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PRELIMINARY NOTE

Synthesis of α-Fluoromethyl Ketones via Allene Epoxides

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SUMMARY

α-Fluoromethyl ketones are formed via the reaction of allene epoxides with tetrabutylammonium fluoride trihydrate ($TBAF \cdot 3H_2O$) in THF.

The syntheses of fluorine-containing analogues of some biologically active ketones have attracted considerable attention, owing to their activity as competitive enzyme inhibitors [1]. Whereas efficient mild methods for preparation of trifluoromethyl ketones have recently been developed [2,3], the corresponding monofluorinated derivatives [3] remain less accessible.

In 1976 Chan and coworkers have reported [4] that mono-substituted methyl ketones may be prepared from aldehydes or ketones and 1-lithio-1-(trimethylsilyl)ethylene in a four-step procedure involving allene epoxides (cf. the Scheme). Different α-substituted ketones have been prepared by this method [4]; however, no formation of α-fluoromethyl ketones was observed.

In the present studies the original procedure of these authors was modified to permit an efficient approach to a wide range of fluorine-substituted ketones. The modification consists of the application of different leaving groups for allene epoxide formation, and of the use of nucleophilic fluorine in the reaction with allene epoxide.

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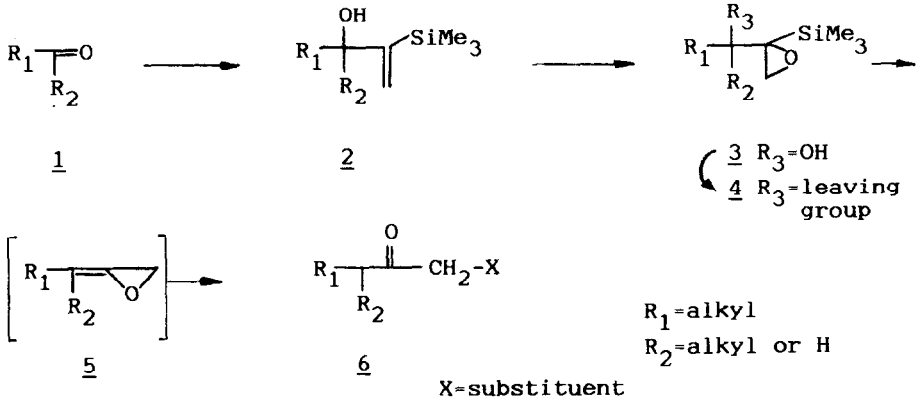

Scheme

Treatment of aldehyde or ketone 1 with 1-lithio-1-(trimethylsilyl)ethylene in the presence of boron trifluoride etherate, followed by epoxidation of the double bond of the corresponding allylic alcohols 2 using t-BuOOH/$VO(acac)_2$ [5], afforded epoxides 3 in a 60-85% yield. Transformation of the hydroxyl groups of epoxysilanes 3 into the leaving groups afforded compounds 4. The crucial step of the synthesis, i.e. formation of allene epoxides 5 and α-fluoromethyl ketones 6 (X=F), was achieved from compounds 4 in a single step, using tetrabutylammonium fluoride ($TBAF \cdot 3H_2O$) in a tetrahydrofuran (THF) solution. All resulting fluoroketones showed in IR absorption at 1730 cm^{-1} (C=O), and in the ^1H NMR - characteristic coupling constant J(HF) of 48 Hz at δ~4.8 ppm. Preparation of fluoroketones 6 from epoxides 4 required 2-2.2 equivalents of the fluorine anion per 1 eq. of compound 4. The first equivalent is consumed by molecule 4 for allene epoxide formation, and the second one reacts with intermediate 5, giving the title α-fluoromethyl ketone.

Several α-fluoromethyl ketones were prepared by the presented method (cf. Table) in good yields (fluoromethylcyclododecane ketone - 70%, 3β-tetrahydropyranyloxy-21-fluoro-5-pregnen-20-one - 71%). However, hydrolysis of trifluoracetates (mainly prepared from tertiary alcohols as the leaving groups),

TABLE

	Carbonyl compound 1	R_3 of 4	Yield 4→6	Selected analytical and spectrocsopic data of compound 6 (X=F)
A	cyclohexanone	$OCOCF_3$	23%	oil; ^{1}H NMR 60 MHz, $CDCl_3$, δ ppm: 4.83 [2H, d, J(HF)=48Hz, $C\underline{H}_2F$]
B	cyclododecanone	$OCOCF_3$	70%	m.p. 48 °C (hexane-Et_2O); ^{1}H NMR 60 MHz, $CDCl_3$, δ ppm: 4.82 [2H, d, J(HF)=48 Hz, $C\underline{H}_2F$]
C	5ß-cholestan-3-one	$OCOCF_3$	73%	m.p. 84-87 °C (hexane-Et_2O); ^{1}H NMR 500 MHz, $CDCl_3$, δ ppm: 0.75 (3H, s, 18-H), 0.79 and 0.80 (6H, 2s, J=2.3 Hz, 26-H and 27-H), 0.83 (3H, d, J=6.6 Hz, 21-H), 0.88 (3H, s, 19-H), 2.61 (1H, m, W/2=22 Hz, 3ß-H), 4.81 [2H, d, J(HF)=48 Hz, $C\underline{H}_2F$]
D	3ß-tetrahydro-pyranyloxy-5-androsten-17-one	$OCOCF_3$	71%	m.p. 118-122 °C (hexane-Et_2O); ^{1}H NMR 400 MHz, $CDCl_3$, δ ppm: 0.75 and 0.98 (6H, 2s, 18-H and 19-H), 2.71 (1H, dd, J(1)=2.8 Hz, J(2)=9.3 Hz, 17α-H), 3.48 (2H, m, -OCH), 3.89 (1H, m, 3α-H), 4.71 [1H, dd, J(HH)=16 Hz, J(HF)=48 Hz, $C\underline{H}_2F$], 4.78 [1H, dd, J(HH)=16 Hz, J(HF)=48 Hz, $C\underline{H}_2F$]; ^{19}F NMR 400 MHz, $CDCl_3$, δ-104.61 (t)
E	decanal	$OCOCF_3$ OSO_2CH_3 Cl	5% 72% 49%	oil; ^{1}H NMR 60 MHz, $CDCl_3$, δ ppm: 4.80 [2H, d, J(HF)=48 Hz, $C\underline{H}_2F$]

caused by nucleophilic attack of the fluorine ion on the carbonyl function, competed with the desired formation of allene epoxides 5, thus reducing the yield of the expected product 6 (cf. examples 6A and 6E - R_3=CF_3COO in Table). Application of more resistant leaving groups for attacking the fluorine ion can overcome the undesired process (cf. 6E - R_3=OSO_2CH_3 or R_3=Cl in Table). One of these syntheses, that of 3β-tetrahydropyranyloxy-21-fluoro-5-pregnen-20-one 6D, exemplifies the suitability of the presented method for preparation of some useful 21-fluoro pregnane derivatives [6] characterized by a wide range of biological activities [7].

Studies on the extension of the presented method and on its application for the synthesis of fluorine analogues of natural products are under way.

Typical experimental procedure (steps 4 --➨6)

Compound 4 (1 mmol) was dissolved in THF (5 ml) and treated with a single portion of TBAF·$3H_2O$ (2.2 mmol) in a THF (5 ml) solution at room temperature for 10 min. Subsequently water was added and the product was extracted with Et_2O. The organic layer was washed with water and dried. After evaporation of solvent, the residue was chromatographed on a silica gel column to yield compound 6.

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