Electrolytic Partial Fluorination of Organic Compounds. 8.[1] Highly Regioselective Anodic Monofluorination of β-Lactams

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Summary: Anodic partial fluorination of β-lactams has been performed for the first time. α-Phenylsulfenyl β-lactams were monofluorinated highly regioselectively in excellent yields and with high current efficiencies, and this anodic method is superior to conventional chemical methods.

Partially fluorinated heterocycles have been the focus of much biological interest. However, their synthesis requires multistep routes and is limited in many cases. Although direct fluorination is the simplest procedure for the synthesis of such compounds, the existing methods are not always straightforward and often use dangerous reagents.[3] On the contrary, electrochemical partial fluorination seems to be an ideal method for direct fluorination since it can be performed in one step under safe conditions.[4] However, only limited examples of anodic fluorination of heterocycles have been reported up to date.[5] In all cases, the yields and selectivity of the products are generally quite low owing to the low nucleophilicity of fluoride ions.

Recently, we[6] and Laurent *et al.*[7] found independently that electron-withdrawing groups promote anodic α-monofluorination of sulfides. Furthermore, we have reported regioselective anodic monofluorination of 4-thiazolidinones and their novel transformation into monofluorinated β-lactams.[8] Monofluoro β-lactams are used not only as synthetic intermediates for the preparation of fluorinated β-lactam antibiotics but also as building blocks for carbohydrates and amino acids. However, there are only limited reports on the synthesis of such compounds.[9] To the best of our knowledge, only two examples of direct fluorination of β-lactam derivatives have been reported to date. Slusarchyk *et al.*[10] and Spitzer *et al.*[11] have performed monofluorination of cephalosporin and penicillin derivatives, respectively. However, in both cases, dangerous $FClO_4$ was used as the fluorinating reagent, and the reactions must be performed at low temperature. Furthermore, no data on yields of the fluorinated products are given in these papers.

In this paper, we report the first successful regioselective anodic monofluorination of β-lactams. We selected α-phenylsulfenyl β-lactams **1** as a substrate since they have a phenylsulfenyl group α to the electron-withdrawing carbonyl group.[12]

The anodic monofluorination was investigated in detail using *N*-isopropyl-β-lactam **1b** as a model compound. Anodic oxidation of **1b** was carried out at constant potential in acetonitrile containing various fluorides as supporting electrolytes and fluoride ion source using an undivided cell.[13] In order to avoid deposition of polymerized products on the anode, pulse electrolysis [applied potential (90 s)/ 0V (10 s)] was performed.

As shown in Table I, among the fluorides, $Et_3N{\cdot}3HF$ gave the best result and $Et_4NF{\cdot}3HF$ was also effective when compared to pyridine polyfluoride. It was also found that $Et_3N{\cdot}2HF$ was much less effective compared to $Et_3N{\cdot}3HF$, although the former fluoride ions are more nucleophilic than the latter.[14] Since $Et_3N{\cdot}2HF$ is easily oxidized, it was discharged simultaneously during the electrolysis of **1b**, thus causing low yield and current efficiency for the fluorination.

Next, the reaction was successfully extended to various β-lactams **1a** and **1c–1f** using $Et_3N{\cdot}3HF$. The results are summarized in Table II.

The desired α-fluorinated β-lactams **2** were obtained in good to excellent yields regardless of the N-substituent R groups, and their current efficiencies were also satisfactory. Such extremely high yields and good current efficiencies are quite unusual in the anodic partial fluorination of heterocycles.[5] The regioselectivity of the anodic monofluorination observed here is notable because anodic substitutions of β-lactams with oxygen nucleophiles were reported to occur α to the nitrogen atom (ring and N-alkyl substitutions).[15] In the present case, a fluorine atom was introduced α to the carbonyl group, and fluorination α to the nitrogen atom of β-lactams **1** was not observed at all. Although benzylic anodic substitution is known to be facile,

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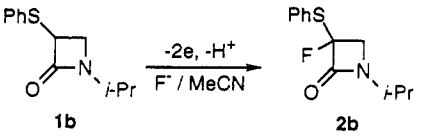
Table I. Anodic Monofluorination of β-Lactam 1b

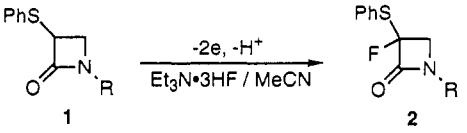


1b 2b

run	supporting electrolyte[a]	electricity F/mol	anodic potential (V vs SSCE)	product yield[b] (%)
1	$Et_3N{\cdot}3HF$	2.3	1.8	77
2	$Et_4NF{\cdot}3HF$	2.0	1.5	64
3	$Py{\cdot}(HF)_n$	2.2	1.9	trace
4	$Et_3N{\cdot}2HF$[c]	13.2	1.7	33[d]

[a] A 10:1 ratio with 1b was used. [b] Determined by ^{19}F NMR spectra. [c] Prepared from $Et_3N{\cdot}3HF$ and Et_3N (2:1).[14] [d] The electrolysis was incomplete.

Table II. Anodic Monofluorination of β-Lactam 1



1 2

run	no.	R	anodic potential (V vs SSCE)	electricity F/mol	product,[a] yield (%)
1	**1a**	Et	1.8	2.5	**2a**, 65
2	**1b**	*i*-Pr	1.8	2.3	**2b**, 69 (77)
3	**1c**	*n*-Bu	1.8	2.4	**2c**, 92
4	**1d**	*t*-Bu	1.9	2.5	**2d**, 67
5	**1e**	c-Hx	1.8	2.5	**2e**, 84
6	**1f**	Bzl	2.0	4.0	**2f**, 68

[a] Isolated yield (^{19}F NMR yield).

benzylic fluorination did not occur at all (Table II, run 6). In addition, no aromatic fluorination was observed. This fluorination is highly regioselective since it seems to be initiated by discharge of the phenylsulfenyl group.[6b]

Hitherto known methods for the preparation of α-fluoro sulfides require expensive, unstable, and dangerous reagents, such as xenon difluoride[16] or DAST.[17] Recently, *N*-fluoropyridinium triflates have also been shown to be effective fluorination reagents.[18] However, fluorination of **1b** as a model compound, for example, with *N*-fluoro-2,4,6-trimethylpyridinium triflate and *N*-fluoro-3,5-dichloropyridinium triflate resulted in no formation of **2b**. Fluorination of the sulfoxide derived from **1b** was also attempted using DAST. However, none of the desired fluorinated product **2b** was formed. Therefore, this electrochemical fluorination is much superior to conventional chemical methods.

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Supplementary Material Available: ^1H NMR, IR, MS, and high-resolution MS data for all new compounds (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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