Electrolytic Partial Fluorination of Organic Compounds. 33. Regioselective Anodic Monofluorination of α-Phenylsulfenyl Lactams and Sulfur-Containing Nitrogen Heterocycles

Akinori Konno, a Wataru Naito b and Toshio Fuchigami b*

aFaculty of Engineering, Shizuoka University and bDepartment of Electronic Chemistry, Tokyo Institute of Technology, Tokyo, Japan

Dedicated to Professor Henning Lund on the occasion of his 70th birthday.


Anodic monofluorination of a variety of nitrogen heterocycles has been investigated in order to ascertain the scope and limitations of the anodic monofluorination method in the synthesis of monofluorinated nitrogen heterocycles. Electrolytic monofluorination of α-(phenylsulfeny1) lactams proceeded effectively, and the regiochemistry and efficiency of the reaction were greatly dependent on the molecular structure (ring size, substitution on the nitrogen atom, etc.) of the lactams. The high yields of monofluorinated lactams observed here are of great synthetic value because the phenylsulfenyl group is known to be easily removed oxidatively and/or reductively.

Heterocyclic organofluorine compounds have attracted much interest because of their potent biological activities.2–5 The synthesis of these compounds, however, often requires multistep sequences and successful examples are limited in many cases because of the strong electron-withdrawing ability of the fluorine atom.6 Recently, various novel fluorinating reagents such as CF3OF, XeF2, Et3NSF3 (DAST), and N-fluoropyridinium triflates (fluoroborates) have been developed.4,5,7–9 However, they are still hazardous, difficult to handle, or very costly. As an alternative, electrochemical fluorination is an ideal method of direct fluorination. Although electrochemical perfluorination has been well established, electrochemical partial fluorination has been unsuccessful in many cases. Indeed, reported electrochemical fluorination of heterocyclic compounds was not successful (yields and product selectivity were low).10–13 Recently, we14 and Laurent et al.15 reported independently the effective electrochemical α-monofluorination of sulfides using Et3N·3HF. We have successfully applied this electrochemical monofluorination method to sulfur-containing heterocycles.16,17 Furthermore, we have reported the preliminary results of the first successful anodic monofluorination of α-phenylsulfenyl lactams.18,19 In this study, we attempted the anodic monofluorination of a variety of nitrogen heterocycles, and present the scope and limitations of this method in the synthesis of monofluorinated nitrogen heterocycles. The oxidation potentials of these nitrogen heterocycles and their reference compounds are also reported.

Results and discussion

Preparation of α-phenylsulfenyl lactams and sulfur-containing nitrogen heterocycles. α-Phenylsulfenyl lactams 1a–d were synthesized by the reaction of the corresponding lactams with lithium diisopropylamide (LDA) and diphenyl disulfide according to Zoreic and Soja’s procedure,20 eqn. (1). N-Substituted 3,4-dihydro-2H-1,4-benzothiazin-3-ones 2b–d were prepared by reaction of 3,4-dihydro-2H-1,4-benzothiazin-3-one (2a) with corresponding halides, eqn. (2).

Oxidation potentials of α-phenylsulfenyl lactams and sulfur-containing nitrogen heterocycles. The anodic peak potentials were measured in anhydrous acetonitrile containing NaClO4 (0.1 M) by cyclic voltammetry (CV). The CV curves were obtained with a three-electrode system using a platinum disk as the working electrode,
a platinum wire as the counter electrode, and a saturated NaCl calomel electrode (SSCE) as the reference electrode. All heterocyclic compounds measured showed irreversible anodic waves. The first oxidation peak potentials $E_{\text{pa}}$ of the $\alpha$-phenylsulfonyl lactams 1a-d and benzothiazinones 2a–c were in the range 1.30–1.54 V. 2d was oxidized at more positive potentials (1.64 V), owing to the presence of the electron-withdrawing benzoyl group. The fact that 3,4-dihydro-2H-1,4-benzothiazin-2-one (5) gave the most positive oxidation potential (1.71 V) in Table 1, is reasonable considering the higher electronegativity of oxygen than of nitrogen. Taking into account the oxidation potential of 1.48 V vs. SSCE for 2-(phenylsulfonyl) cyclohexanone (7) and of 1.2–1.5 V vs. SCE for aliphatic tertiary amides, the phenylsulfonyl group exerts little effect on the oxidation potentials of lactams, and anodic oxidation could occur both at sulfinyl and at amide sites.

**Anodic monofluorination of $\alpha$-phenylsulfonyl lactams.** $\alpha$-Phenylsulfonyl lactams 1 were electrolyzed in Et$_3$N·3HF·CH$_3$CN using Pt plates as both anode and cathode under constant potential electrolysis in a simple undivided cell, eqn. (3). The results are summarized in Table 2. Anodic oxidation of lactams 1a–c (runs 1–3) in

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Anodic potential (V vs. SSCE)</th>
<th>Charge passed (F mol$^{-1}$)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>1.8</td>
<td>2.5</td>
<td>85 (3a)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>1.8</td>
<td>2.5</td>
<td>84 (3b)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2.0</td>
<td>2.2</td>
<td>69 (3c)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>1.9</td>
<td>4.0</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

*Substrate (0.1 M) in 0.37 M Et$_3$N·3HF–MeCN, Pt anode and cathode (2 × 2 cm$^2$), undivided cell. Isolated yields. Two monofluorinated, difluorinated, and dehydrofluorinated products were detected by mass spectroscopy.

0.35 M Et$_3$N·3HF·CH$_3$CN afforded monofluorinated products 3a–c in good chemical and current yields and the fluorination occurred selectively at the $\alpha$-position to the sulfur atom. The yields of monofluorination (69–85%) were remarkably high considering the reported low yields of anodic fluorination of aliphatic heterocycles. It is notable that the regioselectivity in this anodic monofluorination is different from that in the anodic methoxilation of lactams, which was reported to occur at the nitro group.

**Table 1. Oxidation potentials (peak potentials, $E_{\text{pa}}$) of heterocyclic compounds.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$E_{\text{pa}}$ (V vs. SSCE)</th>
<th>Substrate</th>
<th>$E_{\text{pa}}$ (V vs. SSCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1.43</td>
<td>2a</td>
<td>1.30</td>
</tr>
<tr>
<td>1b</td>
<td>1.54</td>
<td>2b</td>
<td>1.42</td>
</tr>
<tr>
<td>1c</td>
<td>1.49</td>
<td>2c</td>
<td>1.44</td>
</tr>
<tr>
<td>1d</td>
<td>1.39</td>
<td>2d</td>
<td>1.64</td>
</tr>
<tr>
<td>7b</td>
<td>1.48</td>
<td>5</td>
<td>1.71</td>
</tr>
</tbody>
</table>

*In 0.1 M NaClO$_4$·MeCN. Sweep rate: 100 mV s$^{-1}$. Concentration of substrate: 5 mM. $^{7}$ 2-(phenylsulfonyl)-cyclohexanone.
is also highly dependent on the ring size of the lactams as also observed in anodic hydroxylation. Such a ring-size dependence has not been reported in either chemical or electrochemical fluorinations. It is interesting that both anodic monofluorination and anodic hydroxylation show similar ring-size dependence in regiochemistry, whereas their reaction mechanisms are different, that is, anodic monofluorination of sulfides has been established to proceed via a unique Pummerer-type mechanism, which is different from the conventional ECEC mechanism of other anodic nucleophilic substitution reactions (methoxylation, acetoxylation, cyanation, etc.) as shown in Scheme 2.

Anodic monofluorinations of sulfur-containing nitrogen heterocycles. 3,4-Dihydro-2H-1,4-benzothiazin-3-one derivatives (2), which contain one sulfur atom in the ring system, were subjected to anodic monofluorination, eqn. (4), (Table 3). Since anodic oxidation of aromatic rings is well known to bring about nucleophilic substitution and/or oxidative coupling, anodic fluorination of 2 could be accomplished by such undesirable reactions.

Pummerer type fluorination mechanism

ECEC mechanism

Scheme 2.

Table 3. Anodic monofluorination of 3,4-dihydro-2H-1,4-benzothiazin-3-one derivatives.*

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Anodic potential V vs. SSCE</th>
<th>Charge passed F mol⁻¹</th>
<th>Product yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2a</td>
<td>3.0</td>
<td>15</td>
<td>0²</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>2.0</td>
<td>2.2</td>
<td>77 (4b)</td>
</tr>
<tr>
<td>7</td>
<td>2c</td>
<td>1.5</td>
<td>2.5</td>
<td>88 (4c)</td>
</tr>
<tr>
<td>8</td>
<td>2d</td>
<td>1.6</td>
<td>2.1</td>
<td>68 (4d)</td>
</tr>
</tbody>
</table>

Substrate (0.1 M) in 0.37 M Et₃N·3HF-MeCN, Pt anode and cathode (2 × 2 cm²), undivided cell. bIsolated yields.

The anodic monofluorination of 2a, which has no substituent on the nitrogen atom, resulted in aniline-like polymerization (run 5) and no desired product was formed. On the other hand, N-substituted derivatives 2b-2d (runs 6-8) were effectively monofluorinated under the same electrolytic conditions. In the cases of 2b and 2c, fluorination at the N-alkyl group was not observed at all. The fluorination of 2b-2d also occurred z to the sulfur atom with high regioselectivity as in the case of lactams 1a-c. Recently, fluoropyridinium triflates have been shown to be effective fluorination reagents. Fluorination of 2c as a model compound with N-fluoro-2,4,6-trimethylpyridinium triflate was attempted. However, no fluorinated product was formed. Therefore, anodic fluorination is superior to chemical fluorination in this system.

2H-1,4-benzoxathian-2-one (5) is an oxygen analogue of 2a. Since both α-(phenylsulfonyl) ester and amide could be successfully fluorinated by anodic fluorination, 5 was expected to be similarly fluorinated. However, anodic fluorination of 5 did not afford any fluorinated products and only starting 5 was recovered (Scheme 3). Using methanol as the solvent instead of acetonitrile, 2a was oxidized anodically to give a methoxyethylated product 6 (13%), in marked contrast with the result of anodic fluorination of 2a, which afforded only polymeric mixtures, vide supra (Scheme 3). This result is in line with that of fluoride-ion-mediated α-methoxylation of sulfides, and could be explained by the much stronger nucleophilicity of a methoxide ion than a fluoride ion.

Conclusions. Electrolytic monofluorination of α-(phenylsulfonyl) lactams proceeded effectively, and the regiochemistry and efficiency of the reaction were greatly
dependent on the molecular structure (ring size, substitution on nitrogen atom, etc.) of the lactams. Sulfur-containing annelated nitrogen heterocycles, 3,4-dihydro-2H-1,4-benzothiazin-2-ones 2b, d, were also monofluorinated regioselectively. The high yields of monofluorinated lactams observed here are of great synthetic value because the phenylsulphenyl group is known to be easily removed oxidatively and/or reductively.

Experimental

Apparatus. $^1$H NMR and $^{19}$F NMR spectra were recorded at 270 MHz on JEOL GX-270 NMR and Hitachi R-1200F NMR spectrometers, respectively. The chemical shifts for $^1$H and $^{19}$F NMR are given in $\delta$ (ppm) downfield from internal Me$_4$Si and from external CF$_3$COOH, respectively. IR spectra were obtained with a Hitachi 295 infrared spectrometer. Mass spectra were obtained with a Shimazu QP2000 GC-mass spectrometer. High resolution mass spectra were measured with a Hitachi M-80B GC-mass spectrometer. Measurement of oxidation potentials by cyclic voltammetry and preparative electrolysis experiments were carried out using a HokutoDenko HA-501 Potentiostat/Galvanostat equipped with a HokutoDenko HF-201 digital coulometer and a Riko Densi F-35A X-Y recorder. The value of $E_{pa}^\infty$ vs. SSCE (saturated NaCl calomel electrode) is the same as that of $E_{pa}^\infty$ vs. SCE under the conditions of our cyclic voltammetry measurements.

Anodic fluorination of 2-phenylsulfonyl lactams. Typical electrochemical monofluorination conditions are as follows. 2-Phenylsulfonyl lactams 1 (5 mmol) were electrolyzed in 0.37 M Et$_3$N·3HF·CH$_3$CN (50 ml) using Pt plates (2 × 2 cm) as both anode and cathode under constant potential electrolysis in an undivided cell. When the starting lactam 1 had almost disappeared (monitoring unreacted 1 by TLC and/or MS), short column chromatography (silica gel; ether as the eluent) of the electrolytic solution afforded almost pure monofluorinated product 3. The fluorinated products gradually decomposed at room temperature. They could be recrystallized from ether, but their crystals were too unstable for melting point determination. Their diluted solutions were quite stable and could be kept for several days in a freezer.

3-Fluoro-1-methyl-3-(phenylthio) pyrrolidin-2-one (3a).

$^1$H NMR ([CD$_3$]$_2$CO): $\delta$ 2.24–2.40 (m, 2 H), 2.86 (s, 3 H), 3.31–3.47 (m, 2 H), 7.39–7.62 (m, 5 H). $^{19}$F NMR: $\delta$ –54.84 (t, $J$ = 12.4 Hz). IR (cm$^{-1}$): 2935, 2321, 1709, 1582, 1440, 1311, 1035, 737. HRMS: calcd. for C$_{15}$H$_{12}$FNO, m/z 225.0624. Found 225.0610.

1-Cyclohexyl-3-fluoro-3-(phenylthio)pyrrolidin-2-one (3b).

$^1$H NMR ([CD$_3$]$_2$CO): $\delta$ 0.93–1.70 (m, 10 H), 2.06–2.26 (m, 2 H), 3.12–3.35 (m, 2 H), 3.57–3.69 (m, 1 H), 7.25–7.48 (m, 5 H). $^{19}$F NMR: $\delta$ –48.8 (t, $J$ = 11.7 Hz). IR (cm$^{-1}$): 2950, 2360, 1705, 1582, 1440, 1293, 1185, 1080, 752. HRMS: calcd. for C$_{16}$H$_{12}$FNO, m/z 293.1250. Found 293.1267.

3-Fluoro-1-methyl-3-(phenylthio) piperidin-2-one (3c).

$^1$H NMR ([CD$_3$]$_2$CO): $\delta$ 1.60–2.23 (m, 4 H), 2.84 (s, 3 H), 3.35 (t, $J$ = 5.0 Hz, 2 H), 7.07–7.67 (m, 5 H). $^{19}$F NMR: $\delta$ –41.6 (t, $J$ = 9.0 Hz). IR (cm$^{-1}$): 2945, 2320, 1665, 1588, 1447, 1340, 1205, 1032, 692. HRMS: calcd. for C$_{15}$H$_{14}$FNO, m/z 239.3139. Found 239.3072.

Anodic fluorination of 3,4-dihydro-2H-1,4-benzothiazin-3-ones. Under the same electrochemical reaction conditions, 3,4-dihydro-2H-1,4-benzothiazin-3-ones 2 (5 mmol) were electrolyzed. When the starting material 2 had almost disappeared, short column chromatography (silica gel; ether as the eluent) of the electrolytic solution afforded crude 4. Pure fluorinated compounds 4 were obtained by recrystallization from ether. Fluorinated benzothiazinones 4 were more stable than the fluorinated lactams 3.

2-Fluoro-4-methyl-3,4-dihydro-2H-1,4-benzothiazin-3-one (4b).

M. P. 90 °C (decomp.). $^1$H NMR (CDCl$_3$): $\delta$ 3.52 (s, 3 H), 5.99 (d, $J$ = 48.2 Hz, 1 H), 6.87–7.52 (m, 4 H). $^{19}$F NMR: $\delta$ –86.4 (d, $J$ = 48.2 Hz). IR (cm$^{-1}$): 3020, 2340, 1662, 1589, 1469, 1380, 1239, 1101, 1041, 954, 830, 740. Anal. Calcd. for C$_{15}$H$_{12}$FNO: C 54.81; H 4.09; N 7.10. Found: C 54.83, H 3.88; N 6.95.

2-Fluoro-4-isopropyl-3,4-dihydro-2H-1,4-benzothiazin-3-one (4c).

M. P. 70.5 °C. $^1$H NMR (CDCl$_3$): $\delta$ 1.51 (d, $J$ = 2.6 Hz, 3 H), 1.60 (d, $J$ = 2.6 Hz, 3 H), 4.70 (sept, $J$ = 2.6 Hz, 1 H), 5.90 (d, $J$ = 46.9 Hz, 1 H), 6.84–7.50 (m, 4 H). $^{19}$F NMR: $\delta$ –92.4 (d, $J$ = 46.9 Hz). IR (cm$^{-1}$): 2940, 1667, 1590, 1480, 1346, 1130, 945, 747. HRMS: calcd. for C$_{15}$H$_{14}$FNO, m/z 225.0624. Found 225.0601.

4-Benzyl-2-fluoro-3,4-dihydro-2H-1,4-benzothiazin-3-one (4d).

M. P. 90 °C (decomp.). $^1$H NMR (CDCl$_3$): $\delta$ 5.99 (d, $J$ = 48.2 Hz, 1 H), 6.68–8.03 (m, 9 H). $^{19}$F NMR: $\delta$ –89.4 (d, $J$ = 48.2 Hz). IR (cm$^{-1}$): 3100, 1690, 1600, 1452, 1350, 1237, 1175, 1088, 977, 890, 761. HRMS: calcd. for C$_{18}$H$_{12}$FNO$\times$S, m/z 287.0416. Found 287.0363.

Anodic methoxylation of 3,4-dihydro-2H-1,4-benzothiazin-3-one (2a).

3,4-Dihydro-2H-1,4-benzothiazin-3-one (2a) (1.5 mmol) was electrolyzed in 0.37 M Et$_3$N·3HF·CH$_3$OH (15 ml) using Pt plates (2 × 2 cm) as both anode and cathode under constant potential electrolysis in an undivided cell. When the starting 2a had almost disappeared, the electrolyte was neutralized with 10% aqueous ammonia solution and the resulting aqueous solution was extracted three times with ether. The combined extracts were dried over anhydrous MgSO$_4$, and the methoxyolated product 6 was isolated by column chromatography (silica gel; ether as the eluent).
2-Methoxy-3,4-dihydro-2H-1,4-benzothiazin-3-one (6). M.p. 190 °C. 1H NMR (CDCl₃): δ 3.43 (s, 3 H), 4.96 (s, 3 H), 6.98–7.36 (m, 4 H), 9.35 (s, 1 H). IR (cm⁻¹): 3235, 3000, 1780, 1593, 1483, 1392, 1258, 1073, 946, 752. MS: m/z 195 (M⁺), 165 (M⁺ +1 – MeO), 164 (M⁺ – MeO), 152, 136. Anal. Calc. for C₁₂H₁₂NO₂S: C 55.37; H 4.65; N 7.17. Found: C 55.38, H 4.76; N 7.02.

References


Received December 8, 1998.