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RADICAL CYCLIZATION TO FLUORINATED DOUBLE BONDS: 5-EXO RING CLOSURE OF BROMOACETALS DERIVED FROM FLUOROALLYL ALCOHOLS

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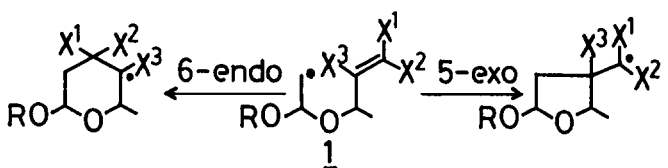
Summary: A radical(1) cyclized to the fluorinated double bond in selective 5-exo mode to afford tetrahydrofuran derivatives(6), and subsequent oxidation provided means for the syntheses of fluorinated γ-butyrolactones(8) and butenolide(9).

Radical conditions for the C-C bond forming ring closure are attracting much attention in synthetic chemistry, and useful regio-, and stereoselective cyclizations for the preparation of five membered rings were explored.[1)] The most commonly used radical initiation is reductive cleavage of the carbon-halogen bond by tributyltin hydride(Bu_3SnH). The carbon-centered radical that is thus generated attacks an intramolecular unsaturated bond. The cyclization process involving functional group(s) which tolerate radical conditions demonstrates the importance of radical cyclization in organic synthesis. Fluorine substitution in the cyclization system should be promising with Bu_3SnH initiation due to high C-F bond strength. Although various radical reactions of fluoroalkyl radicals and fluorinated olefins are known,[2)] intramolecular versions of these reactions have not been observed frequently.[3)] As a part of our study on the synthetic utilization of fluoro-olefinic compounds,[4)] we designed the intramolecular radical cyclization of the bromoacetal to the fluorinated double bond. This paper reports the selective ring closure of this cyclization in the 5-exo mode as well as the syntheses of fluorinated γ-butyrolactones and butenolide.

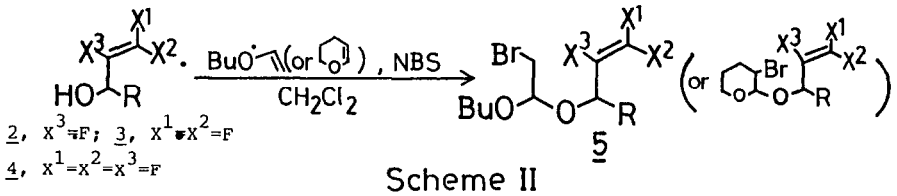


1

X^1=H, X^2=H or alkyl, X^3=F
X^1=X^2=F, X^3=H
X^1=X^2=X^3=F

Scheme I

Two cyclization modes in the ring closure of a radical(1) are possible as evident from Scheme I. To gain some understanding of the effect of fluorine substitution(s) on regioselectivity(5-exo vs. 6-endo), radical cyclization was carried out on monofluoro-, difluoro- and trifluoro-types of bromoacetals. These bromoacetals(5) were prepared by reactions of fluoroallyl alcohols(2,3,4)[5)] with butyl vinyl ether or 3,4-dihydropyran in the presence of N-bromosuccinimide in methylene chloride(Scheme II).



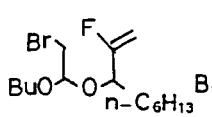
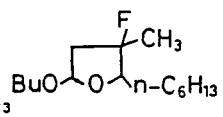
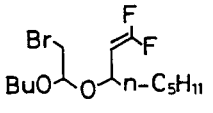
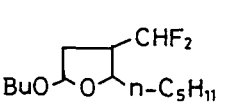
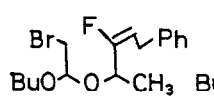
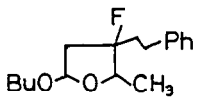
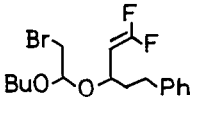
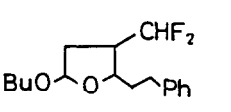
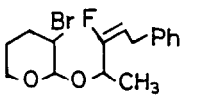
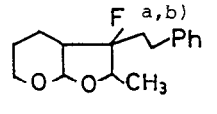
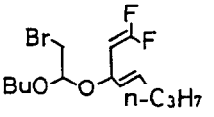
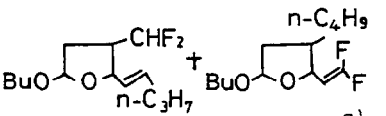
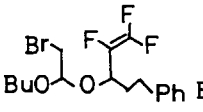
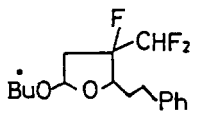
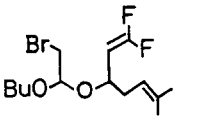
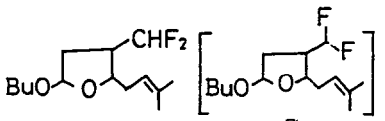
2, X^3=F; 3, X^1=X^2=F

4, X^1=X^2=X^3=F

Scheme II

A typical procedure for the radical cyclization of 5f is given below: In an argon atmosphere, a solution of bromoacetal(5f, 1 mmol), Bu_3SnH(1.1 mmol), and azobisisobutyronitrile(catalytic amount) in benzene(6 ml) was refluxed for 3 hr. After removal of the solvent, the residue was dissolved in ether(5 ml) followed by the addition of 10 % potassium fluoride aq.(3 ml) with stirring.[6] The precipitate was removed by filtration; extraction with ether, drying($MgSO_4$), and purification by column chromatography on silica gel gave tetrahydrofuran derivative(6f) in 89 % yield.[7]

Table: Radical Cyclization of Bromoacetal(5)

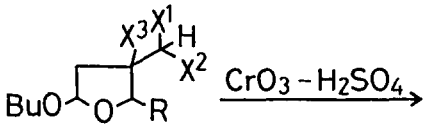
Starting material	Product (yield)	Starting material	Product(s) (yield)
 5a	 6a(78%)	 5e	 6e(70%)
 5b	 6b(79%)	 5f	 6f(89%)
 5c	 6c(67%) a,b)	 5g	 6g(56%, 1:1.2) c)
 5d	 6d(quant.)	 5h	 6h(77%) 7

a) A mixture of two stereoisomers(ca. 2 : 1 estimated by ^{1}H-NMR).
b) The reduction product of 5c was also isolated without cyclization in 28 % yield.
c) The ratio was determined by GLC.

As summarized in the table, the radical cyclization proceeded in 67 % —quantitative yield. The regioselectivity of the ring closure of the radical(1) was the 5-exo mode in all cases and fluorinated tetrahydrofuran derivatives(6) were obtained selectively. Tetrahydropyran via the 6-endo mode could not be detected at all. The radical cyclization of the

unfluorinated system corresponding to 1 has been reported to take a 5-exo course.[8] These results show that fluorine substitution(s) attached to the radical acceptor double bond has no effect on the origin of the ring closure mode of 5-exo. In the reaction of 5g, the radical attacks the gem-difluorinated double bond and trans-substituted double bond in a ratio of 1 : 1.2, which indicates the same reactivities of both double bonds as radical acceptors. In the case of 5h, tandem cyclization(5-exo to the fluorinated double bond followed by 5-exo to the trisubstituted double bond) did not occur, and the ring closure terminated at the first stage to afford 6h. An intermediary carbon radical(7) bearing two fluorine atoms reacted with Bu_3SnH at a rate faster than its addition to the intramolecular double bond.

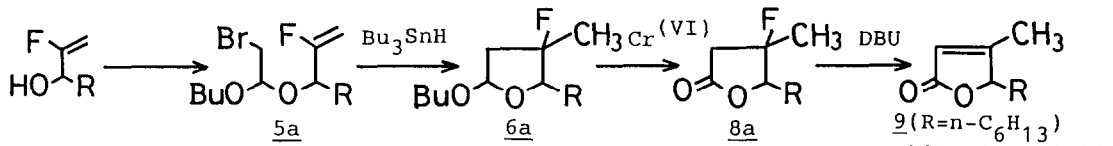
The fluorinated tetrahydrofuran(6) thus obtained was converted to fluorinated γ-butyrolactones(8)[9] by Jones oxidation. Furthermore the reaction of 5a was conducted for the synthesis of butenolide(9)[10] via radical cyclization in three steps(Scheme III).



6a, 6b, 6e, 6f, 6h

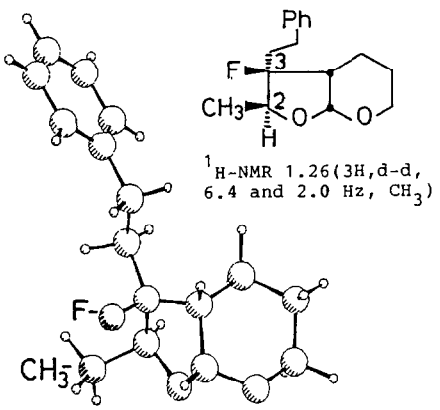
8a(82 %)[a], 8b(67 %)[b], 8e(69 %)[c], 8f[9](71 %), 8h(40 %)

a) A mixture of stereoisomers(6 : 1).
b) A mixture of stereoisomers(ca. 7 : 1 by ^{1}H-NMR).
c) Two steps from cyclization.



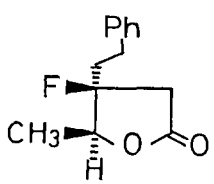
5a → 6a → 8a → 9(R=n-C_6H_{13}) quantitative yield

Scheme III



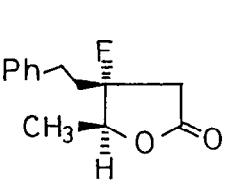
Molecular structure of major isomer of 6c

The stereochemistry of 6c and 8b was established as follows. An X-ray crystallographic analysis of the major isomer of 6c[11] showed a trans configuration of alkyl substituents on C-2 and C-3, and in the NMR spectrum, the ^{1}H resonance assigned to the methyl on C-2 showed a coupling to the syn(cis) fluorine of 2.0 Hz. As expected, in the lactone(8b), the methyl resonance of the major isomer was coupled to syn fluorine(2.2 Hz), whereas in the minor isomer no coupling to anti(trans) fluorine was observed(Scheme IV).



^{1}H-NMR
1.45(3H, d-d, J_{HH}=6.5 and J_{HF}=2.2 Hz, CH_3)
4.43(1H, d-q, J_{HF}=22.1 and J_{HH}=6.5 Hz, CH)

Major isomer of 8b



^{1}H-NMR
1.30(3H, d, J_{HH}=6.9 Hz, CH_3)
4.76(1H, d-q, J_{HF}=20.4 and J_{HH}=6.9 Hz, CH)

Minor isomer of 8b

Scheme IV

Fluorine substitutions for hydrogens in biologically active molecules are important for chemical modification.[12] The present radical cyclization can be applied to the synthesis of fluorinated analogs of some γ-butyrolactones which naturally occur with biological activity.[13] Further studies of radical cyclizations of fluorine-substituted systems and the application of this approach to the synthesis of fluorinated biologically active compounds are now in progress.

References and Notes

1) a) For a review of "Free-Radical Carbon-Carbon Bond Formation in Organic Synthesis", see D. J. Hart, Science, 223, 883 (1984); b) for a review of "Selectivity and Synthetic Applications of Radical Reactions", see B. Giese, Tetrahedron, 41, 3887 (1985).

2) For example, see: a) M. Suda, Tetrahedron Lett., 22, 2395 (1981); b) N. O. Brace and J. E. Van Elswyk, J. Org. Chem., 41, 766 (1976); c) R. D. Chambers, J. Heyes and W. K. R. Musgrave, Tetrahedron, 19, 891 (1963); d) R. D. Chambers, J. Hutchison and W. K. R. Musgrave, Tetrahedron Lett., 1963, 619; e) R. D. Chambers, M. Hole, W. K. R. Musgrave and R. A. Storey, J. Chem. Soc. C., 1967, 53; f) R. N. Haszeldine, J. Chem. Soc., 1953, 3761; g) J. D. LaZerte and R. J. Koshar, J. Am. Chem. Soc., 77, 910 (1955).

3) P. Martin, E. Steiner, J. Streith, T. Winkler and D. Bellus, Tetrahedron, 41, 4057 (1985).

4) a) T. Taguchi, T. Morikawa, O. Kitagawa, T. Mishima and Y. Kobayashi, Chem. Pharm. Bull., 33, 5137 (1985); b) T. Morikawa, I. Kumadaki and M. Shiro, Chem. Pharm. Bull., 33, 5144 (1985).

5) a) Y. Kobayashi, T. Taguchi, M. Mamada, H. Shimizu and H. Murohashi, Chem. Pharm. Bull., 27, 3123 (1979); b) J. F. Normant, J. P. Foulon, D. Masure, R. Sauvetre and J. Villieras, Synthesis, 1975, 122; c) R. Sauvetre and J. F. Normant, Tetrahedron Lett., 22, 957 (1981).

6) J. E. Leibner and J. Jacobus, J. Org. Chem., 44, 449 (1979).

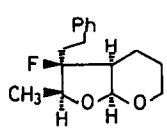
7) Successively, 6f was oxidized by Jones reagent to afford γ-lactone(8f) which gave satisfactory spectral data(see ref. 9).

8) a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya and M. Okawara, J. Am. Chem. Soc., 104, 5564 (1982); b) G. Stork, P. Mook, Jr., S. A. Biller and S. D. Rychnovsky, J. Am. Chem. Soc., 105, 3741 (1983).

9) γ-Lactone(8f): ^{1}H-NMR($CDCl_3$)δ1.99-2.04(2H, m), 2.58-2.91(5H, m), 4.50(1H, d-t, J=7.7 and 5.3 Hz), 5.81(1H, t-d, J=55.7 and 3.9 Hz), 7.19-7.32(5H, m): ^{19}F-NMR($CDCl_3$)δ-59.7(from benzotrifluoride); IR(CCl_4)νcm^{-1}1780-1790(C=O); MS 240(M^+), 200, 180, 129, 177, 91; High Resolution MS: obs. 240.0976, calc. for $C_{13}H_{14}F_2O_2$, 240.0961.

10) Butenolide(9): ^{1}H-NMR($CDCl_3$)δ0.88(3H, t, J=6.8 Hz), 1.24-1.94(10H, m), 2.05(3H, bs), 4.83 (1H, m), 5.79(1H, m); IR(CCl_4)νcm^{-1}1765(C=O); MS 182(M^+), 153, 113, 111, 98, 97, 69; High Resolution MS: obs. 182.1302, calc. for $C_{11}H_{18}O_2$, 182.1305.

11) Tentatively, the minor isomer of 6c is assigned as follows:



^{1}H-NMR($CDCl_3$)δ1.40(3H, d-d, J=6.6 and 3.2 Hz), 1.77-2.17(7H, m), 2.69(1H, d-d-d, J=13.3, 12.3 and 5.1 Hz), 2.78(1H, d-d-d, J=13.3, 12.5 and 4.9 Hz), 3.44(1H, m), 3.94(1H, m), 4.17(1H, d-q, J=20 and 6.6 Hz), 5.04(1H, d, J= 4.1 Hz), 7.18-7.32(5H, m).

12) "Biomedicinal Aspects of Fluorine Chemistry", ed. by R. Filler and Y. Kobayashi, Kodansha Ltd. (Tokyo), Elsevier Biomedical Press, 1982.

13) For example, difluoro-γ-lactone(8h) is an analog of (±)-eldanolide, the wing gland pheromone of Eldana saccharina(wlk); G. Kunesch, P. Zagatti, J. Y. Lallemand, A. Debal and J. P. Vigneron, Tetrahedron Lett., 22, 5271 (1981).

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