Preparation of Masked 2,2-Difluoro-1,3-diols and 2,2-Difluoro-1,3,4butanetriol via Photochemical and Thermal Addition of Oxygenated Radicals to 2,2-Difluorovinyl Carbamate

Takashi Okano,* Akira Nakajima, Shoji Eguchi

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan Fax +81-52-789-3199; E-mail: okano@apchem.nagoya-u.ac.jp Received 14 June 2001

Abstract: Photoreaction of difluorovinyl carbamate in some alcohols except for methanol gave radical addition products as masked forms of 2,2-difluoro-1,3-diols. 1,3-Dioxolane also gave a radical product in thermal radical reaction initiated bynzoyl peroxide. Radical product of 2,2-Dimethyl-1,3-dioxolane was converted into masked 2,2-difluoro-1,3-propanediol.

Key words: acetals, fluorine, free radicals, diols, photochemistry

Difluoromethylene compounds are attracting increasing interests in the view of potential biological activities.¹ However, the synthetic methods for the difluoromethylene building blocks² are still limited except for the usually employed moderately reactive Reformatsky reagent derived from BrCF₂CO₂Et and the modified reagents.³ Our synthetic strategy for the difluoromethylene compounds is trapping of alkyl radicals with the suitably substituted *gem*-difluoro olefins.⁴ Steric effect and destabilizing effect of fluoroolefins caused by $n-\pi$ repulsive interaction between the fluorine atom and the C–C double bond control the regiochemistry of the addition of alkyl radicals. We report here radical addition of α -hydroxy or alkoxy radicals to 2,2-difluorovinyl carbamate to yield masked 2,2-difluoro-1,3-diols and 2,2-difluoro-1,3,4-butanetriol.

2,2-Difluorovinyl N,N-diethylcarbamate (1) was prepared according to the procedure reported by Percy et al.⁵ UV irradiation of 1 by a 100-W high-pressure mercury lamp with a quartz filter in ethanol for 32 h at 5.0 mmol scale gave 2,2-difluoro-3-hydroxybutyl carbamate (2a) in 82% yield.⁶ The photochemically generated α -hydroxyethyl radical⁷ reacted with **1** at the fluorinated carbon as expected. The regiochemistry was confirmed by the ¹⁹F NMR spectrum, in which two diastereotopic fluorine peaks coupled each other $(J_{F-F} = 262 \text{ Hz})$ showed also coupling with three vicinal protons. In a similar manner, both 1-propanol and 2-propanol gave the corresponding difluoro-1,3-diol monocarbamates 2b,c in 81% and 88% yields, respectively (Table). However, photochemical generation of hydroxymethyl radical is unlikely to occur, and no addition product was obtained in the reaction of 1 in methanol. Prolonged reaction caused replacement of fluorine by methoxide followed by hydrolysis to dimethoxyacetate probably via dark ionic reaction. Addition of an alternative C1-block radical was performed by the photoreaction of **1** in 1,3-dioxolane to give ethylene acetal of α , α -difluoroaldehyde 3 accompanied with an isomeric product 4a in 86% yield as a mixture (**3**: **4a** = 83: 17). The reaction time depends on the stability of the generated oxygenated radicals. The reaction in 2-propanol, in which a stable tertiary hydroxyisopropyl radical is involved, took 4 h for 1.0 mmol of **1** to disappear from the reaction mixture. 1,3-Dioxolan-2-yl radical is also stable and photoreaction of 1.0 mmol of **1** in 1,3-dioxolane took 7 h.

Table Photoreaction¹⁾ of Difluorovinyl Carbamate 1 in Alcohols

F F	OCON(C	+ 2H5)2		R1 F F OCON(C ₂ H ₅) ₂ OH 2a-c
	R ¹	R ²	Reaction time (h)	Products (Yield %)
	CH ₃	н	32 ²⁾	2a (82)
	C_2H_5	Н	31 ²⁾	2b (81)
	CH ₃	CH ₃	20 ²⁾	2c (88)
	Н	Н	80	3)

¹⁾A 100-W high-pressure mercury lamp and a quartz filter were used. ²⁾Reaction time for 100% conversion of 5.00 mmol of **1**. ³⁾Slow methanolysis of **1** was observed.

For a preparative scale of the synthesis of **3**, photoreaction takes long time, so that we tried thermal radical reaction using radical initiators. While azobisisobutyronitrile was not effective because of low energy of the generated radical, reaction of carbamate **1** in 1,3-dioxolane at 80 °C initiated by benzoyl peroxide gave a mixture of **3** and **4a** (73: 27) in 75% yield with small amounts of some unidentified products. Although neither photochemical nor thermal reaction conditions gave radical adduct in ethylene glycol, thermal radical addition of 2,2-dimethyl-1,3-dioxolane to **1** initiated with benzoyl peroxide gave the addition product **4b** in 63% yield without regiochemical problem^{8,9} (Scheme 1).

Acetals 3 and 4 would be the versatile precursors as the masked forms of multifunctional difluoromethylene compounds. Thus, deacetalization of 3 was attempted using typical acidic conditions. However, the acetal structure of 3 is surprisingly stable to acid even at such strong condi-



Scheme 1 Reagents and conditions: i) hv; ii) $(C_6H_5COO)_2$, 80 °C; iii) HCl/CH₃OH rt; iv) NaIO₄, rt; v) NaBH₄/CH₃OH, rt.

tions as refluxing in *conc*. HCl (12 M) because of the carbocation-destabilizing inductive effect of the difluoro substitution at the α -carbon. On the contrary, isopropylidene acetal **4b** was readily deacetalized with *conc*. HCl in CH₃OH (1:10) at room temperature to hydroxy carbamate **5** in 76% yield. Oxidative cleavage of diol **5** with sodium periodate followed by NaBH₄ reduction of the resulting mixture of the corresponding aldehyde and aldehyde–hydrate gave the desired masked 2,2-difluoro-1,3propanediol derivative **6** in 71% yield from **5** (Scheme 1).

Monoalcohol **6** was utilized for the synthesis of a potentially ferroelectric material **7**, which has two major (CF₂) and four minor (-O-) parallel dipoles perpendicular to the long molecular axis.¹⁰ Bis-ether formation to **8** was achieved with *m*-bisbromomethylbenzene and NaH in THF followed by transesterification with KOH in refluxing 2-propanol to give diol **9** in 56% yield from **6**. Bisbenzylation of diol **9** with benzyl bromide and NaH in THF led tetrafluorinated linear ether **7** in 56% yield (Scheme 2).

In summary, alcohols **2a-c**, **5** and **6** were prepared by the radical reaction initiated by irradiation or benzoyl peroxide. These polyol derivatives are expected to be employed as the starting materials for the synthesis of biologically active compounds and functional materials including potentially ferroelectric **7**.

References and Notes

- Recent examples: Esler, W. P.; Kimberly, W. T; Ostaszewski, B. L.; Diehl, T. S.; Moore, C. L.; Tsai, J.-Y.; Rahmati, T.; Xia, W.; Selkoe, D. J.; Wolfe, M. S. *Nat. Cell Biol.* **2000**, *2*, 428. Shiozaki, M.; Arai, M.; Macindoe, W. M.; Mochizuki, T.; Wakabayashi, T.; Kurakata, S.; Tatsuta, T.; Maeda, H.; Nishijima, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1149.
- (2) For reviews of preparation of difluoromethylene compounds, see: (a) Burton, D. J., Drakesmith, F. G.; Hutchinson, J.; Kitazume, T.; Lu, L.; Percy, J. M.; Sanford, G.; Yamazaki, T. In *Organofluorine Chemistry, Techniques and Synthesis*; Chambers R. D., Ed.; Springer: Berlin, 1997. (b) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.
- (3) Fried, J.; Hallinan, E. A.; Szwedo, Jr., M. F. J. Am. Chem. Soc. 1984, 106, 3871. Hallinan, E. A.; Fried, J. Teterhedron Lett. 1984, 25, 2301. Kitagawa, O.; Taguchi, T.; Kobayashi, Y. Tetrahedron Lett. 1988, 29, 1803. Lang, R. W.; Schaub, B. Tetrahedron Lett. 1988, 29, 2943. Kitagawa, O.; Murata, A.; Kobayashi, Y.; Taguchi, T. Chem. Lett. 1990, 1011. Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. Chem. Lett. 1990, 1307.
- (4) Okano, T.; Takakura, N.; Nakano, Y.; Okajima, A.; and Eguchi, S. *Tetrahedron* **1995**, *51*, 1903. Okano, T.; Ishihara, H.; Takakura, N.; Tsuge, H.; Eguchi, S.; Kimoto, H. *J. Org. Chem.* **1997**, *62*, 7192.
- (5) Benett, A. J.; Percy, J. M.; Rock, M. H. Synlett **1992**, 483. Lee, J.; Tsukazaki, M.; Sniekus, V. Tetrahedron Lett. **1993**, 34, 415.
- (6) Experimental procedure for the photoreaction of difluoro olefin **1** in ethanol: A stirred mixture of **1** (895 mg, 5.0 mmol) in EtOH (70 mL) at room temperature was irradiated by a 100-W high-pressure-mercury lamp with a quartz filter under Ar atmosphere for 32 h until no **1** was detected by GLC. The solvent was removed under reduced pressure. The residue was purified by distillation with a Kugel-Rohr distillation apparatus to give pure alcohol **2a** as colorless oil: 917 mg (82%); bp 150 200 °C/ 3 mmHg; ¹H NMR (CDCl₃, 300 MHz) δ 1.150 (6 H, t, *J* = 7.5 Hz), 1.309 (3 H, d, *J* = 6.6 Hz), 3.31 (4 H, m), 3.857 (1 H, dqd, *J* = 19.8, 6.6, 3.6 Hz), 4.151 (1 H, td, *J* = 12.6, 6.9 Hz), 4.731 (1 H, ddd, *J* = 23.4, 12.6, 6.0 Hz): ¹⁹F NMR [CDCl₃, 282 MHz, internal standard: CF₃COOC₂H₅ (δ -75.75 from CFCl₃)] δ -115.6 (ddd, 1 F, *J* = 262, 24, 12 Hz), -126.5 (ddt, 1 F, *J* = 262, 19, 6 Hz).
- (7) Elad, D. Organic Photochemistry, Vol. 2; Chapman, O., Ed.; Marcel Dekker: New York, 1969; p 168.
- (8) Experimental procedure for the radical reaction of difluoroolefin 1 in 2,2-dimethyl-1,3-dioxolane: To a stirred solution of 1 (1.00 g, 5.6 mmol) in 2,2-dimethyl-1,3-dioxolane (10 mL) at 80 °C, benzoyl peroxide (200 mg, 0.83 mmol) was periodically (every 20 min) added in portions. After



Scheme 2 Reagents and conditions: i) m-(BrCH₂)₂C₆H₄, NaH/THF, rt.; ii) KOH/(CH₃)₂CHOH, reflux; iii) HCl; iv) C₆H₅CH₂Br, NaH/THF, rt.

Synlett 2001, No. 9, 1449-1451 ISSN 0936-5214 © Thieme Stuttgart · New York

disappearance of olefin **1** in the gas chromatogram, excess dioxolane was removed by distillation (bp 93 °C). The residue was chromatographed on a silica gel column (hexane – EtOAc, 2: 1) to afford **4b** as colorless oil: 983 mg, 63%. ¹H NMR (CDCl₃, 500 MHz) δ 1.144 (t, 6 H, *J* = 7.2 Hz), 1.371 (s, 3 H), 1.454 (s, 3 H), 3.30 (m, 4 H), 4.134 (dd, 1 H, *J* = 9, 8Hz), 4.213 (dd, 1 H, *J* = 9, 5 Hz), 4.52 – 4.25 (m, 3 H): ¹⁹F NMR (CDCl₃, 282 MHz) δ –115.8 (dtd, 1 F, *J* = 261, 17, 5 Hz), – 123.4 (dddd, 1 F, *J* = 261, 21, 12, 5 Hz).

(9) During the course of this research, photochemical and thermal radical reactions of 1,3-dioxolane and 2,2-dimethyl-1,3-

dioxolane with some perfluoroolefins have been reported while the reported method can not provide 1,3-diol derivatives: Církva, V.; Paleta, O. *J. Fluorine Chem.* **1999**, *94*, 141.

(10) T. Furukawa, Phase Transitions 1989, 18, 143.

Article Identifier:

1437-2096,E;2001,0,09,1449,1451,ftx,en;Y21501ST.pdf