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A Convenient Stereoselective Synthesis of Fluorinated α-Alkylidene-γ-Butyrolactone Derivatives

Xiyan Lu*, Zhong Wang and Jianguo Ji

Shanghai Institute of Organic Chemistry, Academia Sinica,
354 Fenglin Lu, Shanghai 200032, China

Abstract Fluorinated α-alkylidene-γ-butyrolactone derivatives were synthesized stereoselectively via a sodium dithionite initiated radical perfluoroalkylation-cyclization of acyclic allylic alkynoates in high yields under mild conditions.

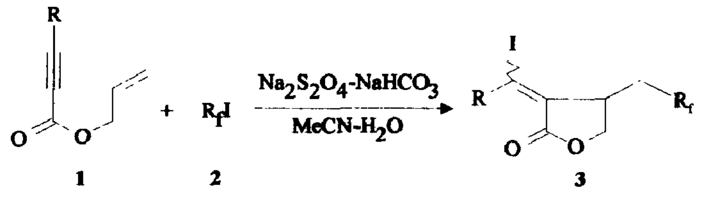
Organofluorine chemistry nowadays plays an important role in searching and inventing new biologically active compounds due to the profound effects on biological properties through introduction of fluorine atoms into organic molecules[1,2] In this respect, synthesis of partially fluorinated natural products is a project of special interest. [2,3] α-Methylene-γ-butyrolactone derivatives are a major class of skeleton in naturally occurring sesquiterpene lactones which exhibit important physiological activities; their syntheses have been attracting more and more interest.[4] However, despite the abundance of research on this subject, synthesis of their fluorinated analogs has not been reported yet.

Recently, we developed a new methodology for the synthesis of α-methylene-γ-butyrolactone derivatives via a divalent palladium catalyzed cyclization of acyclic 2-alkynoates.[5,6] Lee applied a radical cyclization to construct the lactone ring from allylic 2-alkynoates.[7] Huang et al. utilized sodium dithionite to initiate the addition of R_fI to olefinic and acetylenic compounds.[8] We wish to report herein the synthesis of fluorinated α-alkylidene-γ-butyrolactone derivatives via a novel selective perfluoroalkyl radical addition-cyclization reaction of allylic alkynoates initiated by sodium dithionite.

In the presence of sodium dithionite and sodium bicarbonate, perfluoroalkyl iodides **2A-D** smoothly reacted with allylic alkynoates **1a-c** at 10-15°C in aqeous acetonitrile to give cyclic products(Table 1).[9] In most cases, the reactions were completed within a few minutes. When R=n-C_8H_{17} or R_f=Cl(CF_2)$_8$, the reactions were somehow slower, but still completed within 30 minutes (entries 7-9). Best yields were obtained for allyl 2-butynoate (**1b**, entries 4-6). Allyl propynoate (**1a**) gave lower yields probably due to the high reactivity of the terminal triple bond (entries 1-3).

The configuration of the exocyclic C=C double bond in **3** was determined by comparing the chemical shifts of the vinylic protons (R=H) or the allylic protons in the R group (R=CH_3, n-C_8H_{17}).[5,6] In the case of unsubstituted propynoate (**1a**), the stereoselectivities were poor (entries 1-3). While in the case of substituted propynoates (**1b-c**), (E)-forms of **3** were predominantly obtained (entries 4-9). This significant change was striking but not completely unexpected. A proposed mechanism is outlined in Scheme I. Sodium dithionite generates the perfluoroalkyl radical by transferring an electron to R_fI,[10] thus initiates the reaction. Due to the electrophilic nature of $R_f\cdot$, it then preferrentially adds to the electron rich allylic double bond, in contrast to Lee's report[7] in which tributyltin radical adds to the electron deficient triple bond. The cyclization of the intermediate radical **4** is then followed by iodine atom transfer from R_fI to the resulting vinyl radical **5**, thus completes the chain transfer step. Vinyl radicals were reported to undergo rapid inversions even at very low temperatures.[11] When R is methyl or a larger alkyl group, a 1,3-allylic interaction between R and R_fCH_2 is present in (Z)-**5**,[12] therefore this isomerization equilibrium favors (E)-**5**, which upon iodine atom abstraction affords (E)-**3**. The stereoselectivity (E/Z >95:5) is much higher than that reported by Curran in a trisubstituted vinyl iodide(E/Z=1:1),[13] and is similar to the results of Malacria[14] and Weiler[15] in which hydrogen atom from Bu_3SnH, instead of iodine, transfers to exocyclic

Table 1 $Na_2S_2O_4$**-**$NaHCO_3$ **initiated reaction of** R_fI**(2) with allylic 2-alkynoates(1)**[a]



entry	1 R	2 R_f	Time (min)	Product[b]	Combined isolated yield(%)	E:Z
1	**H(1a)**	CF_3**(2A)**[d]	10	**3aA**	44	32:68[c]
2	**H(1a)**	$Cl(CF_2)_2$**(2B)**	10	**3aB**	47	60:40[c]
3	**H(1a)**	$Cl(CF_2)_4$**(2C)**	10	**3aC**	50	52:48[e]
4	CH_3**(1b)**	CF_3**(2A)**[d]	5	**3bA**	80	95: 5[c]
5	CH_3**(1b)**	$Cl(CF_2)_2$**(2B)**	10	**3bB**	83	>97: 3[e]
6	CH_3**(1b)**	$Cl(CF_2)_4$**(2C)**	10	**3bC**	82	>97: 3[e]
7	CH_3**(1b)**	$Cl(CF_2)_8$**(2D)**	30	**3bD**	92	>97: 3[e]
8	n-C_8H_{17}**(1c)**	$Cl(CF_2)_2$**(2B)**	20	**3cB**	60	>97: 3[e]
9	n-C_8H_{17}**(1c)**	$Cl(CF_2)_4$**(2C)**	20	**3cC**	62	>97: 3[e]

a. Reaction conditions. The mixture of **1**(1mmol), **2**(1mmol), $Na_2S_2O_4$(256mg, 1.5mmol), $NaHCO_3$(126mg, 1.5mmol), MeCN(3mL) and H_2O(2mL) was stirred at 10-15°C.

b. The products were confirmed by ^1H NMR, ^{19}F NMR, IR and mass spectra data.

c. E/Z ratios were determined by isolation.

d. Gaseous CF_3I was passed through a stirred mixture of **1**, $Na_2S_2O_4$, $NaHCO_3$, MeCN and H_2O.

e. Isomers were not separated, and E/Z ratio was determined by ^1H NMR spectra.

alkenyl radicals (E/Z=100:0 and 98:2 respectively). This might be rationalized by assuming that the rate of iodine atom tranfer from R_fI is slower than that from RI but approximates the rate of hydrogen atom transfer from low concentration Bu_3SnH, which allows the preliminary equilibrium of inverting vinyl radicals.[16] When R=H, (E)-5 and (Z)-5 are similar in energy because of the absence of 1,3-allylic interaction, the reaction gives comparable amount of two isomers (E/Z around 1).

Scheme I

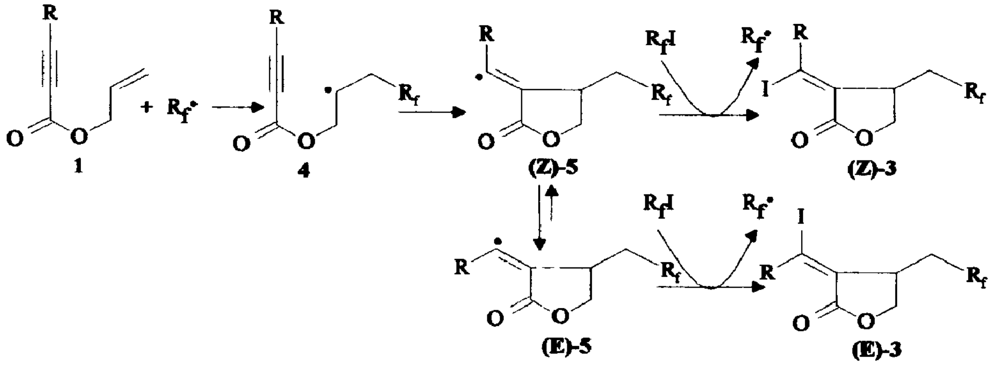
Initiation

$$S_2O_4^{2-} \rightleftarrows 2\,SO_2^{\bullet -}$$

$$SO_2^{\bullet -} + R_fI \longrightarrow R_fI^{\bullet -} + SO_2$$

$$R_fI^{\bullet -} \longrightarrow R_f^{\bullet} + I^-$$

Propagation



Changing perfluoroalkyl iodides seemed to have little effects on the stereoselectivity and yield of the reaction. Water content of the solvent mixture is crucial, and the optimum volume ratio of H_2O to MeCN is 0.6-1. A lower or a higher water content results in poor mutual solubility of different reactants. A slightly excess sodium dithionite and sodium bicarbonate may help to accomplish the transformation quickly.

In summary, the sodium dithionite initiated perfluoroalkylation-cyclization is an efficient method to synthesize fluorinated α-alkylidene-γ-butyrolactone derivatives with good stereoselectivity; and it has great practical prospect because of the ready availability of starting materials and ease of manipulation.

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References and notes:

1 Filler, R.; Kobayashi, Y. "Biomedicinal Aspects of Fluorine Chemistry", Kodansha, Tokyo, 1982.
2 Welch, J. T. Tetrahedron, 1987, **43**, 3123.
3 Rozen, S. Acc. Chem. Res. 1988, **21**, 307. For recent examples, see Hu, C. -M.; Qiu, Y. -L. J. Chem.

Soc. Perkin. Trans. 1 , 1993 , 331; Phililion, D. P.; Cleary, D. G. J. Org. Chem. 1992, **57**, 2763; Tsukamo, T.; Kitazume, T. J. Chem. Soc. Chem. Commun. 1992, 540.

4 Oliver, E. J.; Fischer, H. D. in "Progress in the Chemistry of Organic Natural Products", Herz, W.; Griesebach, H.; Kirby, G. W.(eds) 1979, vol.**38**, Springer-Verlag, New York, p47; Hoffman, H. M. R.; Rabe, J. Angew. Chem. Int. Ed. Engl. 1985, **24**, 94; Petragnani, N.; Ferraz, H. M. C.; Siwa, G. V. Synthesis, 1986, 157.

5 Ma, S.; Lu, X. J. Chem. Soc. Chem. Commun. 1990, 773; Ma, S.; Lu, X. J. Org. Chem. 1991, **56**, 5120.

6 Ma, S.; Lu, X. J. Org. Chem. 1993, **58**, 1245.

7 Lee, E.; Ko, S. B.; Jung, K. W.; Chang, M. H. Tetrahedron Lett. 1989, **30**, 827.

8 Huang, W. -Y.; Wang, W.; Huang, B. N. Acta Chim. Sin. 1985, **43**, 409; Chem. Abstr. 1986, **104**, 50507; Huang, W. -Y.; Lu, L.; Zhang, Y. -F. Chin. J. Chem. 1990, 348; Chem. Abstr. 1991, **114**, 142603.

9 Typical spectral and analytical data: (E)-**3aB:** mp 60-62°C. ^{1}H NMR (300MHz, CDCl$_3$) 8.01(d, J=2.1Hz, 1H), 4.52 (dd, J=9.8Hz, J=7.3Hz, 1H), 4.44(dd, J=9.8Hz, J=2.1Hz, 1H), 3.45-3.60 (m, 1H) , 2.60-2.86(m,1H), 2.23-2.47(m, 1H); ^{19}F NMR (60MHz, CCl$_4$/CFCl$_3$) -71.0(s, 2F), -112.6(brs, 2F); MS(m/z): 374(M+(37Cl)), 372(M+(35Cl)), 342, 328, 314, 245, 195, 167, 101, 85, 65, 57; IR: 3050, 1760, 1630, 1180, 1100, 1050, 740, 530cm^{-1}; HRMS: Calc. for $C_8H_6ClF_4IO_2$: 371.9036, Found: 371.9085. (E)-**3bC:** mp 53-55°C. ^{1}H NMR (300MHz, CDCl$_3$) 4.40(d, J=10.1Hz, 1H), 4.36(d, J=10.1Hz, -111.0(brs, 2F), 119.5(s, 2F), -122.6 (2F); MS(m/z): 486(M+(35Cl)), 359, 315, 295, 279, 209, 149, 1H), 3.48-3.58(m, 1H), 3.13(s, 3H), 2.2-2.7(m, 2H); ^{19}F NMR (60MHz, CCl$_4$/CFCl$_3$) -67.5(s, 2F), 85, 65; IR: 2930, 1760, 1640, 1180, 1120, 1080, 1020, 770, 530 cm^{-1} HRMS: Calc. for $C_{11}H_8ClF_8O_2$: 359.0084, Found: 359.0069.

10 Huang, W. -Y. J.Fluorine Chem. 1992, **58**, 1.

11 Whitesides, G. M.; Cassey, C. P.; Krieger, J. K. J. Am. Chem. Soc. 1971, **93**, 1379; Curran, D. P.; Chen, M. H.; Kim, D. J. Am. Chem. Soc. 1989, **111**, 6265.

12 Singer, L. A.; Kong, N. P. J. Am. Chem. Soc. 1966, **88**, 5213; Kampmeier, J. A; Chen, G. J. Am. Chem. Soc. 1965, **87**, 2508; Liu, M. S.; Soloway, S.; Wedogaert, D. K.; Kampmeier, J. A. J. Am. Chem. Soc. 1971, **93**, 3809.

13 Curran, D.P.; Chang, C. T. Tetrahedron Lett. 1987, **28**, 2477.

14 Journet, M.; Malacria, M. J. Org. Chem. 1992, **57**, 3085; Journet, M.; Malacria, M. Tetrahedron Lett. 1992, **33**, 1893.

15 Lowinger, T. B.; Weiler, L. J. Org. Chem. 1992, **57**, 6099.

16 Curran, D. P.; Chen, M. H.; Kim, D. J. Am. Chem. Soc. 1986, **108**, 2489.

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