Communications to the Editor

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ELECTROPHILIC CYCLIZATION REACTION OF gem-DIFLUOROOLEFIN DERIVATIVES: SYNTHESES OF 6,6-DIFLUOROTETRAHYDRO-2-PYRONES AND 2,2-DIFLUOROTETRAHYDROPYRAN via HALOGEN INDUCED CYCLIZATION

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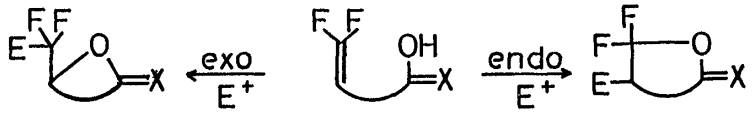
The halocyclization reactions of gem-difluoroolefin derivatives (**4**, **5** and **8**) with iodine in acetonitrile proceed in the 6-endo mode selectively providing 6,6-difluorotetrahydro-2-pyrones (**9**) and 2,2-difluorotetrahydropyran (**10**), respectively.

KEYWORDS—gem-difluoroolefin; 6,6-difluorotetrahydro-2-pyrone; iodolactonization; halocyclization; 2,2-difluorotetrahydropyran; fluorinated lactone

Terminal difluoroolefins (1,1-difluoro-1-olefins), readily accessible from the aldehydes, seem to be versatile synthetic units bearing two fluorine atoms. Although the reactions of difluoroolefins with various nucleophiles have been studied extensively, only a little work has been done on their reactions with electrophiles.[2)] We planned the syntheses of fluorinated cyclic compounds via electrophilic cyclization of gem-difluoroolefin-carboxylic acid derivatives (**1**) and -alcohol derivatives (**2**).(See Chart 1)

Chart 1

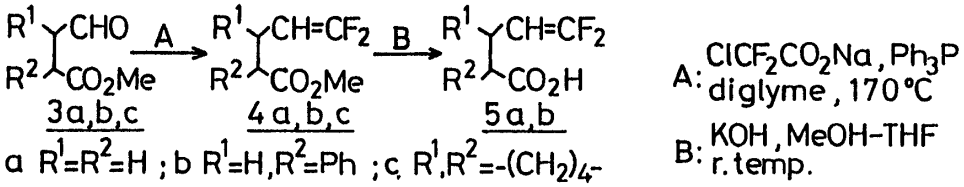


1 X=O, **2** X=H,H

The halocyclization reaction provides a useful method for the conversion of unsaturated acids or alcohols into lactones or cyclic ethers and now plays an important role in synthetic chemistry.[3)] In the ring closure, two possible cyclization modes, endo or exo, are involved as shown in Chart 1. The halolactonization of unfluorinated 4,5-unsaturated carboxylic acids generally gives the 5-exo products. First, we examined the effect of fluorine atoms in the reaction of 5,5-difluoro-4-pentenoic acid derivatives with iodine, and found that only 6-endo products were obtained. The same reaction of a 5,5-difluoro-4-pentenol derivative also gave a 6-endo cyclization product.

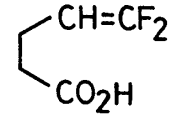
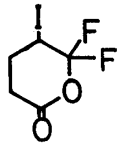
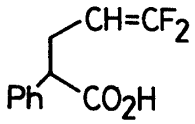
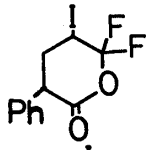
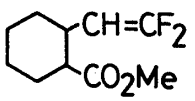
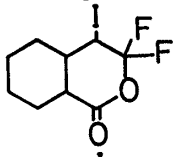
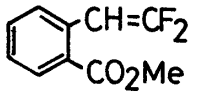
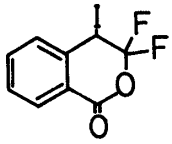
The starting materials were obtained by the modified Wittig reaction[4)] of aldehyde-esters (**3a,b,c**, **6**, and **7**). The difluoroolefinic esters were hydrolyzed to the carboxylic acids (**5a** and **5b**) or an alcohol (**8**) as shown in Chart 2.[5)]

Chart 2



The reaction of **5a** under standard iodolactonization conditions (I_2-KI-$NaHCO_3$/water or water-ether) resulted in the recovery of the starting material. This may be attributed to the high electronegativity of fluorine atoms which reduces the reactivity of the olefinic part toward electrophiles. Next, we examined the reaction of the carboxylic acids or esters with iodine in acetonitrile, and found that the cyclization was regioselective. The results are summarized in Table I.

Table I. Halolactonization of 5,5-Difluoro-4-pentenoic Acid Derivatives

Entry	Starting material	Condition	Product (yield %)	IR ($\nu_{C=O}$)	^{19}F-NMR[a]
1	**5a** 	Room temp. 15 h	 **9a**(31)	1790cm^{-1}	+3.3
2	**5b** 	51°C 13 h	 **9b**(36)	1790cm^{-1}	+3.4, +4.8
3	**4c**[b] 	57°C 12 h	 **9c**(73)[c]	1790cm^{-1}	-11.9-[c] +2.9
4	**4d** 	52°C 15 h	 **9d**(77)	1765cm^{-1}	+4.0, +7.5

a) Benzotrifluoride is used as an internal standard: + indicates higher field.
b) A mixture of stereoisomers (ca.7:3 estimated by GLC).
c) A mixture of three stereoisomers.

The reaction of **5a** and **5b** with iodine in acetonitrile proceeded without addition of a base. The esters with a cyclic system (**4c** and **4d**) reacted by themselves without hydrolysis. This may be due to the conformational advantage.

For the determination of the ring size of lactones, the absorption of the carbonyl group in the infrared (IR) spectrum is generally used. The difluorolactones obtained here showed absorptions in the range of γ-lactones. However, we had no information about the 1,1-difluorooxy structure for comparison. Therefore, to determine the structure of the lactones, a single crystal X-ray analysis of **9b** was performed. An ORTEP drawing of the molecular structure is shown in Fig. 1.

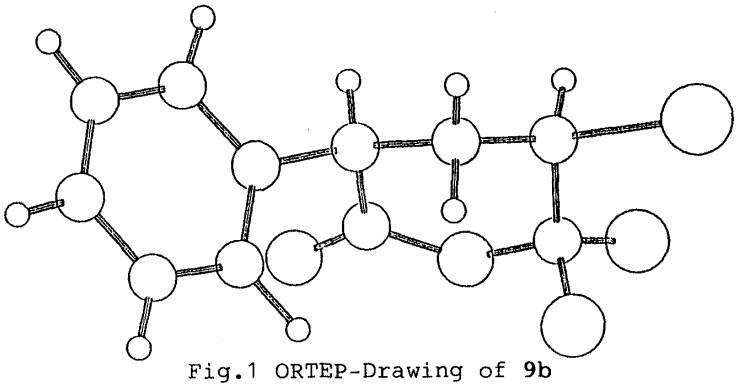


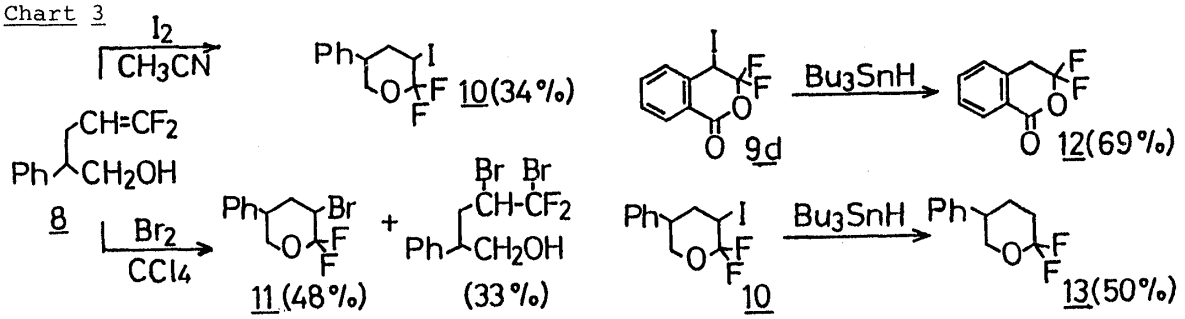
Fig.1 ORTEP-Drawing of **9b**

All the products are found to be δ-lactones. This is in a good contrast with the halolactonization of non-fluorinated 4-pentenoic acids, which give γ-lactones preferentially.[6] The high regioselectivity in our case may be attributed to the effect of the fluorine atoms. Namely, fluorine atoms stabilize the carbonium ion to which they are bound. This effect must be quite large since **4d** did not give the γ-lactone, which would be formed through a cation intermediate stabilized by the phenyl group.

Application of this reaction to the alcohol (8) under the same conditions afforded the 2,2-difluorotetrahydropyran (**10**) in the selective 6-endo closure. Thus, we found that easily accessible 5,5-difluoro-4-pentenoic acids or alcohols gave difluoro six-membered compounds selectively. Bromine induced cyclization of **8** gave dibromo compound (**11**) by the competitive addition of bromine to the double bond. (See Chart 3)

The reduction of halolactones to the corresponding lactones is a process of great importance in organic synthesis. Deiodination of iododifluoro lactones with tributyltin hydride gave the corresponding difluoro compounds, as shown in Chart 3. The present cyclization provides a convenient method for the synthesis of fluorinated lactones and pyrans. Investigation of the scope and applications of this reaction to the synthesis of fluorine analogue of natural products is in progress.

Chart 3



REFERENSES AND NOTES

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2) M. Suda, Tetrahedron Lett., **21**, 2555 (1980).
3) M. D. Dowle and D. I. Davies, Chem. Soc. Rev., **8**, 171 (1979).
4) S. A. Fuqua, W. G. Dancan and R. M. Silverstein, Org. Synth., **46**, 49 (1967).
5) Reaction of **4d** with MeOK resulted in nucleophilic attack to the difluoroolefin.
6) D. H. R. Barton and D. Ollis (Ed.), "Comprehensive Organic Chemistry", Pergamon Press, Oxford, Vol. 2, 1979, p.749.

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