Electrochemical Direct Fluorination of Lactams

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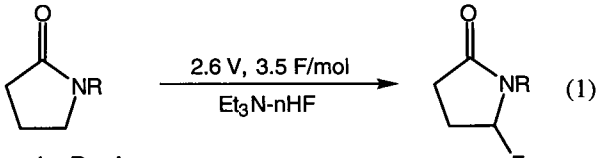
Abstract. The electrochemical fluorination of a variety of *N*-protected lactams was carried out and Et_3N–5HF was found to be superior to Et_3N–3HF as the electrolyte. When 5- and 6-membered *N*-acetyl or ethoxycarbonyl lactams were used as substrates, the fluorination reaction selectively took place at the α-position of the lactam nitrogen and the corresponding monofluoro products could be obtained in good yields.

INTRODUCTION

Fluorinated compounds have been of great interest to synthetic and medical chemists due to the unique physical and biological properties imparted by fluorine.[1] Among them, fluorinated lactams are particularly attractive because of their roles as the building blocks in the preparation of the fluorinated analogs of natural products as well as their own biological properties.[2] The electrochemical fluorination method is useful for introducing a fluorine atom into organic molecules because the desired fluorinated compounds can be prepared without toxic metal reagents or hazardous fluorinating reagents.[3] However, the direct introduction of a fluorine atom into the α-position of the lactam nitrogen is difficult and activation by the substituents such as sulfur[4] or silyl groups[5] is necessary. Recently, Sono et al. reported the direct introduction of a fluorine atom into the α-position of the lactam nitrogen having no substituents at that position using Et_3N–3HF as the supporting electrolyte.[6] Though the direct preparation of the desired fluorinated lactams was possible by their method, the yields were too low. We found that the Et_3N–5HF complex is more stable than Et_3N–3HF under electrochemical oxidation conditions and suitable for the electrolyte in the electrochemical fluorination reaction of the substrates having a high oxidation potential.[7a] In this paper, the direct fluorination of lactams is examined using the Et_3N–5HF complex as the electrolyte and fluorine source.

RESULTS AND DISCUSSION

First, the fluorination reaction of 1-acetyl-2-pyrrolidinone (**1a**) was carried out in Et_3N–3HF or –5HF and a variety of solvents to find the suitable reaction conditions (eq 1). Platinum electrodes (2 × 2 cm) and an undivided cell made of Teflon PFA were used, and 3.5 F/mol of electricity was passed under the controlled potentials (2.6 V vs. Ag/Ag^+). When the reaction was carried out in Et_3N–3HF and CH_3CN, most of **1a** remained unchanged (Entry 1 in Table 1). As the electrolytic oxidation of Et_3N–3HF takes place at a relatively low potential (2.0V vs. Ag/Ag^+),[7a] most of the electricity was used for the oxidation of Et_3N–3HF at this reaction potential (2.6 V vs. Ag/Ag^+). On the other hand, Et_3N–5HF is not oxidized up to 2.8V[7a] and is stable enough as the electrolyte for the oxidation of **1a**. As expected, **1a**



(1)

1a, R = Ac
1b, R = COOEt
1c, R = COPr-i
1d, R = Me

2a-e

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Table 1. Effect of solvent and electrolyte in the fluorination of **1a**[a]

entry	solvent	electrolyte	temp. (°C)	conversion (%)	yield of **2a** (%)[b]
1	CH_3CN	Et_3N–3HF	18	23	7
2	CH_3CN	Et_3N–5HF	18	98	70
3	CH_2Cl_2	Et_3N–5HF	18	68	45
4	CF_3CO_2Et	Et_3N–5HF	18	94	56
5	CH_3CO_2Et	Et_3N–5HF	18	84	58
6	CH_3CN	Et_3N-5HF	0	99	71
7	CH_3CN	Et_3N-5HF	–45	98	81 (70)

[a]The reactions were carried out using 1 mmol of **1a**, 5 mL of Et_3N–nHF, and 10 mL of solvent at 2.6 V (vs. Ag/Ag^+) until 3.5 F/mol of electricity was passed; [b]GC yields based on **1a** used, in parenthesis, isolated yield.

was consumed almost completely using Et_3N–5HF instead of Et_3N–3HF and 1-acetyl-5-fluoro-2-pyrrolidinone (**2a**) was obtained in good to moderate yields (Entries 2–5). We finally succeeded in obtaining **2a** in the highest yield by carrying out the reaction at –45 °C in Et_3N–5HF and CH_3CN (Entry 7). The fluorination reaction selectively took place at the 5-position of **1a**.

The electrochemical fluorination of a variety of lactams was carried out in Et_3N–5HF and MeCN at –45 °C under controlled potentials. The electricity was passed until most of the starting materials were consumed. The results are shown in Table 2. In the reaction of *N*-methyl-2-pyrrolidinone (**1d**), many products were formed and the desired 5-fluoro product (**2d**) was only obtained in low yields.[6] As for the protecting groups of nitrogen, the acetyl and ethoxycarbonyl groups gave good results. When an unprotected 2-pyrrolidinone was used, the spontaneous formation of a polymer film on the electrodes restricted the electrical current and the reaction. From the five- and six-membered lactams (**1**, **3**, and **7**), the fluorinated products (**2**, **4**, and **8**) were obtained in good yields. On the other hand, during the fluorination of the four- and seven-membered lactams (**5** and **9**), the competitive formation of polar products could not be prevented and the desired fluorinated products (**6** and **10**) were obtained in a lower yield.

EXPERIMENTAL

IR spectra were recorded using a Hitachi 260-30 infrared spectrometer. ^1H NMR spectra and ^{19}F NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-A400 FT NMR and chemical shifts, δ, are referred to tetramethylsilane (TMS) (^1H) and $CFCl_3$ (^{19}F), respectively. Mass spectra and elemental analyses were taken at the Center for Instrumental Analysis, Hokkaido University. Et_3N–3HF and –5HF were prepared from freshly distilled Et_3N and anhydrous HF as previously reported.[7a] The unprotected lactams were obtained from Tokyo Chemical Industry Co. or Aldrich Chemical Co. and converted to the *N*-protected derivatives by the reported methods.[8] Cyclic voltammetry was carried out using an undivided cell (30 mL) made of Teflon PFA. The working electrode was a smooth Pt wire (1 mm × 10 mm), and the counter electrode was a smooth Pt sheet (20 mm × 20 mm). The reference electrode was $Ag/AgNO_3$ (0.01 M) in MeCN containing Et_4NBF_4 (0.1 M). The potential was scanned with a potential scanner (Nichia ES 512A) connected to a potentio-galvanostat (Nicia NP-100M), and the voltammograms were recorded on an X-Y recorder (Riken Denshi F-35).

*Electrochemical Fluorination of 1-Acetyl-2-pyrrolidinone (**1a**)*

Under an inert atmosphere of nitrogen, 1-acetyl-2-pyrrolidinone **1a** (127 mg, 1 mmol) was dissolved in a mixture of Et_3N-5HF (5 mL) and dry CH_3CN (10 mL) in an undivided cell at room temperature and this mixture was cooled to –45 °C. The electrolysis was carried out at 2.6 V (vs. Ag/Ag^+) and the anode and cathode were exchanged every 2 s to avoid the formation of polymer films on the electrode. The reaction was monitored by GC, and when 3.5 F/mol of electricity had passed, the consumption of **1a** was confirmed. The reaction mixture was then poured into ice water and extracted four times with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of $MgSO_4$ by filtration, 1-acetyl-5-fluoro-2-pyrrolidinone (**2a**) was isolated by column chromatography (silica gel/hexane-ether) in 70% yield: colorless liquid; IR (neat) 1750(C=O), 1715(C=O) cm^{-1}. ^1H NMR δ = 2.11–2.34 (2H, m), 2.54 (3H, s), 2.54–2.95 (2H, m), 6.52 (1H, dd, J = 60.1, 4.9Hz). ^{19}F NMR δ = –137.1–136.8 (m, 1F). HRMS(EI) Calcd. for $C_6H_8O_2NF$: 145.0539. Found: *m/z* 145.0544.

*1-Ethoxycarbonyl-5-fluoro-2-pyrrolidinone (**2b**)*

Colorless liquid; IR (neat) 1805, 1775(C=O), 1740(C=O) cm^{-1}. ^1H NMR δ = 1.38 (3H, t, J = 7.1Hz), 2.16–2.31 (2H, m), 2.49–2.87 (2H, m), 4.37 (2H, q, J = 7.1Hz), 6.29–6.46 (1H, m). ^{19}F NMR δ = –136.3–136.0 (m, 1F). MS *m/z* (%) 172 (11), 157 (47), 84 (100).

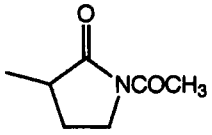
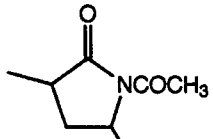
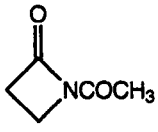
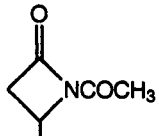
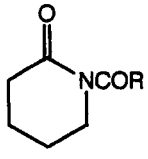
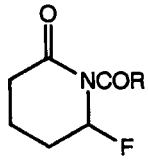
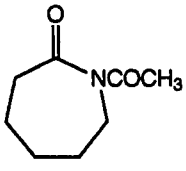
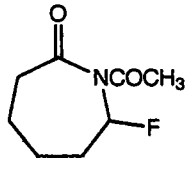
*1-Isobutyryl-5-fluoro-2-pyrrolidinone (**2c**)*

Colorless liquid; IR (neat) 1750(C=O), 1710(C=O) cm^{-1}. ^1H NMR δ = 1.16–1.20 (6H, m), 2.11–2.33 (2H, m), 2.53–2.96 (2H, m), 3.47–3.70 (1H, m), 6.54 (1H, dd, J = 60.2, 4.1Hz). ^{19}F NMR δ = –137.0–136.7 (m, 1F). MS *m/z* (%) 170 (0.3), 153 (27), 84 (100).

*1-Acetyl-5-fluoro-3-methyl-2-pyrrolidinone (**4**)*

(A 3:2 mixture of two diastereomers); colorless liquid; IR (neat) 1750(C=O), 1720(C=O) cm^{-1}. ^1H NMR δ = 1.28 (1.8H, d, J = 6.9Hz), 1.43 (1.2H, d, J = 7.6Hz), 1.68–2.04 (1H, m), 2.31–3.06 (2H, m), 2.55 (3H, s), 6.54 (1H, dd, J = 60.2, 4.4Hz). 6.34–6.60 (1H, m). ^{19}F NMR δ = –137.1–136.8 (m, 1F). HRMS(EI) Calcd. for $C_7H_{10}O_2NF$: 159.0696. Found: *m/z* 159.0687.

Table 2. Electrochemical fluorination of lactams[a]

substrate	reaction potential (V vs. Ag/Ag$^+$)	electricity (F/mol)	product	yield (%)[b]
1a	2.60	3.5	**2a**	81(70)
1b	2.70	2.7	**2b**	(72)
1c	2.60	4.0	**2c**	60(50)
1d	2.10	2.5	**2d**	0
 **3**	2.60	3.5	 **4**	79(71)
 **5**	2.75	5.0	 **6**	(25)
 **7a; R=CH$_3$**	2.60	4.0	 **8a; R=CH$_3$**	60(47)
7b; R=OEt	2.50	2.6	**8b; R=OEt**	(51)
 **9**	2.55	4.5	 **10**	35(30)

[a]The reactions were carried as shown in experimental part; [b]GC yields based on lactams used. In parentheses, isolated yields.

1-Acetyl-4-fluoro-2-azetidinone (6)

Colorless liquid; IR (neat) 1805(C=O), 1715(C=O) cm^{-1}. ^{1}H NMR δ = 2.40 (3H, s), 3.13–3.39 (2H, m), 5.46 (1H, ddd, *J* = 67.8, 4.0, 1.2Hz). ^{19}F NMR δ = –151.6–151.3 (m, 1F). HRMS(EI) Calcd. for $C_5H_6O_2NF$: 131.03826. Found: *m/z* 131.0401.

1-Acetyl-6-fluoro-2-piperidinone (8a)

Colorless liquid; IR (neat) 1705(C=O) cm^{-1}. ^{1}H NMR δ = 1.73–1.92 (2H, m), 2.29–2.77 (4H, m), 2.55 (3H, s), 6.55–6.67 (1H, m). ^{19}F NMR δ = –137.6–137.3 (m, 1F). MS *m/z* (%) 157 (0.6), 139 (20), 115 (10), 97 (85).

1-Ethoxycarbonyl-6-fluoro-2-piperidinone (8b)

Colorless liquid; IR (neat) 1775, 1725(C=O) cm^{-1}. ^{1}H NMR δ = 1.37 (3H, t, *J* = 7.1Hz), 1.80–2.32 (4H, m), 2.47–2.74 (2H, m), 4.36 (2H, q, *J* = 7.1Hz), 6.32–6.47 (1H, m). ^{19}F NMR δ = –134.3–134.0 (m, 1F). MS *m/z* (%) 187 (9), 171 (38).

1-Acetyl-7-fluoroperhydro-2-azepinone (10)

Colorless liquid; IR (neat) 1705(C=O) cm^{-1}. ^{1}H NMR δ = 1.52–2.01 (6H, m), 2.42–2.73 (2H, m), 2.47 (3H, s), 6.81–6.94 (1H, m). ^{19}F NMR δ = –156.1–155.8 (m, 1F). HRMS(EI) Calcd. for $C_8H_{12}O_2NF$: 173.0852. Found: *m/z* 173.0863.

REFERENCES AND NOTES

(1) (a) Schlosser, M. *Tetrahedron* **1978**, *34*, 3–17. (b) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123–3197. (c) Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (d) Resnati, G. *Tetrahedron* **1993**, *49*, 9385–9445. (e) Kukhar', V.P.; Soloshonok, V.A., Eds.; *Fluorine-containing Amino Acids*; Wiley: Chichester, UK, 1995.

(2) (a) Spitzer, W.A.; Goodson, T., Jr.; Chaney, M.O.; Jones, N.D. *Tetrahedron Lett.* **1974**, *15*, 4311–4314. (b)

Brennan, J.; Hussain F.H.S.; Virgili, P. *Tetrahedron Lett.* **1986**, *27*, 3199–3202. (c) Edmunds, J.J.; Motherwell, W.B. *J. Chem. Soc., Chem. Commun.* **1989**, 1348–1349. (d) Araki, K.; Wichtowski, J.A.; Welch, J.T. *Tetrahedron Lett.* **1991**, *32*, 5461–5464. (e) Chupp, J.P.; Hemmerly, D.M.; Freeman, J.J. *J. Org. Chem.* **1993**, *58*, 245–248.

(3) (a) Childs, W.V.; Christensen, L.; Klink, F.W.; Kolpin, C.F. *Organic Electrochemistry*; Lunt, H.; Baizer, M.M., Eds.; Marcel Dekker: New York, 1991; Chapter 26. (b) Childs, W.V.; Fuchigami, T., Eds.; *Electrochemistry in the Preparation of Fluorine and its Compounds*; Electrochemical Society: Pennington, NJ, 1997 and references therein.

(4) Narizuka, S.; Fuchigami, T. *J. Org. Chem.* **1993**, *58*, 4200–4201.

(5) Suda, K.; Hotoda, K.; Aoyagi, M.; Takanami, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1327–1329.

(6) Sono, M.; Toyoda, N.; Shimizu, K.; Noda, E.; Shizuri, Y.; Tori, M. *Chem. Pharm. Bull.* **1996**, *44*, 1141–1145.

(7) (a) Yoneda, N.; Chen, S.-Q.; Hatakeyama, T.; Hara, S.; Fukuhara, T. *Chem. Lett.* **1994**, 849–850. (b) Hara, S.; Chen, S.-Q.; Hatakeyama, T.; Fukuhara, T.; Sekiguchi, M.; Yoneda, N. *Tetrahedron Lett.* **1995**, *36*, 6511–6514. (c) Hara, S.; Chen, S.-Q.; Hoshio, T.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1996**, *37*, 8511–8514. (d) Chen, S.-Q.; Hatakeyama, T.; Fukuhara, T.; Hara, S.; Yoneda, N. *Electrochim. Acta* **1997**, *42*, 1951–1960.

(8) Greene, T.W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.