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Electrosynthesis of 4,4-Dimethyl-2-ethoxycarbonyl-5-fluoro-3-thiolanones: Highly Potent Human Type II PLA_2 Inhibitors[1]

Satoru Narizuka and Toshio Fuchigami*

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226, Japan

Abstract: Anodic monofluorination of 2-methyl- and 2-benzyl-4,4-dimethyl-2-ethoxy-carbonyl-3-thiolanones **1** and **2** was successfully performed to provide the corresponding 5-fluorinated products **3** and **4**, respectively in good yields. The stereoisomeric mixture of **4** was found to possess comparable or even stronger *in vitro* human type II phospholipase A_2 inhibitory activity compared with the known inhibitor, manoalide, and the cis isomer of **4** exhibited higher activity than the trans isomer.

Incorporation of fluorine(s) into organic molecules sometimes enhances their biological activities.[2] In fact, fluoroketones, fluorobenzylamines, and fluorinated 4-aminobutyrophenones have been reported to be potent inhibitors of phospholipase A_2.[3] In order to develop such pharmaceutically active compounds, selective direct fluorination of organic molecules has been increasingly important. However, the fluorination is not always straightfoward because conventional direct fluorination usually requires dangerous, troublesome, or costly fluorinating reagents.[4] Recently, we have demonstrated that anodic fluorination was much superior to conventional chemical methods.[5]

In this paper, we report anodic monofluorination of 2-methyl- and 2-benzyl-4,4-dimethyl-2-ethoxycarbonyl-3-thiolanones **1** and **2** together with human type II phospholipase A_2 (PLA_2) inhibitiory activities of the monofluorinated products. Anodic fluorination of 3-thiolanone derivatives **1** and **2** were performed as follows. Constant potential electrolysis was carried out at a platinum cathode and anode (2x2cm) in 0.37M $Et_3N{\cdot}3HF$/MeCN (15mL) containing 1.5mmol of **1** or **2** in a cylindrical one-compartment glass cell. After the starting material was completely consumed, the electrolysis solution was passed through a short column of silica gel (CH_2Cl_2). The products **3** and **4** were isolated by silica gel column chromatography (hexane, ether=2:1~4:1). The cis and trans stereoisomers of **4**[6] could be separated by TLC (hexane, ether=3:1) and their structures were determined by X-ray crystallographic analysis. On the other hand, attempts to separate the isomers of **3**[7] were unsuccessful until now although assignment of ^{19}F NMR spectrum of each isomer could be done.

As shown in Scheme 1, desired monofluorinated products **3** and **4** were obtained in rather good yields. In both cases, trans isomers were major products. For each of these monofluorinated products and starting materials, the *in vitro* human type II phospholipase A_2 inhibitory activity was assayed.[8]

Table 1 shows the results for **3** and cis and trans isomers of **4** together with the known PLA_2

inhibitor, manoalide[9], as the reference compound. A comparison of IC_{50} values clearly indicates the potential of the monofluorinated heterocycles **4** as an anti-inflammatory substance, which showed more effective nature than manoalide in inhibition of human type II phospholipase A_2. In sharp contrast to **4**, starting nonfluorinated **2** and fluorinated **3** did not possess such activity. Furthermore, it was also found that the cis isomer of **4** showed higher activity than the trans isomer.

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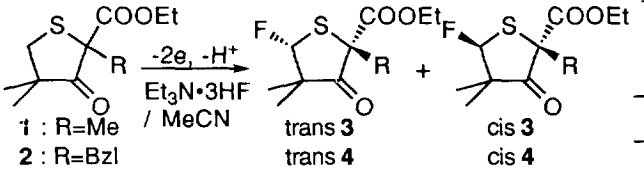

1: 2.1V vs SSCE (5.1F/mol) **3**: 74 % (trans/cis = 74/26)
2: 2.4V vs SSCE (8.2F/mol) **4**: 71 % (trans/cis = 61/39)

(Scheme 1)

Table 1. Human Type II Phospholipase A_2 Inhibitory Activity *in vitro*[8]

Compound	IC_{50} (μg/mL)
4 (cis/trans mixture)	0.20
cis-**4**	0.21
trans-**4**	1.27
manoalide	0.34

References and Notes

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6) cis-**4**: colorless oil. ^{19}F NMR ($CDCl_3$) δ -69.24 (dd, $J_{H,F}$=56.44, 2.48 Hz). ^1H NMR ($CDCl_3$) δ 1.12 (d, 3H, $C(CH_3)_2$, J=2.97 Hz), 1.24 (t, 3H, CH_2CH_3, J=6.93 Hz), 1.27 (s, 3H, $C(CH_3)_2$), 3.16 (d, 1H, CH_2Ph, J=13.53 Hz), 3.52 (d, 1H, CH_2Ph, J=13.86 Hz), 4.19 (q, 2H, CH_2CH_3, J=6.93 Hz), 5.62 (d, 1H, CHF, J=57.07 Hz), 7.22-7.26 (m, 5H, aromatic H).
trans-**4**: colorless solid, mp 83.5-84.0 °C. ^{19}F NMR ($CDCl_3$) δ -69.88 (d, $J_{H,F}$=56.41Hz). ^1H NMR ($CDCl_3$) δ 0.41 (d, 3H, $C(CH_3)_2$, J=1.32 Hz), 1.24-1.26 (m, 6H, CH_2CH_3, & $C(CH_3)_2$), 3.27 (d, 1H, CH_2Ph, J=14.18 Hz), 3.51 (d, 1H, CH_2Ph, J=14.52 Hz), 4.12-4.33 (q, 2H, CH_2CH_3, J=6.93 Hz), 5.49 (d, 1H, CHF, J=56.41 Hz), 7.12-7.28 (m, 5H, aromatic H). IR (KBr, neat) 3036, 2982, 2934, 2903, 1743, 1728, 1605, 1493, 1472, 1456, 1387, 1366, 1333, 1275, 1232, 1205, 1145, 1119, 1080, 1046, 1026, 999, 966, 924, 860, 808, 758, 704 cm^{-1}. MS: m/z 310 (M^+), 262, 203, 135, 91. HRMS: calcd for $C_{10}H_{19}FO_3S$ 310.1037, found 310.1029.

7) cis/trans mixture: colorless oil. ^{19}F NMR ($CDCl_3$) trans isomer δ -67.2 (d, $J_{H,F}$=58.0 Hz); cis isomer δ -71.2 (d, $J_{H,F}$=56.0 Hz). ^1H NMR ($CDCl_3$) δ 1.23-1.37 (m, 9H, CH_2CH_3, & $C(CH_3)_2$), 1.67 (s, 3H, CH_3; cis isomer), 1.76 (s, 3H, CH_3; trans isomer), 4.16-4.24 (m, 2H, CH_2CH3), 5.27 (d, 1H, CHF, J=56.08 Hz), 5.29 (d, 1H, CHF, J=55.75 Hz). MS m/s: trans isomer 234 (M^+), 161, 59; cis isomer 234 (M^+), 161, 59.

8) The inhibitory activity was assayed with 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine as a substrate, according to the method described by Tojo et al. with a slight modification: Tojo, H.; Ono, T.; Okamoto, M. *Methods in Enzymology*, **1991**, 197, 390.

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