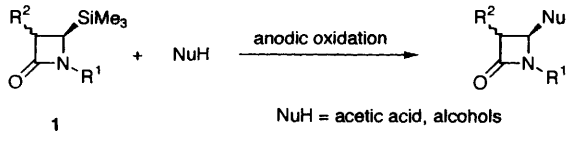
Electrochemical fluorination of 4-trimethylsilylazetidin-2-ones: an efficient and regioselective preparation of 4-fluoroazetidin-2-ones

Kohji Suda,*[a] Katsumi Hotoda,[b] Mitsuaki Aoyagi[a] and Toshikatsu Takanami[a]
[a] *Meiji College of Pharmacy, 1-35-23, Nozawa, Setagaya, Tokyo 154, Japan*
[b] *Shiratori Pharmaceutical Co., Ltd., 6-11-24, Tsudanuma, Narashino, Chiba 275, Japan*

Anodic oxidation of 4-trimethylsilylazetidin-2-ones in the presence of $Et_3N{\cdot}3HF$ gave 4-fluoroazetidin-2-ones in high yields under very mild conditions.

Much effort has been directed toward the synthesis of fluorine-containing heterocycles owing to their potential biological activity.[1,2] Fluoroazetidin-2-ones are attractive compounds not only as synthetic intermediates for the preparation of fluorinated β-lactam antibiotics but also as a building block for the preparation of fluorinated carbohydrates and amino acids. However, few syntheses of such compounds have been reported.[3-5] Of the methods developed, electrochemical fluorination of organic compounds[2] is of continuing interest since it allows direct introduction of fluorine into organic molecules.†[,5,6] Recently, we reported that electrochemical oxidation of 4-trimethylsilylazetidin-2-ones, **1**, resulted in facile cleavage of the carbon–silicon bond and introduction of OR and OCOMe onto the carbon (Scheme 1).[7] We, therefore, thought that electrochemical oxidation of **1** in the presence of fluoride ion as a nucleophile would provide 4-fluoroazetidin-2-ones, **2**. We report here such a facile and highly regioselective reaction.



1 NuH = acetic acid, alcohols

Scheme 1

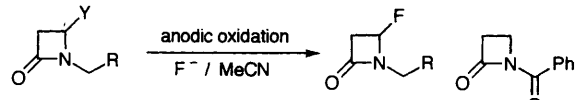
As a model substrate for the electrochemical fluorination, 1-benzyl-4-trimethylsilylazetidin-2-one, **1a**, was chosen, and its reactivity toward various fluorine sources was investigated. The electrolysis of **1a** was carried out in acetonitrile with a fluorine source in an undivided cell equipped with both a graphite plate anode and cathode under constant current conditions.

As shown in Table 1, $Et_3N{\cdot}3HF$ was the most effective fluoride source examined, and the yield of **2a** was in the order: $Et_3N{\cdot}3HF$ (80%) > Py·*n*HF (66%) > $Et_3N{\cdot}2HF$ (49%) (runs 1–3).‡ Although Yoshida *et al.* have reported that electrochemical fluorination of α-silyl ethers bearing carbon–carbon double bonds can be achieved in dichloromethane with Bu_4NBF_4 as a fluoride source,[9] a similar anodic oxidation of **1a** gave only tarry materials, with none of the desired product **2a** (run 4).

It should be noted that our fluorination of **1a** is completely regioselective, providing **2a** as a single product. The fluorination of 1-butyl-4-trimethylsilylazetidin-2-one, **1b**, also took place smoothly in acetonitrile with $Et_3N{\cdot}3HF$, giving the corresponding 4-fluoro derivative, **2b**, as a single product in 78% yield (run 5). In the both cases, a fluorine atom was selectively introduced into the C-4 position of the β-lactam ring, neither fluorination of the *N*-alkyl substituents at the α position nor perfluorination of the substrates being observed. In contrast, electrochemical oxidation of the corresponding non-silylated azetidin-2-ones, **3** and **4**, in acetonitrile with $Et_3N{\cdot}3HF$ gave no fluorine-containing product: carbonylation at the benzylic position of **3** to give **5** and decomposition of **4** occurred, respectively (runs 6 and 7). It is clear, therefore, that a 4-silyl group in azetidin-2-ones completely controls both the number and regiochemistry of fluorine atoms introduced, by enhancing the reactivity of the β-lactam ring towards anodic oxidation.§

Under the conditions adopted in run 1, we next examined the fluorination of various 4-silylazetidin-2-ones. All the substrates, **1c–e**, could easily be transformed into the corresponding 4-fluoro derivatives, **2c–e**, in good to excellent yields (Table 2). In the reactions of *E*-**1c** and *Z*-**1c**, the stereochemistry of their alkylidene side chains was kept during the electrolyses, and *E*-**2c**

Table 1 Electrochemical fluorination of **1a**, **1b**, **3** and **4**



1a Y = $SiMe_3$, R = Ph
1b Y = $SiMe_3$, R = Pr
3 Y = H, R = Ph
4 Y = H, R = Pr

2a R = Ph
2b R = Pr
5

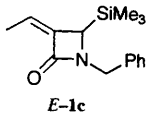
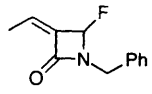
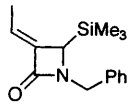
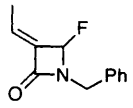
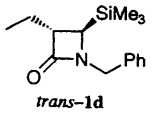
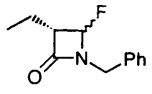
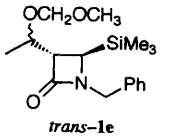
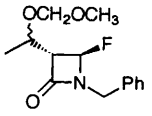
Run	Substrate	Electrolyte (mol dm^{-3})	Electricity (F mol^{-1})	Product	Yield (%)[a]
1	**1a**	$Et_3N{\cdot}3HF$ (0.37)	8.0	**2a**	80
2	**1a**	$Et_3N{\cdot}2HF$ (0.56)	20.0	**2a**	49
3	**1a**	Py·nHF (0.15)	4.0	**2a**	66
4	**1a**	Bu_4NBF_4[d] (0.24)	4.0	Tar	—
5	**1b**	$Et_3N{\cdot}3HF$ (0.37)	18.0	**2b**	78
6	**3**	$Et_3N{\cdot}3HF$ (0.37)	20.0	**5**	58
7	**4**	$Et_3N{\cdot}3HF$ (0.37)	30.0	Tar	—

[a] Isolated yield. [b] CH_2Cl_2 was used as solvent.

† Electrochemical monofluorination of β-lactams at the C-3 position has already been reported by Fuchigami *et al.* (see ref. 5*a*).
‡ $Et_3N{\cdot}2HF$ was prepared from $Et_3N{\cdot}3HF$ and Et_3N (2:1) (see ref. 8).

§ Silyl and stannyl groups have recently been used as 'electro-auxiliaries', which can promote the electron transfer from the heteroatoms β to silicon or tin (see refs. 7, 9 and 10).

Table 2 Electrochemical preparation of 4-fluoroazetidin-2-ones **2**

Substrate	Electricity (F mol^{-1})	Product	Yield (%)[a]
1a	8.0	**2a**	80
1b	18.0	**2b**	78
 *E*-**1c**	10.0	 *E*-**2c**	68
 *Z*-**1c**	6.0	 *Z*-**2c**	80
 *trans*-**1d**	14.0	 **2d** (*cis* / *trans* = 1 / 1)	88
 *trans*-**1e**	10.0[b]	 *trans*-**2e**	75[b]

[a] Isolated yield. [b] A mixture of two diastereoisomers (1 : 2)

and *Z*-**2c** were obtained, respectively, as single isomers. The electrolysis of *trans*-**1d** provided a 1 : 1 mixture of *cis*- and *trans*-isomers, whereas the fluorination of *trans*-**1e** proceeded in highly stereoselective manner to give only *trans*-**2e**, none of the corresponding *cis*-isomer being detected in the ^{1}H NMR spectrum of the crude products.¶

In summary, effective and highly regioselective preparation of 4-fluoroazetidin-2-ones has been achieved by the anodic oxidation of 4-trimethylsilylazetidin-2-ones in acetonitrile with Et_3N·3HF under very mild conditions. Although several methods for the preparation of 4-fluoroazetidin-2-ones have been reported, these methods require expensive, unstable and dangerous reagents such as $FClO_3$, 4-*tert*-butyliodobenzene difluoride and trimethyloxonium tetrafluoroborate, and the yields are quite low (14–40%).[3] The present transformation of **1** to **2** is superior to the methods so far developed in facility and yields, and should be regarded as the first practical method for the preparation of 4-fluoroazetidin-2-ones. Studies concerning the reaction mechanism and synthetic applications are underway.

¶ The stereochemistry of *trans*-**2e** was established by comparison of the ^{1}H NMR spectral data with those of a 1 : 1 mixture of *trans*- and *cis*-**2d**. In the ^{1}H NMR spectra of these compounds, no vicinal coupling between 3-H and 4-H is observed in *trans*-**2d** and *trans*-**2e**, while it is observed in *cis*-**2e** (3.5 Hz); δ_H(270 MHz; $CDCl_3$) data of a 1 : 1 mixture of *trans*- and *cis*-**2d**, and *trans*-**2e** (a 1 : 2 mixture of diastereoisomers) are as follows: a 1 : 1 mixture of *trans*- and *cis*-**2d** δ 0.99 (3/2 H, t, *J* 7.4), 1.03 (3/2 H, t, *J* 7.4), 1.53–1.86 (2 H, m), 3.08–3.20 (1 H, m), 4.13 and 4.63 (each 1/2 H, d, *J* 13.9), 4.17 (1/2 H, dd, *J* 14.4 and 2.6), 4.57 (1/2 H, d, *J* 14.4), 5.32 (1/2 H, d, *J* 75.2, 4-H of *trans*-**2d**), 5.60 (1/2 H, dd, *J* 76.7 and 3.5, 4-H of *cis*-**2d**), 7.25–7.38 (5 H, m); *trans*-**2e** δ 1.27–1.32 (3 H, m), 3.20–3.38 (4 H, m), 4.02–4.16 (2 H, m), 4.51–4.74 (3 H, m), 5.52 (1/3 H, d, *J* 76.2, 4-H of *syn*- or *anti*-form), 5.67 (2/3 H, d, *J* 75.9, 4-H of *syn*- or *anti*-form) and 7.27–7.36 (5 H, m).

Experimental

4-Trimethylsilylazetidin-2-ones **1** were prepared from *cis*-1,3,4-tris(trimethylsilyl)azetidin-2-one, which could easily be obtained by nitrogen-inserting ring-enlargement of *cis*-2,3-bis(trimethylsilyl)cyclopropanone with trimethylsilyl azide in the presence of a catalytic amount of sodium azide–15-crown-5.[7b]

General procedure for the electrochemical preparation of 4-fluoroazetidin-2-ones 2

In an undivided cell equipped with both a graphite plate anode and cathode and a Teflon stir bar were placed an acetonitrile solution (10 cm^3) containing a substrate **1** (0.5 mmol) and Et_3N·3HF (0.37 mol dm^{-3}). A constant electric current of 50 mA was applied to the solution. After 6–18 F mol^{-1} of electricity had been consumed, the mixture was poured into brine (50 cm^3) and extracted with CH_2Cl_2 (30 cm^3 × 3). The combined extracts were dried ($MgSO_4$) and concentrated under a reduced pressure and the residue was purified by short column chromatography on silica gel with hexane–AcOEt (3 : 1) as eluent to give **2**. All the products gave satisfactory IR, NMR and high resolution mass spectra; **2a** δ_H(270 MHz, $CDCl_3$) 3.00 (1 H, dd, *J* 15.2 and 7.3), 3.13 (1 H, ddd, *J* 15.2, 6.4 and 3.3), 4.18 and 4.57 (each 1 H, d, *J* 15.2), 5.64 (1 H, dd, *J* 75.2 and 3.3) and 7.24–7.37 (5 H, m); δ_F(254 MHz, $CDCl_3$, CF_3CO_2H was used as an external standard) −149.85 (dt, *J* 75.6 and 6.9).

Acknowledgements

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