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

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

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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-(phenylsulfenyl)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 CF_3OF, XeF_2, Et_2NSF_3 (DAST), and *N*-fluoropyridinium triflates (fluoroborates) have been developed.[4,7–9] 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, we[14] and Laurent *et al.*[15] reported independently the effective electrochemical α-monofluorination of sulfides using $Et_3N \cdot 3HF$. 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 Zoretic and Soja's procedure,[20] eqn. (1). *N*-Substituted 3,4-dihydro-2*H*-1,4-benzothiazin-3-ones **2b–d** were prepared by reaction of 3,4-dihydro-2*H*-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 $NaClO_4$ (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,

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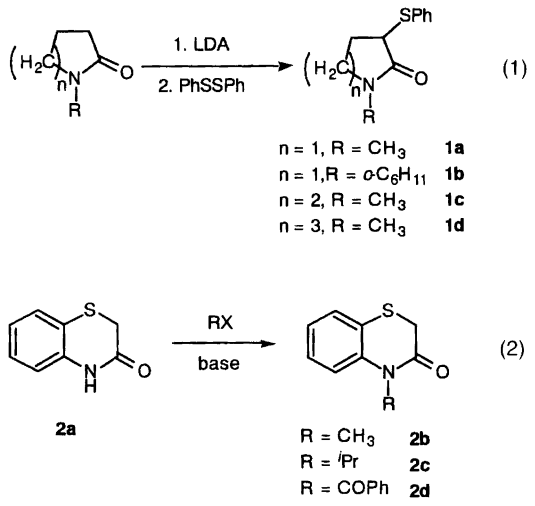


a platinum wire as the counter electrode, and a saturated NaCl calomel electrode (SSCE) as the reference electrode. All heterocyclic compounds measured showed irreversible anodic waves. The first oxidation peak potentials E_p^{ox} of the heterocyclic compounds are given in Table 1. E_p^{ox} of the α-phenylsulfenyl 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-2*H*-1,4-benzoxathian-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-(phenylsulfenyl)cyclohexanone (**7**) and of 1.2–1.5 V vs. SCE for aliphatic tertiary amides,[21] the phenylsulfenyl group exerts little effect on the oxidation potentials of lactams, and anodic oxidation could occur both at sulfide and at amide sites.

Anodic monofluorinations of α-phenylsulfenyl lactams. α-Phenylsulfenyl lactams **1** were electrolyzed in $Et_3N \cdot 3HF$–CH_3CN 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 1. Oxidation potentials (peak potentials, E_p^{ox}) of heterocyclic compounds.[a]

Substrate	E_p^{ox} V vs. SSCE	Substrate	E_p^{ox} V vs. SSCE
1a	1.43	**2a**	1.30
1b	1.54	**2b**	1.42
1c	1.49	**2c**	1.44
1d	1.39	**2d**	1.64
7[b]	1.48	**5**	1.71

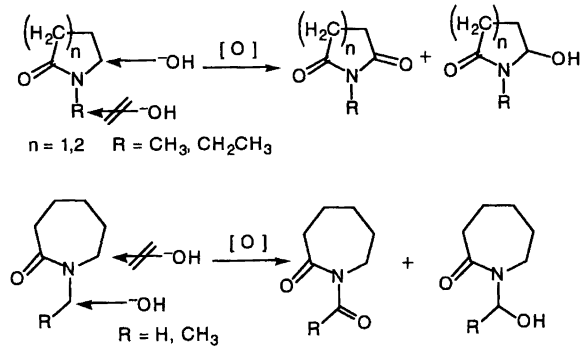
[a]In 0.1 M $NaClO_4$–MeCN. Sweep rate: 100 mV s^{-1}. Concentration of substrate: 5 mM. [b]**7**: 2-(phenylsulfenyl)-cyclohexanone.

Table 2. Anodic monofluorination of α-phenylsulfenyl lactams[a]

Run	Substrate	Anodic potential V vs. SSCE	Charge passed F mol^{-1}	Product yield[b] %
1	**1a**	1.8	2.5	85 (**3a**)
2	**1b**	1.8	2.5	84 (**3b**)
3	**1c**	2.0	2.2	69 (**3c**)
4	**1d**	1.9	4.0	Complex mixture[c]

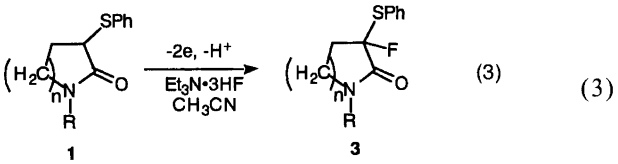
[a]Substrate (0.1 M) in 0.37 M $Et_3N \cdot 3HF$–MeCN, Pt anode and cathode (2 × 2 cm^2), undivided cell. [b]Isolated yields. [c]Two monofluorinated, difluorinated, and dehydrofluorinated products were detected by mass spectroscopy.

0.35 M $Et_3N \cdot 3HF$–CH_3CN afforded monofluorinated products **3a–c** in good chemical and current yields and the fluorination occurred selectively at the α-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.[10] It is notable that the regioselectivity in this anodic monofluorination is different from that in the anodic methoxylation of lactams, which was reported to occur α to the nitrogen atom.[22,23] In the present case, fluorination occurred only at the position α to the sulfur atom, and fluorination α to the nitrogen atom of lactams **1** was not observed at all. In contrast with the case of **1a–c**, anodic fluorination of ε-caprolactam derivative **1d** afforded a complex mixture (run 4). After 4 F mol^{-1} of charge had passed, the electrolyte was subjected to GC–MS analysis and many fluorinated products (two monofluorinated, difluorinated, and dehydrofluorinated products) were detected. Fragmentation patterns observed in MS suggested that fluorination occurred at a variety of positions. Closely related results concerning the regiochemistry of anodic nucleophilic substitution reactions of lactams have been reported.[24] The regiochemistry of anodic oxidation was greatly influenced by the ring size of the lactams, that is, the reaction site shifted from ring carbon to side chain in the position α to the nitrogen atom when the ring size of the lactams changed from 5, 6 to 7, respectively (Scheme 1). The regiochemistry of anodic monofluorination observed here



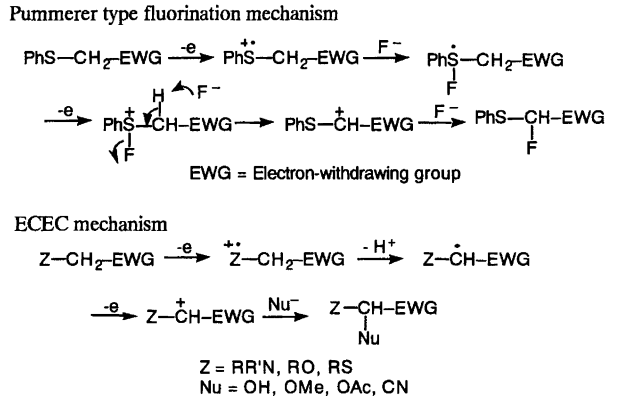
Scheme 1.

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,[25] which is different from the conventional ECEC mechanism of other anodic nucleophilic substitution reactions (methoxylation, acetoxylation, cyanation, etc.) as shown in Scheme 2.



(3)

Anodic monofluorinations of sulfur-containing nitrogen heterocycles. 3,4-Dihydro-2*H*-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 accompanied by such undesirable reactions.



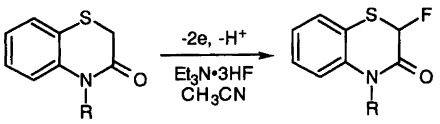
Scheme 2.

Table 3. Anodic monofluorination of 3,4-dihydro-2*H*-1,4-benzothiazin-2-ones.[a]

Run	Substrate	Anodic potential V vs. SSCE	Charge passed F mol^{-1}	Product yield[b] %
5	**2a**	3.0	15	0[c]
6	**2b**	2.0	2.2	77 (**4b**)
7	**2c**	1.5	2.5	88 (**4c**)
8	**2d**	1.6	2.1	68 (**4d**)

[a]Substrate (0.1 M) in 0.37 M $Et_3N \cdot 3HF$–MeCN, Pt anode and cathode (2×2 cm^2), undivided cell. [b]Isolated yields. [c]Polymerization.

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–d** (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–d** also occurred α 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.[26] 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.

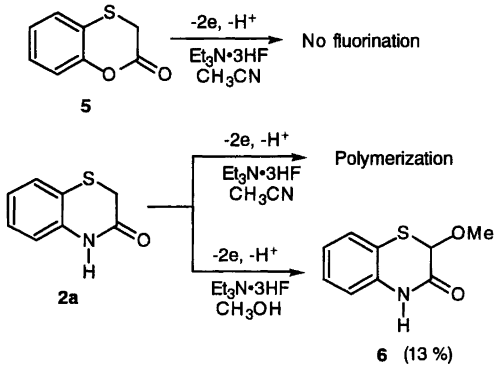


(4)

R = H **2a**
R = CH_3 **2b**
R = ^{i}Pr **2c**
R = COPh **2d**

2*H*-1,4-benzoxathian-2-one (**5**) is an oxygen analogue of **2a**. Since both α-(phenylsulfenyl) 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 methoxylated 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,[27] and could be explained by the much stronger nucleophilicity of a methoxide ion than a fluoride ion.

Conclusions. Electrolytic monofluorination of α-(phenylsulfenyl) lactams proceeded effectively, and the regiochemistry and efficiency of the reaction were greatly



Scheme 3.

dependent on the molecular structure (ring size, substitution on nitrogen atom, etc.) of the lactams. Sulfur-containing annelated nitrogen heterocycles, 3,4-dihydro-2*H*-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 phenylsulfenyl 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 δ (ppm) downfield from internal Me_4Si and from external CF_3COOH, 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 obtained 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_p^{ox} vs. SSCE (saturated NaCl calomel electrode) is the same as that of E_p^{ox} vs. SCE under the conditions of our cyclic voltammetry measurements.

Anodic fluorination of α-phenylsulfenyl lactams. Typical electrochemical monofluorination conditions are as follows. α-Phenylsulfenyl lactams **1** (5 mmol) were electrolyzed in 0.37 M $Et_3N \cdot 3HF$–CH_3CN (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 of **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 [$(CD_3)_2CO$]: δ 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: δ −45.84 (t, J = 12.4 Hz). IR (cm^{-1}): 2935, 2321, 1709, 1582, 1440, 1311, 1035, 737. HRMS: calcd. for $C_{11}H_{12}FNOS$, m/z 225.0624. Found 225.0610.

1-Cyclohexyl-3-fluoro-3-(phenylthio)pyrrolidin-2-one (**3b**). ^{1}H NMR [$(CD_3)_2CO$]: δ 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: δ −48.8 (t, J = 11.7 Hz). IR (cm^{-1}): 2950, 2360, 1705, 1582, 1440, 1293, 1185, 1080, 752. HRMS: calcd. for $C_{16}H_{20}FNOS$, m/z 293.1250. Found 293.1267.

3-Fluoro-1-methyl-3-(phenylthio)piperidin-2-one (**3c**). ^{1}H NMR ($(CD_3)_2CO$): δ 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: δ −41.6 (t, J = 9.0 Hz). IR (cm^{-1}): 2945, 2320, 1665, 1588, 1447, 1340, 1205, 1032, 692. HRMS: calcd. for $C_{12}H_{14}FNOS$, 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-2*H*-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 ($CDCl_3$): δ 3.52 (s, 3 H), 5.99 (d, J = 48.2 Hz, 1 H), 6.87–7.52 (m, 4 H). ^{19}F NMR: δ −86.4 (d, J = 48.2 Hz). IR (cm^{-1}): 3020, 2340, 1662, 1589, 1469, 1380, 1239, 1101, 1041, 954, 830, 740. Anal. Calc. for C_9H_8FNOS: 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 ($CDCl_3$): δ 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: δ −92.4 (d, J = 46.9 Hz). IR (cm^{-1}): 2940, 1667, 1590, 1480, 1346, 1130, 945, 747. HRMS: calcd. for $C_{12}H_{14}FNOS$, m/z 225.0624. Found 225.0601.

4-Benzoyl-2-fluoro-3,4-dihydro-2H-1,4-benzothiazin-3-one (**4d**). M.p. 90 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ 5.99 (d, J = 48.2 Hz, 1 H), 6.68–8.03 (m, 9 H). ^{19}F NMR: δ −89.4 (d, J = 48.2 Hz). IR (cm^{-1}): 3100, 1690, 1600, 1452, 1350, 1237, 1175, 1088, 977, 890, 761. HRMS: calcd. for $C_{15}H_{10}FNO_2S$, m/z 287.0416. Found 287.0363.

Anodic methoxylation of 3,4-dihydro-2H-1,4-benzothiazin-3-one (**2a**). 3,4-Dihydro-2*H*-1,4-benzothiazin-3-one (**2a**) (1.5 mmol) was electrolyzed in 0.37 M $Et_3N \cdot 3HF$–CH_3OH (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 methoxylated product **6** was isolated by column chromatography (silica gel; ether as the eluent).

*2-Methoxy-3,4-dihydro-2*H*-1,4-benzothiazin-3-one* (**6**). M.p. 190 °C. ^{1}H NMR ($CDCl_3$): 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 $C_9H_9NO_2S$: C 55.37; H 4.65; N 7.17. Found: C 55.38, H 4.76; N 7.02.

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