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Microwave-Assisted Fluorination of 2-Acylpyrroles: Synthesis of Fluorohymenidin

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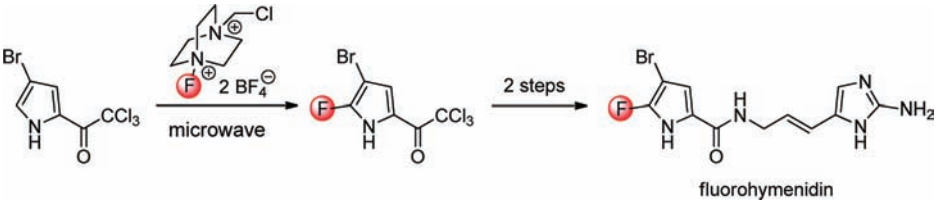
ABSTRACT



Treatment of mono- and nonbrominated 2-acylpyrroles with Selectfluor under microwave conditions leads to fluorination of the pyrrole ring in the 5-position. In particular, 2-trichloroacetylated pyrrole can be fluorinated. As an example, dihydrofluorohymenidin was synthesized and dehydrogenated to fluorohymenidin as the first fluorinated pyrrole-imidazole alkaloid. Introduction of the vinyl double bond was achieved by chlorination of the 2-aminoimidazole moiety, followed by dehydrochlorination at 100 °C in DMF.

Pyrrole-imidazole alkaloids constitute a prominent group of marine natural products exclusively isolated from sponges.[1] Fluorinated pyrrole-imidazole alkaloids such as fluorohymenidin (**1**, Figure 1), an analog of the natural product hymenidin (**2**),[2] may be of interest for biosynthetic studies[3] and for monitoring complex chemical reactions by ^{19}F NMR spectroscopy. Surprisingly, fluorinated pyrrole-imidazole alkaloids have never been synthesized.

In this communication, we report on the microwave-assisted electrophilic fluorination of 2-acylpyrroles employing Selectfluor (**3**).[4] Selectfluor has been used for the fluorination of pyrazole,[5] thiophene,[6] thiazole,[7] and indole[8] derivatives. Regarding the fluorination of pyrrole with Selectfluor, there is only one paper reporting the fluorodecarboxylation of pyrrole-2-carboxylic acids.[9] Other methods

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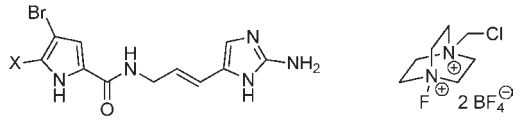


Figure 1. Structures of hymenidines and Selectfluor (**3**).

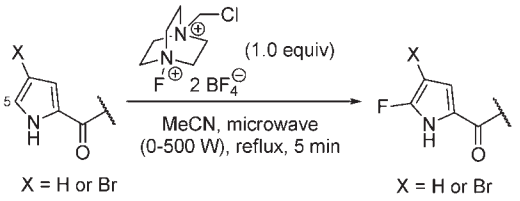
of pyrrole fluorination include the Schiemann reaction,[10] anodic fluorination,[11] and use of fluorine,[12] XeF_2,[13] and *N*-fluorobenzenesulfonimide (NFSI).[14] Microwave-assisted reactions with Selectfluor have led to aryl fluorination of anisole[15] and pyrazole derivatives,[5b] α-fluorination of carbonyl compounds,[16] and desilylation of aliphatic silylethers.[17]

As starting materials, we chose eight mono- and nonbrominated 2-acylpyrrol derivatives. Trichloromethylketones **4** and **5** were synthesized as described.[18] Esters **6**, **7** and amides **8**, **9**, **10**, **11** were obtained by reaction of **4** and **5** with isobutanol, isobutylamine, and aqueous ammonia/MeCN,[19] respectively.

At room temperature, the reaction of **4** with 1 equiv of Selectfluor (**3**) was sluggish with only poor yields of product formed after 24 h. However, reactions with Selectfluor (**3**, 1 equiv) under microwave conditions (continuous power input, 0−500 W) under reflux (no sealed tube) in acetonitrile (0.1 M) gave a single product (Scheme 1).

GC analysis showed that fluorination of ester **6** was over after 5 min with an almost equal amount of starting material remaining, together with minor side products. Similar behavior was observed for all other entries. With the exception of the pyrrole-2-carboxamides **10** and **11**, yields of more than 40% were obtained, comparing well with other examples of electrophilic fluorination with Selectfluor.[5a,7b] Fluorinated pyrroles **13**−**19** are new compounds. Trichloromethylketone **12** has been obtained by Wang and Scott via fluorodecarboxylation of 5-(2,2,2-trichloroacetyl)-1*H*-pyrrole-2-carboxylic acid with XeF_2 (33%).[13a] Under nonmicrowave reflux conditions longer reaction times were needed leading to formation of higher

Scheme 1. Fluorination of 2-Acylpyrroles (starting material 0.1 M, isolated yields, RSM = recovered starting material)



entry	starting material	product	yield (%)	RSM (%)
1	**4**	**12**	44	42
2	**5**	**13**	43	40
3	**6**	**14**	40	42
4	**7**	**15**	41	39
5	**8**	**16**	42	38
6	**9**	**17**	45	30
7	**10**	**18**	19	34
8	**11**	**19**	18	32

amounts of side products. Dibrominated pyrroles did not react.

We had no success on employing *N*-fluorobenzenesulfonimide (NFSI), which had been used by Yamamoto and co-workers for the 2-fluorination of free pyrrole in the presence of substoichiometric amounts of $ZrCl_4$ (53%).[14] The yield of 5-fluoropyrroles could not be enhanced by using more than 1 equiv of Selectfluor. Instead, formation of 2-hydroxypyrrolones was observed. Starting from trichloromethylketone **4** in MeCN−water (50:1), product **20** was isolated in a yield of more than 30% (Scheme 2). The presence of water increased the yield. The reaction was also successful for monobrominated trichloromethylketone

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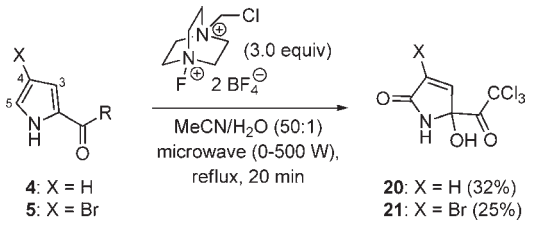
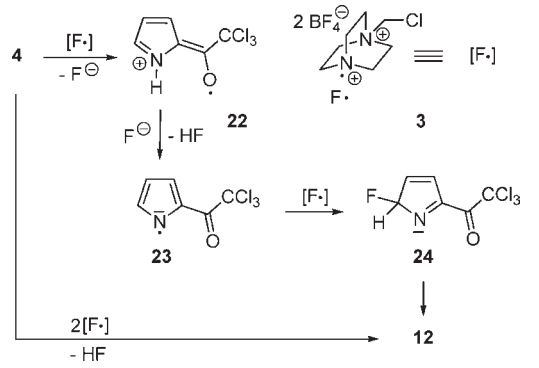
Scheme 2. Oxidation of Trichloromethylketones **4** and **5**



5 affording **21** (25%). Mixtures of starting material **4**, monofluorinated product **12**, and hydroxypyrrolone **20** were obtained when less than 3 equiv of Selectfluor were used.

The structures of the 5-fluoropyrroles and hydroxypyrrolones were deduced from 2D NMR spectra. Coupling constants of vicinal protons 3-H and 4-H were determined as 4.3 Hz (**12**) and 10.3 Hz (**20**), respectively, with 3-H exhibiting HMBC correlations to the exocyclic carbonyl carbon in both series. F−C coupling constants $^{1}J_{FC}$ −259.2 Hz, $^{2}J_{FC}$ 12.0 Hz (to C-4), and $^{3}J_{FC}$ 3.7 Hz (to C-3) and 1.0 Hz (to C-2) were measured for 5-fluoropyrrole **16**, agreeing with the literature.[20]

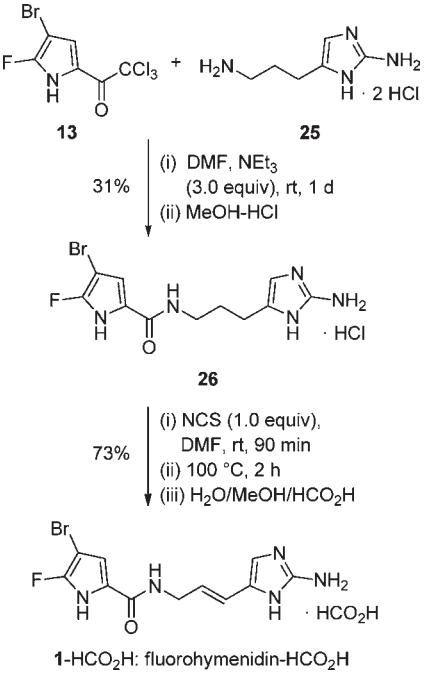
Scheme 3. Possible SET Mechanism of 5-Fluorination



Interestingly, electrophilic bromination of trichloromethylketone **4** with bromine in HOAc occurs at C4,[21] whereas fluorination with Selectfluor takes place at C5. Scheme 3 outlines an SET mechanism which could account for the formation of 5-fluoropyrroles. Electrophilic fluorination agents other than Selectfluor and congeners are generally expected to be sources of atomic fluorine, rather than of "F^{+}", as summarized by Wong and co-workers.[4] For Selectfluor-type agents, it is considered to be very difficult to prove the intermediacy of F· with the currently available methods.

Oxidation of trichloromethylketone **4** may afford radical cation **22** which is deprotonated to radical **23**. Addition of a second equivalent of F· would lead to 5-fluoro-5*H*-pyrrole **24**, followed by tautomerization to 5-fluoro-1*H*-pyrrole **12**. Overall, 2 equiv of Selectfluor would be consumed, limiting the yield to 50%. An SET mechanism is corroborated by an earlier finding by Wang and Scott,[9] who reported fluorodecarboxylation of a series of pyrrole-2-carboxylic acids on treatment with Selectfluor in DCM−aqueous $NaHCO_3$. It was not possible to convert a 5-fluoropyrrole to the corresponding hydroxypyrrolone by treatment with Selectfluor, indicating the possibility of two distinct reaction pathways starting from nonfluorinated pyrrole.

Scheme 4. Synthesis of Fluorohymenidin (**1**) via One-Step Dehydrogenation of Dihydrofluorohymenidin (**26**)



We used 5-fluorinated trichloromethylketone **13** for the synthesis of fluorohymenidin **1** (Scheme 4). Coupling of diamine **25**[22] with the fluorinated building block **13** gave access to fluorodihydrohymenidin (**26**, 31%). For the introduction of the vinyl double bond we employed a new procedure via electrophilic chlorination of the 2-aminoimidazole moiety.[23] Addition of NCS (1 equiv) to **26** in DMF at room temperature selectively formed the corresponding chloroimidazole. After complete conversion (monitored by TLC), elimination of HCl was induced by heating to 100 °C. At higher temperatures, decomposition occurred. Reversed phase chromatography (H_2O/MeOH/HCOOH) afforded fluorohymenidin formate (**1**, 73%). The ^{1}H NMR spectrum of **1** shows the characteristic doublet ($^{3}J_{HH}$ 16.1 Hz) and doublet of triplets ($^{3}J_{HH}$ 16.1 Hz and $^{3}J_{HH}$ 5.5 Hz) of the side chain *E*-double bond. The ^{13}C

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NMR signal of C4 is shifted from 97.5 ppm for **2** to 74.9 ppm for **1**.

In summary, use of Selectfluor under microwave conditions makes 5-fluorinated 2-acylpyrrole derivatives accessible, in particular trichloromethylketone **13**, which may become of use for the synthesis of other pyrrole-imidazole alkaloids carrying a fluorine label at the pyrrole ring.

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Supporting Information Available. Experimental procedures, characterization data, NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.