



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

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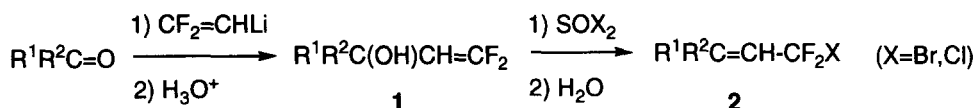
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Abstract: A highly regio- and stereo-selective method for the introduction of a bromo- (or chloro-) difluoromethylene group into various unsaturated systems is described. The key step is the treatment of 1,1-difluoro-1-alken-3-ols with thionyl bromide 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 ($\text{X}=\text{Br}, \text{Cl}$) moiety in an allylic position of intermediate synthons appears to be a potent tool for the construction of more elaborate molecules³⁻⁹.

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 difluorovinyl lithium to carbonyl compounds¹⁰).



The results of this halogenation are summarized in the following table. The reaction proceeds in diethyl ether in a few hours at room temperature¹¹, and the alkenes **2** are $\text{S}_{\text{N}}2'$ substitution products, afforded with high stereoselectivity (if $\text{R}^2=\text{H}$, the *E* isomer is $\geq 99\%$ except for $\text{R}^1=\text{alkynyl}$). The results obtained suggest that the halogenation process involves a transition state with significant carbocation character (previously, we have described such $\text{S}_{\text{N}}2'$ substitution reactions on the same alcohols **2** by a fluorinating agent¹² or a hydride¹³).

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 \equiv C	H	Cl	10	92/8	-51.4	-48.0	6/20
n-Bu-C \equiv C	H	Br	68	88/12	-46.6	-42.6	3/20

a- Yield for the second step (reaction with SOX₂) in distilled product (except thienyl)

b- E/Z ratio determined by ¹⁹F NMR

c- 1:1 Mixture of the two possible S_N2' regioisomers, MeCHClCH=CH-CH=CF₂ and Me(CH=CH)₂CF₂Cl

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- SOX₂ (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 Et₂O (60 ml). Stirring is continued at 20°C (see table) and the solution is diluted by addition of water.
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