ELSEVIER

Journal of Fluorine Chemistry 84 (1997) 45–47

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of 2-fluorotetronic acid

Ping Ge, Kenneth L. Kirk *

Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA

Received 20 November 1996; accepted 25 February 1997

Abstract

Fluorination of 2-bromotetronic acid (**7**) in ethanol produces 2-bromo-3-ethoxy-2-fluoro-γ-butyrolactone (**8**). Tributyltin hydride reduction of **8** gives 2-fluorotetronic acid in good yield.

Keywords: 2-Fluorotetronic acid

1. Introduction

Increasing interest in tetronic acid (**1**) in recent years has been prompted in part by the fact that a number of natural products and synthetic derivatives that contain this moiety have been shown to have important biological activities [1–3]. We have investigated fluorination of this small but chemically versatile molecule in anticipation of the significant and potentially useful alterations in physical and chemical properties that should result.

Halogenation of tetronic acid was reported decades ago [4,5], but fluorination of **1** has not been reported. Kitazume described a synthesis of 2-fluoro-4-substituted tetronic acids by ultrasound-promoted Reformatsky-type reactions between *O*-trimethylsilylated cyanohydrins (**2**) and ethyl α-fluorobromoacetate (**3**) [6,7]. Recently, several stable electrophilic fluorinating reagents have become available, including the *N*-F reagents such as *N*-fluorobenzenesulfonimide (NFSi) and SELECTFLUOR™ reagent (**6**) [8–10]. These convenient and easily handled fluorinating agents have made many electrophilic fluorinations routine procedures. We now wish to report a facile synthesis of 2-fluorotetronic acid (**4**) from **1,** based on a key electrophilic fluorination step using **6**.

2. Results and discussion

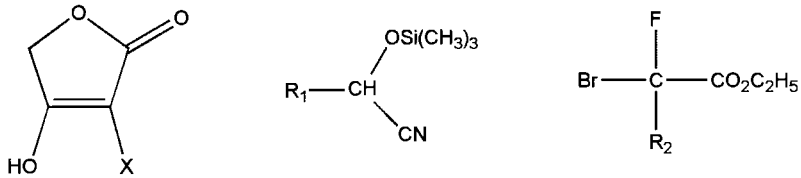
When **6** was added to the solution of **1** in CH_3CN or THF, only trace amounts of **4** were detected (Scheme 1), whereas attempted fluorination of the sodium salt of **1** resulted mostly in degradation of the starting material. This result suggests that electrophilic fluorination of **1** in CH_3CN or THF is a slow process, possibly owing to the low nucleophilicity of the enolic double bond of the acidic **1** ($pK_a = 3.76$) [11]. In contrast, when fluorination was attempted in EtOH, a 2,2-difluoro hemiacetal derivative **5** was the only isolated product. The structural assignment of **5** was based on its ^1H and ^{13}C NMR spectra. In the presence of ethanol, formation of the hemiacetal at C-3 may permit lactone enolization (C1=C2 double bond) that is subject to electrophilic fluorination. In this case, rapid enolization of the monofluoro product apparently is followed by further fluorination to produce **5** in a process too rapid to allow detection of the monofluoro intermediate.

Based on these results, a strategy was devised to take advantage of this apparent rapid fluorination of the hemiacetal intermediate. In contrast to our experience with fluorination, monobromination is a facile process (Scheme 1). Therefore, tetronic acid was first brominated to 2-bromotetronic acid (**7**) in quantitative yield, using NBS. Consistent with our rationalization for formation of **5**, fluorination of **7** by **6**, without isolation, rapidly gave 2-bromo-2-fluoro hemiacetal (**8**). Saturation of the 2,3 double bond introduced two chiral centers, and, as expected, the NMR spectrum revealed that **8** was present as a mixture of diastereoisomers. The bromine in compound **8** proved to be quite reactive and reduction by *n*-tributyltin hydride, followed by treatment with aqueous acetic acid, gave the target compound **4** in overall yield of 45%.

Our synthesis of **4** completes the series of 2-halo-tetronic acids. We are now applying the strategy reported here to

* Corresponding author. Fax: +1 301 402 4182.

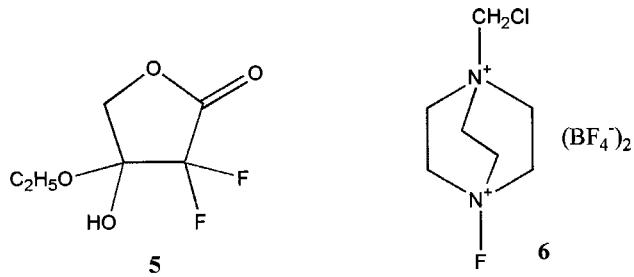
PII S0022-1139(97)00028-6



1: X = H
4: X = F

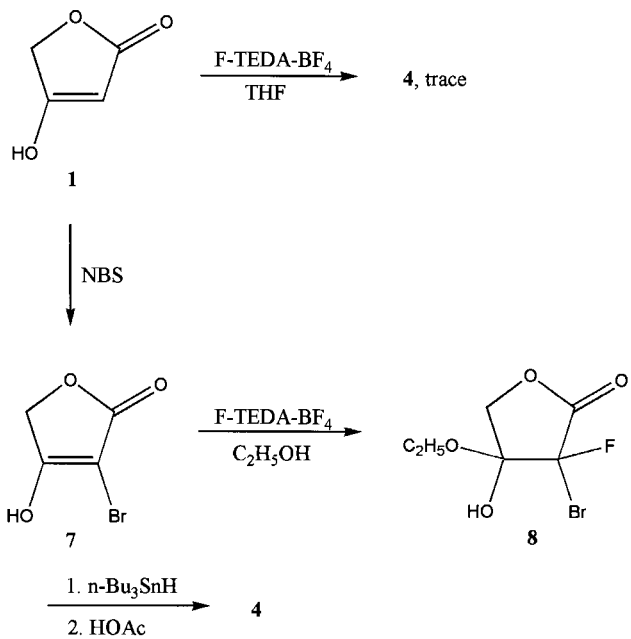
2

3



5

6



Scheme 1.

fluorination of more complex tetronic acid derivatives, including 2-deoxy-L-ascorbic acid [12].

3. Experimental details

The melting point was determined in an open-end capillary tube on a Thomas Hoover capillary melting point apparatus and is uncorrected. Proton and carbon-13 NMR spectra were recorded on a Varian Gemini 300 spectrometer and chemical shifts are reported in ppm relative to tetramethylsilane. TLC analyses were performed on Uniplate GHLF silica gel (Analtech). Solvents and reagents were purchased from Aldrich or Fluka. Chromatographic separations were performed by flash column chromatography on silica gel. Chromatographic spots on TLC were visualized by UV or by phosphomolybdic acid (5% solution in ethanol) with heating. Fluorine analysis was carried out by Galbraith Laboratories, Inc., Knoxville, TN. SELECTFLUOR™ reagent **6** was a gift from Air Products and Chemicals, Inc.

3.1. 2,2-Difluoro-3-ethoxy-3-hydroxy-γ-butyrolactone (5)

To a solution of tetronic acid (**1**) (50 mg, 0.5 mmol) in ethanol (2 ml) was added **6** (180 mg, 0.5 mmol). The resulting mixture was stirred at room temperature for 10 h and then filtered. The filtrate was evaporated and the residue was purified by column chromatography (silica gel, eluting with 25% EtOAc in petroleum ether) to give the product as a colorless oil (30 mg, 67%). ^{1}H NMR (DMSO-d_6) δ ppm: 1.18 (t, 3H, J = 6.9 Hz, CH_3), 3.60–3.78 (m, 2H, CH_2), 4.30–4.51 (m, 2H, 4-H), 7.69 (s, 3-OH), 8.04 (d, J = 1.5Hz, 3-OH). ^{13}C NMR (DMSO-d_6) δ ppm: 15.50 (s, CH_3), 58.45 (s, CH_2), 72.41, 72.45 (s, C-4), 91.91, 94.67 (t, J = 20.2 Hz, C-3), 110.18 (dd, J = 261.2 and 264.1 Hz, C-2), 110.11 (dd, J = 254.4 and 260.0 Hz, C-2), 164.86 (t, J = 31.87 Hz, C-1).

3.2. 2-Bromo-3-ethoxy-2-fluoro-3-hydroxy-γ-butyrolactone (8)

To a solution of tetronic acid (500 mg, 5 mmol) in ethanol (5 ml) was added *N*-bromosuccinimide (885 mg, 5 mmol) at room temperature. The resulting solution was stirred for 10 min. TLC and ^{1}H NMR showed that **7** had been formed quantitatively. ^{1}H NMR (DMSO-d_6) δ ppm: 4.78 (s, 4-H). To this solution was then added **6** (1.8 g, 5 mmol). The resulting mixture was stirred at room temperature for 10 h then filtered. The filtrate was evaporated and the residue was purified by column chromatography (silica gel, eluting with 25% EtOAc in petroleum ether) to give the product as a colorless liquid (1.06 g, 87%). ^{1}H NMR (DMSO-d_6) δ ppm: 1.19 (t, 3H, J = 6.9 Hz, CH_3), 3.64–3.79 (m, 2H, CH_2), 4.16–4.36 (m, 2H, 4-H), 7.98 (s, 1H, 3-OH). MS-EI m/e: 242 (M^+).

3.3. 2-Fluorotetronic acid (**4**)

To a solution of compound **8** (400 mg, 1.65 mmol) in THF (1.5 ml) was added *n*-tributyltin hydride (0.9 ml, 3.2 mmol) under nitrogen at 0 °C. The resulting solution was stirred at rom temperature for 10 h, and then evaporated to remove THF. The residue was stirred in 50% HOAc (2 ml) and petroleum ether (4 ml) for 30 min. The acetic acid layer was separated, washed with petroleum ether (3×4 ml), and evaporated to dryness. The residue was then dissolved in sodium carbonate solution (1 N, 5 ml), and the solution was washed with 25% EtOAc in petroleum ether (3×4 ml). The aqueous solution was acidified to pH 1 with 2 N hydrochloric acid, and extracted with EtOAc (5 ml). The organic layer was separated, dried and evaporated to give the product as light yellow solid (95 mg, 49%), mp 145–147 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 4.68 (d, 2H, J = 3.9 Hz), 12.60 (br, 1H, 3-OH). ^{13}C NMR (DMSO-d_6) δ ppm: 64.10 (d, J = 5.7 Hz, C-4), 124.82 (d, J = 244.1 Hz, C-2), 155.65 (d, J = 2.3 Hz, C-1), 166.23 (d, J = 25.1 Hz, C-3). MS-EI m/e: 118 (M^+). Analysis calculated for $C_4H_3O_3F$: F, 15.81. Found: F, 16.09.

References

[1] D. Desmaele, Tetrahedron 48 (1992) 2925 and references cited therein.
[2] S.V. Ley, M.L. Trudell, D.J. Wadsworth, Tetrahedron 47 (1991) 8258.
[3] G. Kohr, U. Heinemann, Neurosci. Lett. 112 (1990) 43.
[4] W.D. Kumler, J. Am. Chem. Soc. 60 (1938) 855.
[5] W.D. Kumler, J. Am. Chem. Soc. 60 (1938) 857.
[6] T. Kitazume, Synthesis (1986) 855.
[7] T. Kitazume, J. Fluorine Chem. 35 (1987) 287.
[8] V. Snieckus, F. Beaulieu, K. Mohri, W. Han, C.K. Murphy, F.A. Davis, Tetrahedron Lett. 35 (1994) 3465.
[9] G.S. Lal, J. Org. Chem. 58 (1993) 2791.
[10] R.E. Banks, N.J. Lawrence, A.L. Popplewell, J. Chem. Soc. Chem. Commun. (1994) 343.
[11] W.D. Kumler, J. Am. Chem. Soc. 60 (1938) 859.
[12] P. Ge, K.L. Kirk, J. Org. Chem., 61 (1996) 8671.