Tetrahedron Letters, Vol.22, No.52, pp 5297-5300, 1981 0040-4039/81/525297-04$02.00/0
Printed in Great Britain

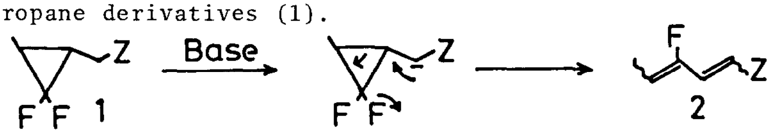
A STEREOSPECIFIC SYNTHESIS OF CONJUGATED FLUORODIENES BY A RING-OPENING REACTION OF gem-DIFLUOROCYCLOPROPANE DERIVATIVES

Yoshiro Kobayashi,* Tsutomu Morikawa, Atsuko Yoshizawa, and Takeo Taguchi

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

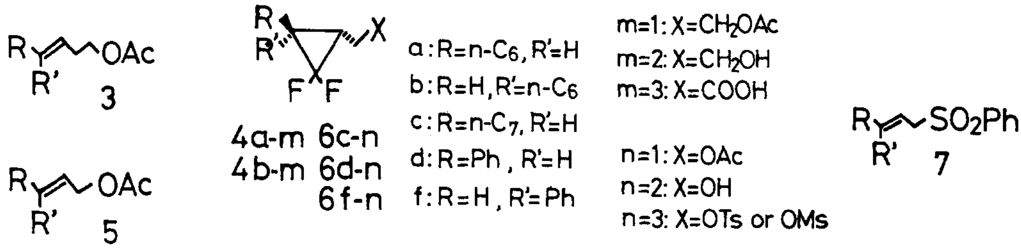
SUMMARY: Ring-opening reactions of trans- and cis-gem-difluorocyclopropane derivatives (1) with appropriate bases proceeded stereospecifically to give (E, E)- and (E, Z)-fluorodiene derivatives (2), respectively.

Fluoropolyenes such as fluororetinoids, fluoroisoprenoids and some other fluoroterpenes, have recently been attracting attentions owing to their biological activities or availabilities to study the biological mechanism of parent compounds.[1,2] Although many synthetic methods for such fluoroolefins have been reported, there are few cases which have satisfactory stereoselectivity for the construction of fluorinated double bond.[2] In the course of our studies to explore the synthetic reactions by utilizing difluorocyclopropane derivatives,[3] a stereospecific synthesis of conjugated fluorodienes (2) was established through the α-carbanion which initiated ring-opening reaction of the gem-difluorocyclopropane derivatives (1).

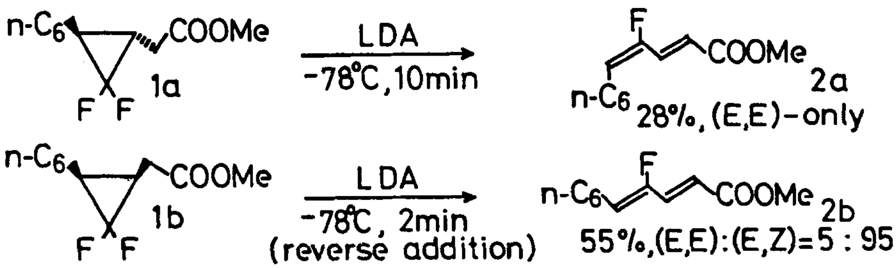


Z = COOMe, CN, SO2Ph

The starting gem-difluorocyclopropanes (1) were synthesized in the following way. The stereospecific cis-addition of difluorocarbene generated by pyrolysis (170-180°C) of sodium chlorodifluoroacetate ($ClCF_2COONa$) to olefinic compounds (3, 5, 7) gave the corresponding difluorocyclopropanes (4a-1, 4b-1, 6c-1, 6d-1, 1e, 6f-1, 1g, 1h). Conversion of 4a-1 and 4b-1 to the corresponding carboxylic acid methyl ester (1a and 1b)[4] was achieved by successive hydrolysis (KOH, MeOH-THF), Jones oxidation (CrO_3-H_2SO_4, acetone) and esterification (CH_2N_2, ether). The nitrile derivatives (1c and 1d) were synthesized from 6c-1 and 6d-1 in three steps: hydrolysis (KOH, MeOH-THF), tosylation (TsCl/Py, CH_2Cl_2) and cyanation (KCN/cat. 18-Crown-6, DMF). The sulfone derivative (1f)[5] was obtained by bromination (LiBr, acetone) of the mesylate (6f-3), followed by sulfonylation ($PhSO_2Na$, DMF).

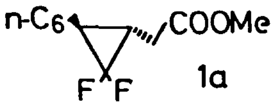
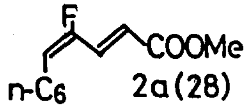
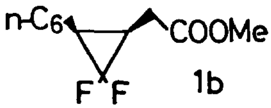
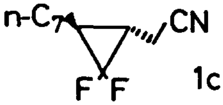
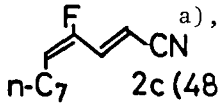
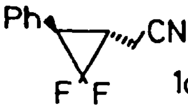
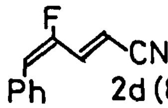
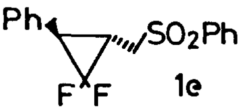
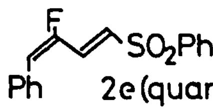
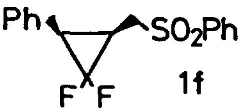
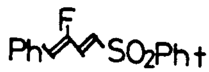
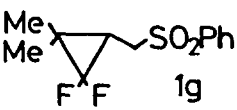
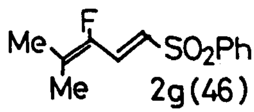
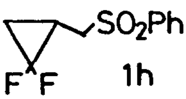
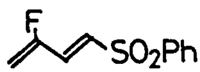


Treatment of trans-difluorocyclopropane (1a) with 1.1 equiv. of LDA in THF at -78°C for 10 min afforded methyl (2E, 4E)-4-fluoro-2,4-undecadienoate (2a) [^{1}H-NMR (CCl_4) δ 5.44 (dt, J=20 and 8 Hz), 6.08 (d, J=16 Hz), 7.22 (dd, J=28 and 16 Hz); ^{19}F-NMR (CCl_4) δ +55.0 (dd, J=28 and 20 Hz)] in 28% yield with recovery of the starting cyclopropane. On the other hand, in the reaction of cis-difluorocyclopropane (1b), 2b (2E, 4Z) [^{1}H-NMR (CCl_4) δ 5.17 (dt, J=35 and 8 Hz), 6.00 (d, J=16 Hz), 6.97 (dd, J=26 and 16 Hz); ^{19}F-NMR (CCl_4) δ +60.5 (dd, J=35 and 26 Hz)] was the major product [55%, (2E, 4Z):(2E, 4E)=17:1], along with recovery of 1b (24%). The configuration of 2 was confirmed by the magnitude of the coupling constant of the olefinic protons and a fluorine in the NMR spectrum. Similar stereospecificity was found when the difluorocyclopropanes (1c, 1d, 1e), except in the case of 1f, were treated with appropriate bases (Table).

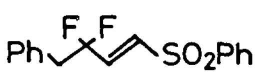


In the case of entry 1-3, LDA was found to be a suitable base and reverse addition of a solution of LDA in THF to difluorocyclopropanes in THF at -78°C (entry 2 and 3) resulted in an increase of the yields of fluorodienes. Although treatment of 1d with 1.1 equiv. of LDA at -78°C for 10 min resulted in trace amount of 2d accompanied by the formation of complex polymer, the use of potassium hydroxide as a base afforded 2d (2E, 4E)[^{1}H-NMR ($CDCl_3$) δ 5.73 (d, J=16 Hz), 6.62 (d, J=18 Hz), 7.13 (dd, J=24 and 16 Hz); ^{19}F-NMR ($CDCl_3$) δ +55.0 (dd, J=24 and 18 Hz)] in a good yield (entry 4). Similarly, 1e gave (1E, 3E)-3-fluoro-4-phenyl-1,3-butadienylphenylsulfone (2e)[mp 92-93°C (from EtOH); ^{1}H-NMR ($CDCl_3$) δ 6.70 (d, J=19 Hz), 6.75 (d, J=15 Hz); ^{19}F-NMR ($CDCl_3$) δ +51.0 (dd, J=26 and 19 Hz)], which readily isomerized to (1E, 3Z)-fluorodiene [mp 127°C (from EtOH); ^{1}H-NMR ($CDCl_3$) δ 6.07 (d, J=36 Hz), 6.62 (d, J=15 Hz); ^{19}F-NMR ($CDCl_3$) δ +54.3 (dd, J=36 and 24 Hz)] by silica gel column chromatography. In contrast to the facile ring-opening of 1e, no ring-opening product was detected

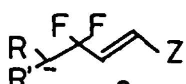
Table. Synthesis of fluorodiene derivatives (2)

Entry	Difluorocyclopropane	Conditions: Base	Conditions: Temp.	Conditions: Time	Fluorodiene (Yield, %)	(E,E):(E,Z)
1	 1a	LDA	-78°C	10 min	 2a (28)	(E,E)-only
2	 1b	LDA	-78°C	2 min	 [a),b)] 2b (55)	5 : 95
3	 1c	LDA	-78°C	0.5 min	 [a),c)] 2c (48)	91 : 9
4	 1d	KOH	r.temp.	7.5 hr	 2d (85)	84 : 4 : 12[d)]
5	 1e	KOH	r.temp.	5 hr	 2e (quant.)	ca. 95 : 5[e)]
6	 1f	KOH	r.temp.	5 hr	2e +  + 8 2f (quant.)	48 : 35 : 17[e)]
7	 1g	LDA	-78°C	3 min	 2g (46)	—
8	 1h	KOH	60°C	24 hr	 2h (49)	—

a) Reverse addition of LDA to difluorocyclopropane.
b) 31% (87:13) by usual addition operation (-78°C, 10 min).
c) 18% (88:12) by usual addition operation (-78°C, 3 min).
d) (E,E):(E,Z):(Z,E).
e) The ratio was determined from the relative intensities of ^{19}F-NMR signals.



8



9

when 1g was treated under the same conditions. A much stronger base (LDA) was necessary to complete the reaction (entry 7). In the case of non-substituted difluorocyclopropane (entry 8), the ring-opening was slow (KOH, H_2O-THF) compared with the cyclopropane having a phenyl substituent (1d and 1e) and the yield of desired fluorodiene (2h) was moderate. It is apparent that the substituent on difluorocyclopropane affects the reactivity of this ring-opening.[6] Non-stereospecificity in the reaction of 1f was observed and difluoro derivative (8) was also isolated. These results may suggest that the course of the ring-opening reaction of difluorocyclopropane (1) does not involve the concerted process, but follows two step pathways, i.e. ring-opening of 1 to provide an intermediary anion (9), and elimination of a fluoride anion to afford 2.[7]

In conclusion, the ring-opening reaction of gem-difluorocyclopropane derivatives (1) proceeds in a stereospecific manner to afford (E, E)-fluorodiene from trans-cyclopropane and (E, Z)-isomer from cis-one. Further investigation and the application to the syntheses of fluorinated biological active compounds are now in progress.

References and Notes

1) B. A. Pawson, K. Chan, J. DeNoble, R. L. Han, V. Piermattie, A.C. Specian, and S. Srisethnil, J. Med. Chem., 22, 1059 (1979), and references cited therein.

2) M. Schlosser, Tetrahedron, 34, 3 (1978).

3) Y. Kobayashi, T. Taguchi, M. Mamada, H. Shimizu, and H. Murohashi, Chem. Pharm. Bull (Tokyo), 27, 3123 (1979); Y. Kobayashi, T. Taguchi, T. Morikawa, T. Takase, and H. Takanashi, Tetrahedron Lett., 21, 1047 (1980).

4) 1a(trans): ^{19}F-NMR (CCl_4) δ +74.8 (dd, J=156 and 13.2 Hz), +77.8 (dd, J=156 and 13.2 Hz); IR (NaCl) 1740 cm^{-1}. 1b(cis): ^{19}F-NMR ($CDCl_3$) δ +63.7 (dt, J=154 and 12.2 Hz), +91.0 (d, J=154 Hz); IR (NaCl) 1750 cm^{-1}; 1b:1a= 97:3 by GLC. Benzotrifluoride is used as internal standard: + indicates high field.

5) 1e(trans): mp 118°C; ^{19}F-NMR ($CDCl_3$) δ +70.7 (dd, J=151 and 12.2 Hz), +75.7 (dd, J=151 and 12.2 Hz); IR (KBr) 1310, 1150 cm^{-1}; MS m/e 308 (M^+). 1f(cis): mp 120-122°C ; ^{19}F-NMR ($CDCl_3$) δ +59.0 (dt, J=159 and 13.2 Hz), +83.3 (d, J=159 Hz); IR (KBr) 1300, 1150 cm^{-1}; MS m/e 308 (M^+).

6) W. E. Parham, W. D. McKown, V. Nelson, S. Kajigaeshi, and N. Ishikawa, J. Org. Chem., 38, 1361 (1973).

7) P. Crabbe, J. Luche, J. Damiano, M. Luche, and A. Cruz, J. Org. Chem., 44, 2929 (1979).

(Received in Japan 5 September 1981)