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Electrophilic Fluorination of a Highly Functionalized Pyrrole

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ELECTROPHILIC FLUORINATION OF A HIGHLY FUNCTIONALIZED PYRROLE

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ABSTRACT: Bromine-lithium exchange of 3-bromo-1-(triisopropylsilyl) pyrrole **6** followed by treatment with N-fluorobenzenesulfonimide gave the fluoropyrrole **8**. Application of this methodology to the highly functionalized pyrrole **1** afforded the fluoropyrrole **4**, which was found to be inaccessible by other approaches.

The introduction of fluorine into biologically active molecules is of wide interest due to the effects of fluorine on the physicochemical properties (and hence the biological activity) of the targeted molecules[1]. In order to investigate the structure-activity relationships in a series of highly functionalized insecticidal pyrroles represented by the halogenated analogs **1-3**[2], we were interested in the preparation of the corresponding fluorinated derivative **4**.

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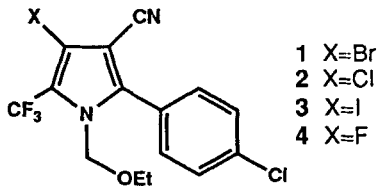
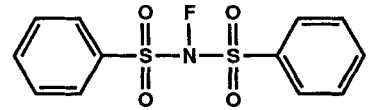


1 X=Br
2 X=Cl
3 X=I
4 X=F



5

Procedures reported for the introduction of fluorine onto a preconstructed pyrrole nucleus have included the reaction[3] of pyrroles with XeF_2 and the conversion of aminopyrroles to fluoropyrroles via the Schiemann reaction.[4] In our hands, approaches toward the highly functionalized fluoropyrrole **4** utilizing these methodologies were unsuccessful. As an alternative approach, we considered the use of electrophilic fluorinating agents containing a nitrogen-fluorine bond. The recently developed N-fluorobenzenesulfonimide **5** appears especially well suited to fluorinate a range of nucleophiles[5]. In particular, the reaction of **5** with aryllithiums to afford good yields of fluoroaromatics suggested that reaction of **5** with the lithiopyrrole derived via bromine-lithium exchange of **1** may afford the desired fluoropyrrole **4**.

As a model study (Scheme I), we examined the reaction of **5** with lithiopyrrole **7**. This simple lithiopyrrole, whose reactivity with a number of electrophiles has been studied, was readily prepared by bromine-lithium exchange of 3-bromo-1-(triisopropylsilyl)pyrrole **6** with *n*-BuLi in THF at -78°C[6]. Treatment of **7** with 1.2 equivalents of N-fluorobenzenesulfonimide **5** for 30 minutes at -78°C, followed by gradual warming to room temperature and quenching with water, afforded the desired 3-fluoro-1-(triisopropylsilyl)pyrrole **8** in 50% yield and 1-(triisopropylsilyl)pyrrole **9** as a major by-product (42% yield). Variation of the reaction conditions, including doubling the amount of

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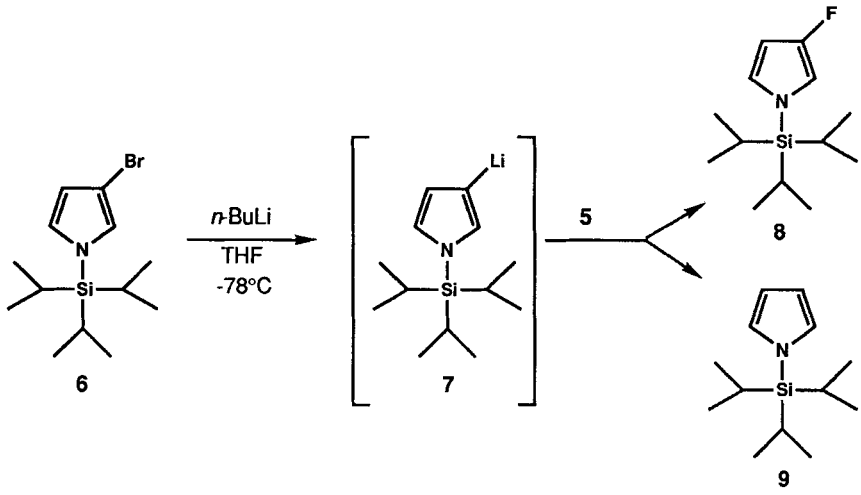

Scheme I

fluorinating reagent, gave no significant difference in product yields. This led us to suspect that **9** was being formed during the course of the reaction rather than by water quenching of unreacted lithiopyrrole **7**. To confirm this suspicion, the reaction mixture was treated with excess methyl iodide before warming to RT and quenching with water. Again, no variation in the product ratio was observed and no 3-methyl-1-(triisopropylsilyl)pyrrole was detected in the product mixture.[7] Based on these results we believe that the formation of **9** is most likely the result of a competing electron transfer reaction. It has been postulated that such electron transfer reactions of N-F bond-containing compounds, such as **5**, with a variety of nucleophiles, especially organometallic nucleophiles, can lead to non-fluorinated products.[8]

Having successfully converted **6** to **8**, we focused our attention on the preparation of the highly functionalized fluoropyrrole **4** utilizing the

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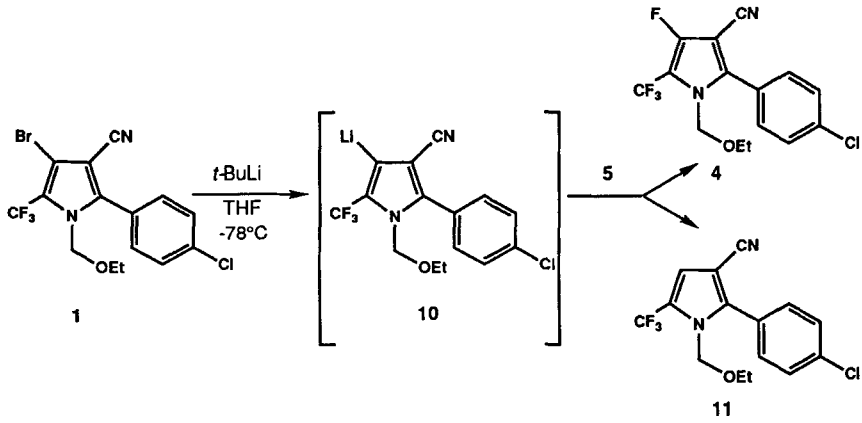

Scheme II

bromopyrrole **1** and similiar methodolgy (Scheme II). Bromine-lithium exchange[9] of **1** with *t*-BuLi in THF at -78°C proceeded smoothly to afford the lithio-compound **10** which, upon treatment with the fluorinating reagent **5** as described above, gave a 6:4 mixture of the fluoropyrrole **4** and **11** by ^{1}H NMR analysis. Repeated flash chromatography of this difficult-to-separate mixture gave pure **4** in 31% yield.

Experimental

Melting points are uncorrected. ^{1}H NMR and ^{19}F NMR spectra were determined on a Varian Unity 300 Spectrometer at 300 MHz and 282 MHz respectively. ^{1}H NMR chemical shifts were measured in ppm using deuterated solvents as internal standards and ^{19}F NMR shifts were measured in ppm using $CFCl_3$ as an external standard. High-resolution mass spectra were recorded on Cyanamid's FTICR[10] mass spectrometer. Infrared spectra were taken on a Perkin Elmer 1420 spectrometer. Microanalyses were performed by Microlit Laboratories, Caldwell, NJ.

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4-Fluoro-1-(triisopropylsilyl)pyrrole (8)

To a stirred solution of **6**[6] (520 mg, 1.72 mmol) in 7 mL of THF at -78°C under N_2 was added *n*-BuLi (0.76 mL, 2.5 M in hexane, 1.89 mmol). After 0.5 h at -78°C, **5**[11] (650 mg, 2.06 mmol) in 3 mL of THF was added in one portion. The reaction was stirred an additional 0.5 h at -78°C, then the cooling bath was removed and the reaction stirred overnight at room temperature. The reaction was then treated with dilute HCl and extracted into EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (elution with petroluem ether) yielded 0.16 g (42%) of **9**[12] and 0.21 g (50%) of **8** as a colorless oil: IR (neat) 2935, 2860, 1470 cm^{-1}; ^1H NMR ($CDCL_3$) δ 1.11 (d, 18 H) , 1.41 (m, 3 H), 6.08 (m, 1 H), 6.49 (m, 2 H); ^{19}F NMR ($CDCL_3$) δ -165.4 (s); HRMS calcd for $C_{13}H_{24}FNSi$ (MH^+) 242.1740, found 242.1740.

2-(4-Chlorophenyl)-1-(ethoxymethyl)-4-fluoro-5-(trifluoromethyl)pyrrole-3-carbonitrile (4)

To a stirred solution of **1**[2] (2.0 g, 4.9 mmol) in 30 mL of THF at -78°C under N_2 was added *t*-BuLi (6.07 mL, 1.7 M in pentane, 10.30 mmol). After 0.5 h at -78°C, **5**[11] (2.01 g, 6.4 mmol) in 10 mL of THF was added in one portion. The reaction was stirred an additional 1 h at -78°C, then the cooling bath was removed and the reaction allowed to stir at room temperature. After 3 h at RT, the reaction was treated with dilute HCl and extracted into EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. ^1H NMR analysis of the residue showed a 4:6 ratio of **11** to **4**. Flash chromatography on silica gel (elution with 1:20 EtOAc-hexanes) yielded 0.53g (33%) of **11**[13] and 0.53 g (31%) of **4** as a white solid: mp 96-98°C (MeOH); IR (nujol mull) 2220, 1610, 1350, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.97 (t, 3 H), 3.24 (q, 2 H), 5.23 (s, 2 H), 7.67 (dd, 4 H); ^{19}F NMR (DMSO-d_6) δ -149.83 (s, F), -55.85 (s, CF_3); HRMS calcd for $C_{15}H_{12}ClF_4N_2O$ (MH^+) 347.0574, found

347.0568. Anal. Calcd for $C_{15}H_{11}ClF_4N_2O$: C, 51.96; H, 3.20; N, 8.08. Found: C, 51.66; H, 2.80; N, 7.90.

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7. Treatment of **7** with methyl iodide affords 3-methyl-1-(triisopropyl silyl)pyrrole in greater than 90% yield as described in reference 6.

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9. Generation of **10** could be achieved by treatment of **1** with *n*-BuLi (1.2 eq) or *t*-BuLi (2.1 eq). However with *n*-BuLi, a small amount of butylated material derived from the reaction of **10** with *n*-BuBr was detected.

10. Meek, J.; Stockton, G. U.S. Patent 4 686 365, 1987.

11. N-fluorobenzenesulfonimide was provided by Allied-Signal Inc.

12. Identical to 1-(triisopropylsilyl)pyrrole, described in reference 6.

13. Identical to 2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoro methyl)pyrrole-3-carbonitrile, described in reference 2b.

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