained in the present study underwent Lewis acid-promoted condensation with a variety of ketones and aldehydes, like ordinary enol silyl ethers,[2a] to afford the corresponding α,α-difluoro-β-hydroxyketones (4)[10] in excellent yields, as shown below.



R=$\underline{n}$-C_6H_{13}: R^1=$\underline{n}$-C_3H_7; R^2=H (77%), R^1=Ph; R^2=H (82%)
R^1=R^2=CH_3 (92%), R^1=R^2=-$(CH_2)_5$- (82%)
R=$\underline{n}$-C_8H_{17}: R^1=Ph; R^2=CH_3 (85%), R^1=Ph; R^2=CF_3 (73%)

Further studies on the application of these fluorinated enol compounds to organic synthesis are now under way in our laboratory.[11]

References and Notes

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4. Chlorodifluoromethyl ketones were prepared in good yields by the reaction of chlorodifluoroacetic acid with the corresponding Grignard reagents.[5]
5. A. Sykes, J.C. Tatlow, and C.R. Thomas, J. Chem. Soc., 835 (1956); R.A. Moore and R. Levine, J. Org. Chem., 29, 1439 (1964).
6. Of the metal powders used for the reaction, which included Zn, Cu, Cd, Sn, and Ti, only zinc metal gave satisfactory results.
7. Reference 1g describes the use of activated zinc for converting α-bromocamphor to the corresponding enol silyl ether, but no reference is made to its generality.
8. 2a: ^{1}H NMR δ 0.20 (s, 9H), 0.90-1.00 (m, 3H), 1.20-1.24 (m, 8H), 1.90-2.15 (m, 2H); ^{19}F NMR (TFA) δ -27.91 (d, J = 86.1 Hz, 1F), -42.60 (dt, J = 86.1 and 4.4 Hz, 1F); IR (neat) 1760, 1250, 1070, 950, 840 cm^{-1}; MS m/e 236 (M^{+}), 73 (100). 2b: ^{1}H NMR δ 0.19 (s, 9H), 0.85-1.00 (m, 3H), 1.19-1.55 (m, 12H), 1.87-2.13 (m, 2H); ^{19}F NMR (TFA) δ -27.90 (d, J = 87.5 Hz, 1F), -42.60 (d, J = 87.5 Hz, 1F); IR (neat) 1765, 1250, 1080, 890, 840 cm^{-1}; MS m/e 264 (M^{+}), 73 (100). 2c: ^{1}H NMR δ 0.19 (s, 9H), 0.90 (d, J = 6.0 Hz, 6H), 1.20-1.57 (m, 3H), 1.90-2.14 (m, 2H); ^{19}F NMR (TFA) δ -28.38 (d, J = 90.3 Hz, 1F), -43.17 (d, J = 90.3 Hz, 1F); IR (neat) 1740, 1240, 1200, 1050, 840 cm^{-1}; MS m/e 222 (M^{+}), 73 (100). 2d: ^{1}H NMR δ 0.26 (s, 9H), 1.00-1.18 (m, 10H), 2.00-2.06 (m, 1H); ^{19}F NMR (TFA) δ -28.98 (d, J = 91.7 Hz, 1F), -40.19 (dd, J = 91.7 and 4.8 Hz, 1F); IR (neat) 1750, 1290, 1240, 1070, 1000, 840 cm^{-1}; MS m/e 234 (M^{+}), 73 (100). 2e: ^{1}H NMR δ 0.13 (s, 9H), 4.15 (dd, J = 4.7 and 2.2 Hz, 2H), 7.00-7.20 (m, 5H); ^{19}F NMR (TFA) δ -28.28 (dt, J = 86.1 and 2.2 Hz, 1F), -42.52 (dt, J = 86.1 and 4.7 Hz, 1F); IR (neat) 1760, 1290, 1250, 1090, 1060, 950, 840, 750, 700 cm^{-1}; MS m/e 242 (M^{+}), 73 (100). 2f: ^{1}H NMR δ 0.08 (s, 9H), 7.00-7.35 (m, 5H); ^{19}F NMR (TFA) δ -21.41 (s, 1F), -33.35 (s, 1F); IR (neat) 1730, 1270, 1170, 1080, 980, 880, 850 cm^{-1}; MS m/e 228 (M^{+}), 73 (100).
9. J. Leroy, J. Org. Chem., 46, 206 (1981).
10. All products were fully characterized by their spectroscopic (IR, MS, ^{1}H and ^{19}F NMR) and analytical data.
11. This work was partially supported by a Grant-in-Aid for Scientific Research No. 56750596 from the Ministry of Education, Science and Culture, Japan.

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