A Facile Synthesis of *gem*-Difluorinated Heterocyclic Compounds Using Anodic Fluorination of 2-Cyano-1-methylpyrrole as a Key Step

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Abstract: Anodic fluorination of 2-cyano-1-methylpyrrole **1** using $Et_3N{\cdot}5HF$ in an undivided cell provided 5,5-difluoro-1-methyl-3-pyrrolin-2-one (**5a**). The Diels–Alder reaction of **5a** with various dienes was successfully carried out to provide *gem*-difluorinated heterocyclic compounds in excellent yields.

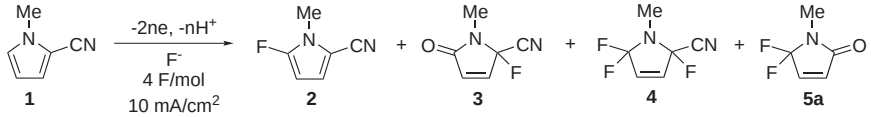
Key words: anodic fluorination, 5,5-difluoro-1-methyl-3-pyrroline-2-one, *gem*-difluoromethylenes, Diels–Alder reaction, dienes

Fluorine-containing heterocyclic compounds have attracted increasing interest in modern bioorganic chemistry due to their remarkable biological activity.[1] Particularly, much attention has been paid to pharmaceutical and agricultural chemicals containing *gem*-difluoromethylene units in recent years.[2] There are two complementary approaches to such an important unit. These are, (a) substitution of a carbonyl or an active methylene group by fluorine,[3] and (b) the use of *gem*-difluoromethylene-containing building blocks.[4] When it comes to fluorinated complex molecules, the former approach cannot be applied because of the reactivity, thermal instability, hazard and cost associated with electrophilic and nucleophilic fluorinating agents. Instead, the latter approach is mainly employed. However, available *gem*-difluoromethylene-containing building blocks are limited. Recently, electrochemical partial fluorination of organic compounds has been shown to be a new powerful method for selective fluorination.[5] However, there have been few reports of direct fluorination of heteroaromatic compounds using electrochemical method.[6] In most cases, yields of fluorinated products are extremely low or unsatisfactory. On the other hand, we found that electron-withdrawing groups promoted the anodic fluorination of heterocyclic compounds.[6,7] With these facts in mind, we attempted the direct anodic fluorination of 2-cyano-1-methylpyrrole (**1**).

At first, we investigated anodic fluorination of 2-cyano-1-methylpyrrole (**1)** using various fluoride supporting salts (1 M) in MeCN (10 mL). Constant current electrolysis (10 mA/cm^2) was carried out at platinum plate electrodes (2×2 cm^2) 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**, **3**, **4**, and **5a** depending on the fluoride salts. The use of $Et_3N{\cdot}5HF$ provided difluorinated product **5a** preferentially. The product **5a** has both a biologically interesting *gem*-difluoromethylene unit and an activated olefin in the heterocyclic ring. Therefore, we attempted the Diels–Alder reaction of **5a** as the dienophile with various dienes.

Table 1 Anodic Fluorination of 2-Cyano-1-methylpyrrole (**1**)



Run	Supporting Electrolyte	Yield (%)[a]			
		2	**3**	**4**	**5a**
1	$Et_3N{\cdot}2HF$	20	trace	32	trace
2	$Et_3N{\cdot}3HF$	5	2	65	3
3	$Et_3N{\cdot}5HF$	0	12	5	54
4	$Et_4NF{\cdot}4HF$	0	21	6	28

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

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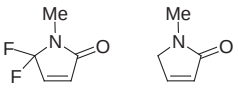
In the [2+4] pericyclic cycloaddition reaction known as the Diels–Alder reaction, compounds having a monofluoro or trifluoromethyl group have been widely used as dienes, dienophiles, or both. However, a few compounds having a *gem*-difluoromethylene unit have been used as dienes, dienophiles, or both.[8] To understand the effect of fluorine on the reactivity of dienophiles and dienes in the Diels–Alder reaction, one must recognize that electron-deficient dienophiles and electron-rich dienes are generally most reactive in 1,3-dipolar cycloaddition. With direct fluorine-substitution not affecting significantly the HOMO or LUMO energies,[9] one would predict that the reactivity of dienes or dienophiles should not be affected drastically by vinylic fluorine substitution. On the other hand, with allylic fluorine-substitution lowering the energies of both HOMO and LUMO, one would expect an enhancement of dienophilic reactivity when a π system has perfluoroalkyl substituents. With these facts in mind, we calculated the HOMO and LUMO energies of **5a** and the corresponding nonfluorinated equivalent **5b**. The calculations were carried out with the MOPAC 2000 program using the AM1. From the calculations, the HOMO and LUMO of **5a** were –10.490 and –0.652 eV, respectively. On the other hand, the HOMO and LUMO of **5b** were –9.564 and 0.076 eV, respectively. Thus, as expected, the difluoromethylene unit was found to have an electron-withdrawing effect, since the HOMO and LUMO energies of **5a** are lower than that of **5b**.



5a **5b**

HOMO	-10.490 eV	-9.564 eV
LUMO	-0.652 eV	0.076 eV

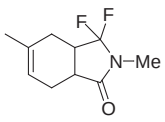
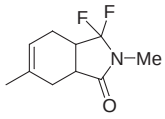
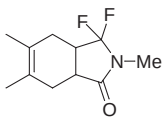
Figure 1 Calculated HOMO and LUMO energies for **5a**

At first, we carried out the Diels–Alder reaction of **5a** with open-chain dienes (Table 2). A mixture of **5a** and a large excess amount (100 equiv) of isoprene was heated at 60 °C for 4 days to give 94% yield of the desired products (**6a** and **6b**) as a regioisomeric mixture. The reaction time was reduced to about half under reflux in toluene, and the almost same yield and regioselectivity were obtained. The Diels–Alder reaction of **5a** with 2,3-dimethylbuta-1,3-diene (5 equiv) was carried out similarly in toluene to afford **7** in quantitative yield.

Next, we extended the Diels–Alder reaction to various cyclic dienes. As shown in Table 3, the reaction proceeded quite smoothly, regardless of the structure of cyclic dienes, to provide the cycloaddition products **8**–**10** in excellent yields. The reaction with furan gave the *endo*-form preferentially while the reaction with cyclopentadiene and cyclohexa-1,3-diene produced the *endo*-form solely. Thus, **5a** was found to be a highly useful building block containing a *gem*-difluoromethylene unit.

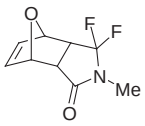
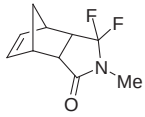
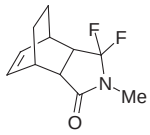
Table 2 The Diels-Alder Reaction of **5a** with Open-Chain Dienes

5a

Diene	Solvent	Temp (°C)	Time (d)	Cycloaddition Products	Yield (%)[a,b]
 (100 equiv)	–	60	4	 **6a**  **6b**	94 (91) (13:7)[c]
 (5 equiv)	toluene	reflux	2.2	**6a**/**6b**	93 (88) (3:2)[c]
 (5 equiv)	toluene	reflux	2	 **7**	quant. (96)

[a] Determined by ^{19}F NMR Spectroscopy.
[b] Isolated yields are given in parenthesis.
[c] Regioisomeric Ratio.

Table 3 The Diels-Alder Reaction of **5a** with Cyclic Dienes

Diene	Solvent	Temp (°C)	Time (d)	Cycloaddition Products	Yield (%)[a]
 (100 equiv)	–	60	3	 **8**	quant. (*endo/exo* = 20:13)
 (5 equiv)	toluene	reflux	0.5	 **9**	quant. (92)[b] (*endo* only)
 (5 equiv)	toluene	reflux	1.5	 **10**	quant. (96) (*endo* only)

[a] Determined by ^{19}F NMR Spectroscopy.
[b] Isolated yields are given in parenthesis.

In conclusion, we have successfully carried out the Diels–Alder reaction using the anodically *gem*-difluorinated product **5a**. Thus, an effective, facile synthetic method of *gem*-difluoromethylated heterocyclic compounds was established in 2 steps, consisting of an anodic *gem*-difluorination and the construction of a heterocyclic skeleton by the Diels–Alder reaction. The products **6a**, **6b**, and **7** are precursors of phthalimidine derivatives,[10] which are physiogically active, prospective isoindole derivatives. In this way, novel synthesis of heterocyclic compounds containing a *gem*-difluoromethylene unit was achieved using anodic fluorination of 2-cyano-1-methylpyrrole (**1**) as a key step.

^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded in $CDCl_3$ at 270, 254 and 68 MHz, respectively. The chemical shifts for ^1H and ^{19}F NMR are given in δ (ppm) from internal TMS and monofluorobenzene (–36.5 ppm), respectively. Mass spectra were obtained with a Shimadzu GC-MSQP-2000A mass spectrometer. High resolution mass spectra were obtained with a Jeol JMS-700 mass spectrometer.

Anodic Fluorination of 2-Cyano-1-methylpyrrole (1)
Electrolysis was carried out at a platinum anode and cathode (2 × 2 cm^2) in a solution of an appropriate fluoride salt (1 M) in CH_3CN(10 mL) containing 2-cyano-1-methylpyrrole **1** (1 mmol) by using an undivided cell under a nitrogen atmosphere at an ambient temperature. Constant current (10 mA/cm^2) was applied until consumption of **1** was mostly achieved (4 F/mol). After the electrolysis, the resulting electrolytic solution was passed through a short column of silica gel using $CHCl_3$ as eluent. The collected solution was evaporated under vacuum. Then, the yields of the fluorinated products **2**–**5a** were calculated by means of ^{19}F NMR by using a known amount of monofluorobenzene as an internal standard. After that, **2**–**5a** were isolated by column chromatography on silica gel using $CHCl_3$.

2-Cyano-5-fluoro-1-methylpyrrole (2)
^1H NMR: δ = 6.66 (m, 1 H), 5.59 (m, 1 H), 3.61 (s, 3 H).

^{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: *m*/*z* calcd for $C_6H_5FN_2$: 124.0437. Found: 124.0443.

5-Cyano-5-fluoro-1-methyl-3-pyrrolin-2-one (3)
^1H NMR: δ = 7.08 (d, *J* = 5.8 Hz, 1 H), 6.48 (d, *J* = 5.8 Hz, 1 H), 3.09 (s, 3 H).

^{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: *m*/*z* calcd for $C_6H_5FN_2O$: 140.0386. Found: 140.0386.

2,5,5-Trifluoro-1-methyl-3-pyrrolin-2-carbonitrile (4)
^{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^+).

5,5-Difluoro-1-methyl-3-pyrrolin-2-one (5a)
^1H NMR: δ = 6.92 (d, *J* = 5.8 Hz, 1 H), 6.30 (d, *J* = 5.8 Hz, 1 H), 2.94 (s, 3 H).

^{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.

Diels–Alder Reaction of 5a with Dienes; General Procedure
To a solution of the 5,5-difluoro-1-methyl-3-pyrrolin-2-one **5a** (1 mmol) in toluene (10 mL) was added a diene (5 mmol). The reaction mixture was stirred for 0.5–4 d under reflux. After the reaction was complete, the reaction mixture was passed through a short column

of silica gel using $CHCl_3$ as eluent. The collected solution was evaporated under vacuum. Then, the yields of the fluorinated products **6a**–**10** were calculated by means of ^{19}F NMR similarly to the cases of **2**–**5a**. After that, **6a**–**10** were isolated by column chromatography on silica gel using $CHCl_3$.

A mixture of **6a** and **6b** was easily isolated. However, their separation failed although **6a** and **6b** appeared separately by GC-MS. We could not separately identify them by ^1H and ^{19}F NMR spectroscopy.

3,3-Difluoro-2,5-dimethyl-3a,4,6,7,7a-pentahydroisoindole-1-one and 3,3-Difluoro-2,6-dimethyl-3a,4,5,7,7a-pentahydroisoindole-1-one (6a/b)

^1H NMR: δ = 5.48 (br s, 1 H), 3.05–2.77 (m, 5 H), 2.48–2.10 (m, 4 H), 1.72 (s, 3 H).

^{19}F NMR: δ = –1.30 (dd, *J* = 185.0, 14.8 Hz), –0.96 (dd, *J* = 185.0, 12.9 Hz), –15.7 (d, *J* = 185.0 Hz), –17.5 (d, *J* = 185.0 Hz).

MS: *m*/*z* = 201 (M^+), 186, 181, 138.

HRMS: *m*/*z* calcd for $C_{10}H_{13}F_2NO$: 201.0965. Found. 201.0944, 201.0935.

3,3-Difluoro-2,5,6-trimethyl-3a,4,7,7a-tetrahydroisoindole-1-one (7)

^1H NMR: δ = 2.94 (m, 2 H), 2.85 (s, 3 H), 2.38–2.08 (m, 4 H), 1.67 (s, 6 H).

^{19}F NMR: δ = 0.98 (dd, *J* = 186.8, 14.8 Hz), –15.6 (d, *J* = 186.8 Hz).

MS: *m*/*z* = 215 (M^+), 200, 195, 152.

HRMS: *m*/*z* calcd for $C_{11}H_{15}F_2NO$: 215.1122. Found: 215.1097.

Selected Spectroscopic Data

5,5-Difluoro-4-methyl-10-oxa-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene-3-one (8)

endo-**8**:

^1H NMR: δ = 6.47–6.21 (m, 2 H), 5.27–5.15 (m, 2 H), 3.61–3.47 (m, 1 H), 3.42–3.28 (m, 1 H), 2.73 (s, 3 H).

^{19}F NMR: δ = 5.54 (dd, *J* = 196.0, 14.8 Hz), –13.7 (d, *J* = 196.0 Hz).

MS: *m*/*z* = 201 (M^+), 172, 132, 114, 95.

HRMS: *m*/*z* calcd for $C_9H_9F_2NO_2$: 201.0601. Found: 201.0588.

exo-**8**:

^1H NMR: δ = 6.56–6.42 (m, 2 H), 5.32 (s, 1 H), 5.23 (s, 1 H), 2.99–2.85 (m, 4 H), 2.76–2.67 (m, 1 H).

^{19}F NMR: δ = 5.12 (dd, *J* = 188.7, 14.8 Hz), –14.9 (d, *J* = 188.7 Hz)

MS: *m*/*z* = 201 (M^+), 132, 114, 95.

HRMS: *m*/*z* calcd for $C_9H_9F_2NO_2$: 201.0601. Found: 201.0601.

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