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Electrolytic Partial Fluorination of Organic Compounds. 6.[1] Highly Regioselective Electrochemical Monofluorination of Aliphatic Nitrogen-Containing Heterocycles

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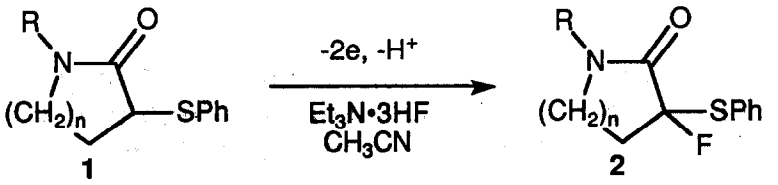
Abstract: Highly regioselective electrochemical monofluorination of α-phenylsulfenyl lactams was carried out in good chemical and current yields. This is the first successful example of anodic monofluorination of aliphatic nitrogen-containing heterocycles.

Organofluorine compounds have been attracted much interest. Especially, a number of heterocyclic organofluorine compounds are reported to show biological activities.[2] The syntheses of these compounds, however, are required multistep or limited in so many cases because of strong electronegativity of a fluorine atom.[3] Although direct fluorinations are, of course, the most simple way for the synthesis of such compounds, methods are not always straightforward and have to use troublesome reagents (explosive, sensitive to air or moisture, expensive).[4] From these view points, electrochemical fluorination is an ideal method for direct fluorination. Although electrochemical perfluorination has been well established, electrochemical partial fluorination has been unsuccessful because electrochemical fluorination is hard to control the selectivity (chemical- and regio-). Indeed, reported electrochemical partial fluorination of heterocyclic compounds was not successful (yields and product selectivity are low).[5] Recently, we[6] and Laurent *et al.*[7] have independently found effective electrochemical α-monofluorination of sulfides using Et_3•3HF. Furthermore, we have reported successful application of this electrochemical monofluorination to sulfur-containing heterocycles.[8] We present here the first successful examples of electrochemical monofluorination of aliphatic nitrogen-containing heterocycles, i.e. α-phenylsulfenyl lactams.

Typical electrochemical monofluorination conditions are as follows. Phenylsulfenyl lactams **1** (5 mmol) were electrolysed in 1.5 mM Et_3N•3HF/CH_3CN (50 ml) using Pt plates (2 x 2 cm) as an anode and a cathode under constant potential electrolysis in a simple undivided cell. After starting lactam **1** was almost consumed (monitoring unreacted **1** by TLC and/or MS), short column chromatography (silica gel: ether as eluent) of the electrolysis solution afforded almost pure monofluorinated product **2**. Results are summarized in Table 1.

Electrochemical monofluorination proceeded in good chemical and current yields and the α-position to the sulfur atom of lactams **1a-c** (runs 1-3) was selectively monofluorinated. Such high yields have

Table1. Electrolytic monofluorination of lactams.



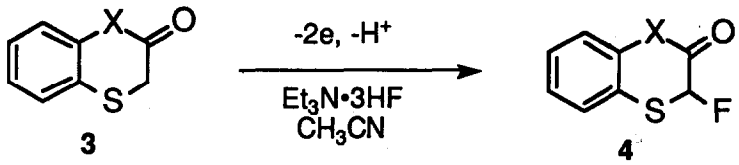
run	n	R	anodic potential (V vs. SSCE)	charge passed (F/mol)	Yield a) (%)
1	1	Me (**1a**)	1.8	2.5	85 (**2a**)
2	1	cyclohexyl (**1b**)	1.8	2.5	84 (**2b**)
3	2	Me (**1c**)	2.0	2.2	69 (**2c**)
4	3	Me (**1d**)	1.9	4.0	b)

a) Isolated yields. b) Complex mixture.

never been achieved in anodic fluorination of aliphatic heterocycles.[5a] The regioselectivity of anodic monofluorination observed here are notable because anodic methoxylation of lactams was reported to occur at α to the nitrogen atom.[9] In the present case, fluorination at α to the nitrogen atom of lactams **1** was not observed at all. This could be explained by easier oxidation of a divalent sulfur atom than that of an amide nitrogen atom. In the case of ε-caprolactam derivative **1d**, the situation changed dramatically and electrolysis afforded a complex mixture (run 4). From GC-MS analysis of the electrolyte, many fluorinated products (two monofluorinated, difluorinated, and dehydrofluorinated products) were found to be formed after 4 F/mol of charge was passed. This can be explained not only by the stability of the fluorinated products but also by a change of selectivity of the fluorination. Closely related results concerning regiochemistry of anodic nucleophilic substitution reaction of lactams were reported previously.[10] In that case, the regiochemistry of anodic oxidation was greatly influenced by the ring size of lactams, that is, the reaction site shifted from ring carbon to side chain α to the nitrogen atom when the ring member of lactams changed from 5,6 to 7, respectively.[11] Although anodic monofluorination of sulfides was established to proceed *via* a unique pummerer-type mechanism,[12] which is different from the conventional ECEC mechanism of other anodic nucleophilic substitution reactions (methoxylation, acetoxylation, cyanation, etc.), it is interesting that regiochemistry of anodic monofluorination observed here is also highly dependent on the ring size of lactams as observed in the anodic hydroxylation.[11] Such ring size dependent fluorination has never been reported in either chemical or electrochemical fluorinations.

Next, we applied this anodic monofluorination to 2H-1,4-benzothiazin-3(4H)-one derivatives (3) which contain one sulfur atom in the ring system (Table 2). The anodic monofluorinations of such lactam-like derivatives annelated by a benzene ring showed another interesting features. The anodic monofluorination of **3a**, which have no substituent on the nitrogen atom, results in aniline-like

Table 2. Electrolytic monofluorination of fused nitrogen-containing heterocycles.



3 4

run	X	anodic potential (V vs. SSCE)	charge passed (F/mol)	Yield a) (%)
5	NH (**3a**)	3.0	15	0
6	N-COPh (**3b**)	2.0	2.2	77 (**4b**)
7	N-isoPr (**3c**)	1.5	2.5	88 (**4c**)
8	N-CH_3 (**3d**)	1.6	2.1	68 (**4d**)

a) Isolated yields.

polymerization (run 5) and no desired product was formed. On the other hand, N-substituted derivatives **3b-d** (runs 6-8) were effectively monofluorinated under the same electrolytic conditions. In the latter two cases, no fluorination at the N-alkyl group was observed at all. Therefore, this fluorination was also highly regioselective. Recently, fluoropyridinium triflates have been shown to be effective fluorination reagents.[13] Therefore, fluorination of **3c** as a model compound with *N*-fluoro-2,4,6-trimethylpyridinium triflate was attempted. However, no fluorinated product was formed.

In conclusion, 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 nitrogen atom, etc.) of lactams. High yields of monofluorinated lactams observed here possess a high synthetic value because the phenylsulfenyl group is known to be easily removed oxidatively and/or reductively.

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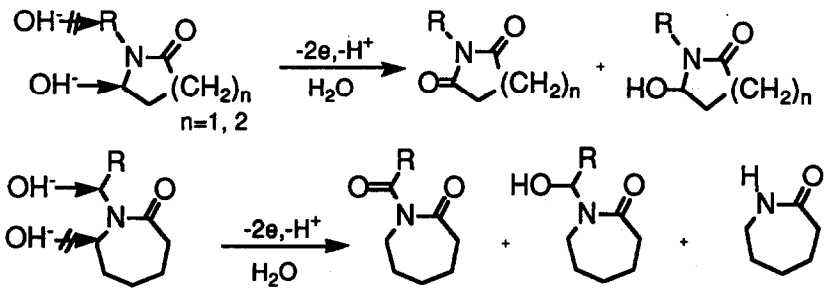

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