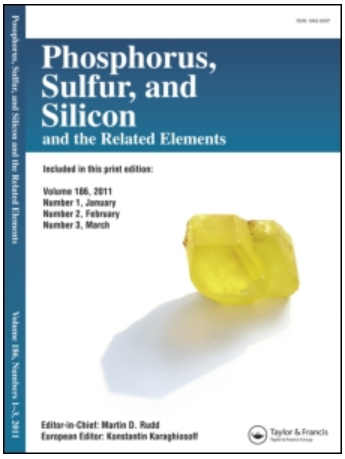

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Toshio Fuchigami

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Selective Anodic Monofluorination of Sulfur-Containing Heterocycles: Potent Applications towards Pharmaceuticals

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

Regioselective anodic monofluorination of 3-thiolanones, 1,3-oxathiolanones, and 1,3-dithiolanones was successfully carried out in MeCN containing Et_3N•3HF or Et_4NF•4HF as a supporting electrolyte. Among the fluorinated products, 2-benzyl-4,4-dimethyl-2-ethoxycarbonyl-5-fluoro-3-thiolanone was found to possess comparable or even stronger *in vitro* human type II phospholipase A2 inhibitory activity compared with the known inhibitor, manoalide.

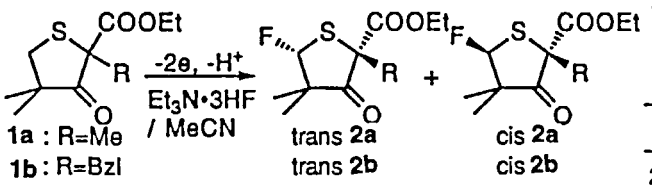
ANODIC FLUORINATION; FLUORINATED HETEROCYCLES; PLA2 INHIBITOR; 3-THIOLANONE; 1,3-OXATHIOLANONE; 1,3-DITHIOLANONE

INTRODUCTION

Since introduction of fluorine atom(s) into organic molecules sometimes enhances markedly their biological activites, the development of efficient direct fluorination methods has been becoming incresingly importnat. Recently, we have shown that an electrolytic method is quite powerful for the selective direct fluorination of heteroatom compounds such as sulfides .[1] In this work, we have attempted anodic monofluorination of various sulfur-containing heterocyles such as 3-thiolanones **1**, 1,3-dithiolanones **3**, 1,3-oxathiolanones **5**. Furthermore, for each of the anodically fluorinated heterocycles and starting materials, *in vitro* biological activities were assayed.

ANODIC MONOFLUORINATION OF HETEROCYCLES

Anodic monofluorination of 3-thiolanones **1** was successfully performed in MeCN containing Et_3N•3HF as a supporting electrolyte to provide the corresponding 5-fluorinated products **2** as a stereoisomeric mixture in good yields.[2] Although anodic benzylic substitution is known to take place easily, a fluorine atom was introduced into the 5-position selectively and benzylic fluorination was not observed at all.
When R is a hydrogen atom, fluorination took place at the 2-position selectively.

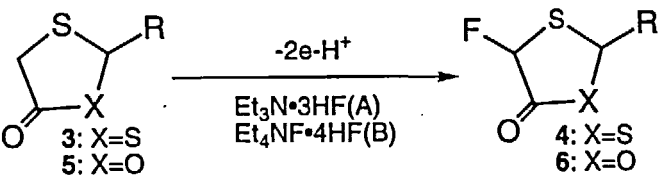


1a : 2.1V vs SSCE (5.1F/mol) **2a**:74 % (trans/cis = 74/26)
1b : 2.4V vs SSCE (8.2F/mol) **2b**:71 % (trans/cis = 61/39)

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

Compound	IC_{50} (μg/mL)
2b (cis/trans mixture)	0.20
cis-**2b**	0.21
trans-**2b**	1.27
manoalide	0.34

Next, anodic fluorination of 1,3-dithiolanones **3** and 1,3-oxathiolanones **5** was similarly carried out. In these cases, $Et_4NF•4HF$ was found to be much superior to $Et_3N•3HF$ for the fluorination.



R=Et,Pr, *i*-Pr, Ph,*o*-Tol

4 (A: 20-55%; B: 54-72%)
6 (A: 0%; B: 67-86%)

BIOLOGICAL ACTIVITIES

For each of these monofluorinated products and starting materials, the *in vitro* human type II phospholipase A_2 inhibitory activity was assayed.

Table 1 shows the results for cis and trans isomers of **2b** together with the known PLA_2 inhibitor, manoalide, as the reference compound.[3] A comparison of IC_{50} values clearly indicates the potential of the monofluorinated heterocycles **2b** 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 **2b**, starting nonfluorinated **1b** and fluorinated **2a** did not possess such activity. Furthermore, it was also found that the cis isomer of **2b** showed higher activity than the trans isomer.

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