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Electrolytic partial fluorination of organic compounds. Part 48: Anodic fluorination of 2-cyano-1-methylpyrrole[†]

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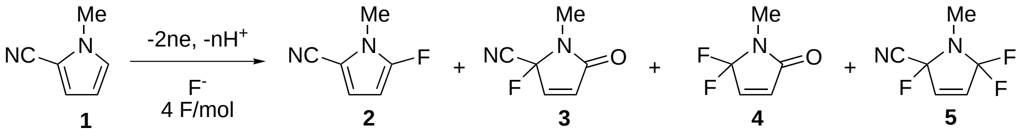
Abstract—Anodic fluorination of 2-cyano-1-methylpyrrole using $Et_3N{\cdot}2HF$ in an undivided cell provided the corresponding 5-fluoropyrrole and 2,5,5-trifluoro-1-methyl-3-pyrrolin-2-carbonitrile while the use of $Et_3N{\cdot}3HF$ afforded selectively the latter product, which was readily hydrolyzed to isolable 5,5-difluoro-1-methyl-3-pyrroline-2-one. This is the first report of successful anodic fluorination of a pyrrole derivative. © 2001 Elsevier Science Ltd. All rights reserved.

Fluorinated aromatic heterocyclic compounds have been of much interest because of their unique biological properties.[2] Although direct fluorination of heteroaromatic rings is the simplest way to prepare fluorinated heterocycles, successful examples of the fluorination are limited. For example, the chemical fluorination of five-membered heteroaromatic compounds such as pyrroles, thiophenes and furans were attempted; however, the yields were extremely low (less than 6%) and the selectivity was also unsatisfactory in all cases.[3] Recently, electrochemical partial fluorination of organic compounds has been shown to be a new powerful method for selective fluorination.[4] However, there have been few reports of direct fluorination of heteroaromatic compounds using an electrochemical method.[5] In most cases, yields of the fluorinated product are extremely

Table 1. Anodic fluorination of 2-cyano-1-methylpyrrole (**1**)



Run	Solvent	Supporting electrolyte	Yield (%)[a]			
			2	**3**	**4**	**5**
1	MeCN	$Et_3N{\cdot}2HF$	20	Trace	Trace	32
2	MeCN	$Et_3N{\cdot}3HF$	5	2	3	65
3	MeCN	$Et_3N{\cdot}5HF$	0	12	47	5
4	MeCN	$Et_3N{\cdot}4HF$	0	21	28	6
5[b]	DME	$Et_3N{\cdot}2HF$	20	0	Trace	12
6	DME	$Et_3N{\cdot}3HF$	8	0	2	51
7	CH_2Cl_2	$Et_3N{\cdot}2HF$	19	Trace	Trace	51
8	CH_2Cl_2	$Et_3N{\cdot}3HF$	0	Trace	Trace	60
9[c]	CH_2Cl_2	$Et_3N{\cdot}5HF$	0	17	0	0
10[c]	CH_2Cl_2	$Et_3N{\cdot}4HF$	0	25	0	0

[a] Determined by ^{19}F NMR spectroscopy.

[b] A large amount of starting **1** was recovered.

[c] Large amounts of unidentified polymeric products were formed.

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low or unsatisfactory. On the other hand, we found that electron-withdrawing groups promoted the anodic fluorination of heterocyclic compounds.[5,6] With these facts in mind, we attempted the direct anodic fluorination of pyrroles having an electron-withdrawing cyano group.

At first, we investigated anodic fluorination of 2-cyano-1-methylpyrrole (**1**) using various fluoride supporting salts and solvents. Constant current electrolysis was carried out at platinum plate electrodes in an undivided cell at room temperature until **1** was mostly consumed (4 F/mol). The results are summarized in Table 1.

Anodic fluorination of **1** took place efficiently to provide four fluorinated products **2**,[7] **3**,[8] **4**[9] and **5**[10] depending on the fluoride salts and solvents. When $Et_3N{\cdot}3HF$ was used, trifluorinated product **5** was selectively (runs 2 and 6) or exclusively formed (run 8) depending on the solvent used. On the other hand, the use of $Et_3N{\cdot}5HF$/MeCN or $Et_4NF{\cdot}4HF$/MeCN provided difluorinated product **4** preferentially (runs 3 and 4), while the use of the same fluoride salts in CH_2Cl_2 afforded **3** exclusively (runs 9 and 10). It is noted that monofluorinated pyrrole **2** was formed in considerable amount along with **5** by using $Et_3N{\cdot}2HF$ regardless of the solvents (runs 1, 5 and 7). The product **2** was easily isolated by column chromatography (hexane/AcOEt, 3:1). In all cases, the *N*-methyl group was not fluorinated at all. This is in sharp contrast to the anodic fluorination of 1-methylpyrazole-4-carboxylates to provide both ring-fluorinated and *N*-methyl fluorinated products.[5c] Thus, the product selectivity was found to be controlled mainly by the fluoride salts used. The oxygen source of the products **3** and **4** seems to be water contaminated in the fluoride salts. Therefore, we carried out anodic fluorination of **1** in $Et_3N{\cdot}3HF$/MeCN in the presence of water (Scheme 1).

In the presence of an equimolar amount of water, the yield of trifluorinated product **5** decreased drastically while that of **4** increased. In this case, a considerable amount of *N*-methylmaleimide was formed. Moreover, after the electrolysis of **1** in $Et_3N{\cdot}3HF$/MeCN, excess water was added to the electrolytic solution and then the reaction mixture was stirred for 4 h to give the difluorinated product **4** in 54% yield (ca. 83% yield from **5** in consideration of run 2) as shown in Scheme 2. These results clearly indicate that **5** was readily hydrolyzed to form **4** efficiently. Therefore, **5** is a precursor to **4**.

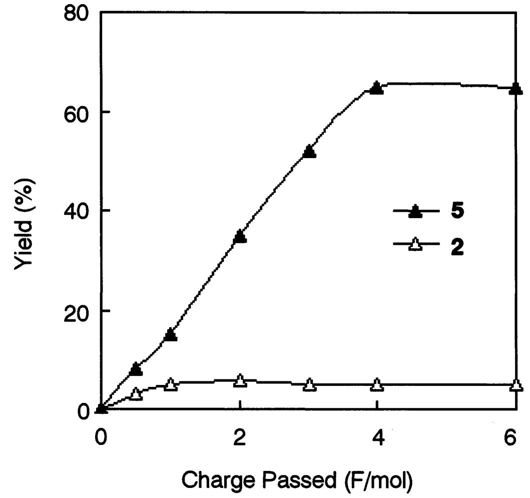
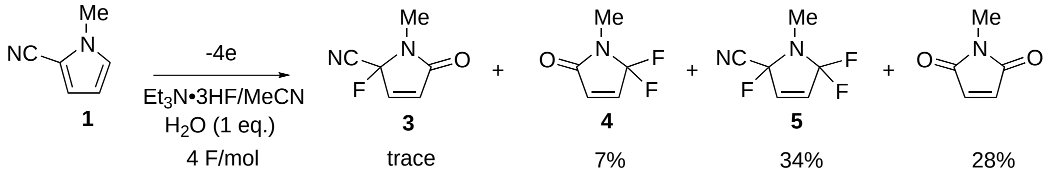
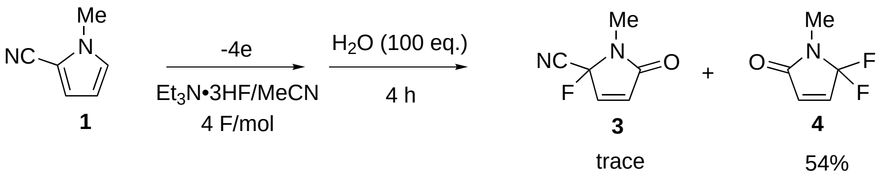


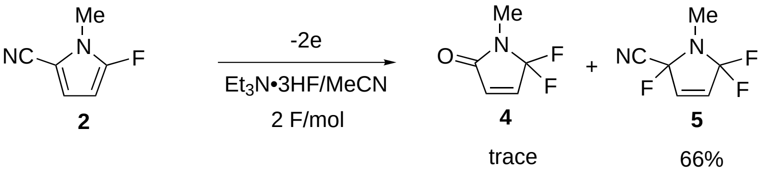
Figure 1. Dependence of yields of **2** and **5** on the charge passed during the anodic fluorination of **1** in $Et_3N{\cdot}3HF$/MeCN.



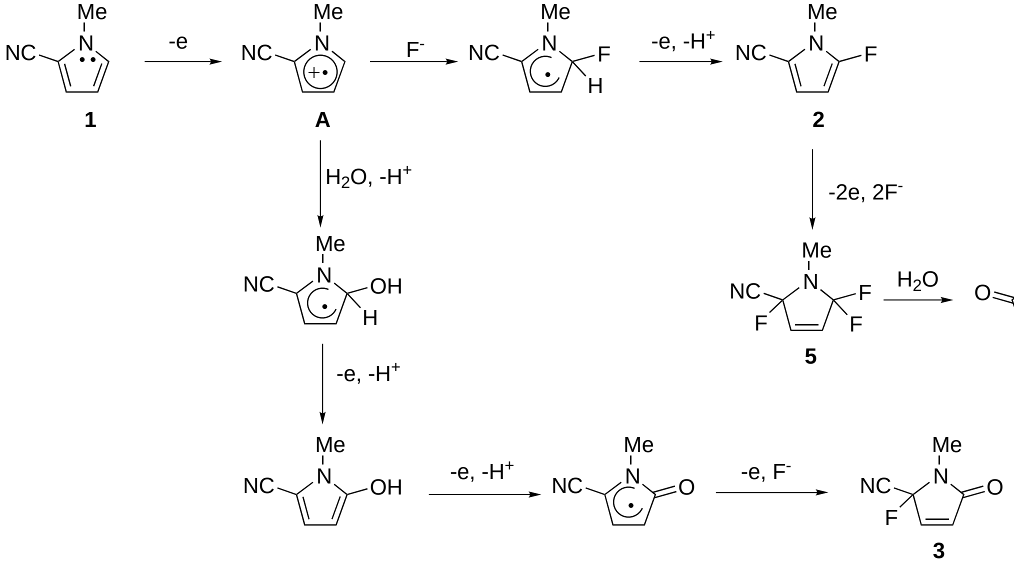
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

In order to clarify the reaction mechanism, the oxidation potentials of **1** and **2** were measured. The oxidation potential of **2** ($E_{\mathrm{P}}^{\mathrm{OX}} = 1.72$ V versus SEC) was found to be slightly less positive compared with **1** ($E_{\mathrm{P}}^{\mathrm{OX}} = 1.77$ V versus SCE). It was also confirmed that anodic fluorination of **2** in MeCN/$Et_3N \cdot 3HF$ provided **5** selectively in good yield (Scheme 3).

Furthermore, the relationship between the product yields and the charge passed was investigated. As shown in Fig. 1, trifluorinated product **5** was formed even at an early stage of the electrolysis, and the yield of **5** increased linearly to 65% with the amount of electricity. In contrast, the yield of **2** is rather low and did not change with the electricity. These facts suggest that **2** is easily oxidized to give **5** immediately after **2** is formed during the electrolysis.

From these results, a possible reaction mechanism was proposed as shown in Scheme 4. This reaction sequence can be explained by a conventional ECEC process. Since **2** is more easily oxidized than **1**, the trifluorinated product **5** is preferentially formed by the further electrochemical oxidation of **2** once formed during the electrolysis. However, since $Et_3N \cdot 2HF$ is easily oxidized, the further oxidation of **2** seems to be suppressed by simultaneous oxidation of $Et_3N \cdot 2HF$. In support of this hypothesis, the use of $Et_3N \cdot 5HF$ and $Et_4NF \cdot 4HF$, which are stable for oxidation, did not provide **2**. The trifluorinated product **5** is unstable; however, it is easily converted to the difluoro compound **4** efficiently by the hydrolysis of **5**. As already mentioned, the use of $Et_3N \cdot 5HF$/MeCN and $Et_4NF \cdot 4HF$/MeCN gave **3** and **4**, while the use of CH_2Cl_2 instead of MeCN provided **3** solely. The reason for such product selectivity is not clear at present. The monofluorinated product **3** seems to be formed by the addition of water to the radical cation **A** (Scheme 4).

In sharp contrast to the case of **1**, the anodic fluorination of pyrrole and 1-methylpyrrole gave only a polymerized product and no fluorinated product was formed.

In conclusion, we have successfully carried out for the first time anodic fluorination of 2-cyano-1-methylpyrrole. The product **4** has a biologically interesting *gem*-difluoromethylene unit in the heterocyclic ring and **2** has also a versatile cyano group and a fluorine atom. Therefore, **2** and **4** seem to be useful fluorinated building blocks. Work on further application and the scope and limitation of the methodology for anodic fluorination is now in progress.

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7. **5-Fluoro-1-methyl-2-pyrrolecarbonitrile (2)**: yellow oil; ^{1}H NMR δ 6.66 (m, 1H), 5.59 (m, 1H), 3.61 (s, 3H); ^{13}C NMR δ 148.2 (d, J=267.2 Hz), 117.9 (d, J=3.9 Hz), 113.3, 96.3 (d, J=2.8 Hz), 88.3 (d, J=11.7 Hz), 30.1 (d, J=1.7 Hz); ^{19}F NMR δ −53.96 (m); MS (m/z) 124 (M^{+}), 109, 84; HRMS calcd for $C_6H_5N_2F$: 124.0437. Found: 124.0443.
8. **5-Cyano-5-fluoro-1-methyl-3-pyrrolin-2-one (3)**: colorless oil; ^{1}H NMR δ 7.08 (d, J=5.8 Hz, 1H), 6.48 (d, J=5.8 Hz, 1H), 3.09 (s, 3H); ^{13}C NMR δ 167.2 (d, J=3.4 Hz), 139.2 (d, J=19.0 Hz), 131.2 (d, J=3.4 Hz), 111.5 (d, J=56.5), 94.6 (d, J=204.6), 25.2; ^{19}F NMR δ −46.41 (s); MS (m/z) 140 (M^{+}), 111, 84; HRMS calcd for $C_6H_5FN_2O$: 140.0386. Found: 140.0386.
9. **5,5-Difluoro-1-methyl-3-pyrrolin-2-one (4)**: colorless oil; ^{1}H NMR δ 6.92 (d, J=5.8 Hz, 1H), 6.30 (d, J=5.8 Hz, 1H), 2.94 (s, 3H); ^{13}C NMR δ 166.6, 138.0 (t, J=27.4 Hz), 130.2 (t, J=3.9 Hz), 122.3 (t, J=243.7), 22.8; ^{19}F NMR δ −23.61 (s); MS (m/z) 133 (M^{+}), 106, 84; HRMS calcd for $C_5H_5F_2NO$: 133.0339. Found: 133.0335.
10. **2,5,5-Trifluoro-1-methyl-3-pyrrolin-2-carbonitrile (5)**: ^{19}F NMR δ −2.54 (dd, J=205.3, 18.5 Hz), −11.31 (dd, J=205.3, 27.7 Hz), −30.36 (dd, 27.7, 18.5 Hz); MS (m/z) 162 (M^{+}).