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Stereoselective Introduction of a Bromo- (or Chloro-) Difluoromethyl Allylic Group

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Abstract: A highly regio- and stereo-selective method for the introduction of a bromo- (or chloro-) difluoromethylene group into various unsaturated systems is described. The key step is the treatment of 1,1-difluoro-1-alken-3-ols with thionyl bromide or chloride.

Fluorinated organic molecules attract much attention due to their unique biological properties. The replacement of hydrogen atoms by fluorine atoms in biological molecules causes a relatively small steric perturbation but leads to major changes in hydrophobicity and polarity factors[1,2]. Some syntheses allowing the preparation of products in which a methylene group α to the double bond is replaced by a CF_2 group have been described. The incorporation of the CF_2X (X=Br,Cl) moiety in an allylic position of intermediate synthons appears to be a potent tool for the construction of more elaborate molecules[3-9].

Herein, we describe the synthesis of 1-bromo (or 1-chloro)-1,1-difluoro-2-alkenes **2** through the reaction of thionyl bromide (or chloride) with 1,1-difluoro-1-alken-3-ols **1** (readily obtained by addition of difluorovinyllithium to carbonyl compounds[10]).

$$R^1R^2C{=}O \xrightarrow[2)\ H_3O^+]{1)\ CF_2{=}CHLi} \underset{\mathbf{1}}{R^1R^2C(OH)CH{=}CF_2} \xrightarrow[2)\ H_2O]{1)\ SOX_2} \underset{\mathbf{2}}{R^1R^2C{=}CH\text{-}CF_2X} \quad (X{=}Br,Cl)$$

The results of this halogenation are summarized in the following table. The reaction proceeds in diethyl ether in a few hours at room temperature[11], and the alkenes **2** are $S_{N}2'$ substitution products, afforded with high stereoselectivity (if R^2=H, the *E* isomer is ≥99% except for R^1=alkynyl). The results obtained suggest that the halogenation process involves a transition state with significant carbocation character (previously, we have described such $S_{N}2'$ substitution reactions on the same alcohols **2** by a fluorinating agent[12] or a hydride[13]).

R^1	R^2	X	Yield[a] (%)	E/Z[b]	^{19}F NMR-δ(ppm)/$CFCl_3$		Experimental conditions (h/°C)
					E	Z	
n-Hex	H	Cl	76	99/1	-49.8	-45.0	24/20
n-Hex	H	Br	81	99/1	-44.3	-39.0	3/20
$(CH_2)_5$		Cl	5	-	-41.6		6/20
$(CH_2)_5$		Br	75	-	-35.7		1/20
Thienyl	H	Cl	50	100/0	-49.1	-	6/20
Thienyl	H	Br	60	100/0	-44.1	-	3/20
CH_3-CH=CH	H	Cl	50[c]	99/1	-49.0(E,E)	-44.2(Z,E)	6/20
CH_3-CH=CH	H	Br	56	99/1	-43.6(E,E)	-38.0(Z,E)	3/20
n-Bu-C≡C	H	Cl	10	92/8	-51.4	-48.0	6/20
n-Bu-C≡C	H	Br	68	88/12	-46.6	-42.6	3/20

a- Yield for the second step (reaction with SOX_2) in distilled product (except thienyl)

b- E/Z ratio determined by ^{19}F NMR

c- 1:1 Mixture of the two possible S_N2' regioisomers, MeCHClCH=CH-CH=CF_2 and Me(CH=CH)$_2CF_2Cl$

In conclusion, this route appears to provide a general and highly regio- and stereo-selective methodology for the allylic introduction of a bromo- (or chloro-) difluoromethyl group into various unsaturated systems; the products obtained constitute useful precursors for synthesizing more complex fluorinated molecules.

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11- SOX_2 (0.025 mol) is added at -80°C (X=Br) or -20°C (X=Cl) to a solution of crude alcohol **1** (0.015 mol) in Et_2O (60 ml). Stirring is continued at 20°C (see table) and the solution is diluted by addition of water.
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