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Preparation of Pentafluorosulfanyl (SF_5) Pyrrole Carboxylic Acid Esters

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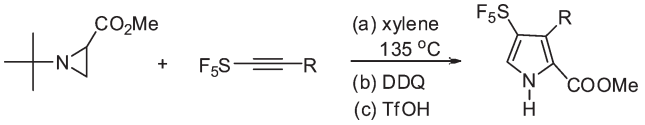

Pyrrole derivatives bearing a pentafluorosulfanyl group are currently unknown. In this paper, a facile preparation of SF_5-substituted pyrrole carboxylic acid esters in good yield is reported. Utilizing the cycloaddition of an azomethine ylide to pentafluorosulfanylalkynes, a series of dihydropyrroles were prepared and oxidized to the respective 1-*tert*-butyl-4-(pentafluorosulfanyl)pyrrole-2-carboxylic acid esters in good yield. Further treatment of these pyrroles with catalytic triflic acid allowed removal of the *tert*-butyl group.

Because of the acknowledged effect of fluorine on the physical and chemical properties of organic compounds[1,2] and in particular its potential influence on the biological activity of pharmaceutical and agrochemical compounds,[3−5] the pentafluorosulfanyl (SF_5) group has increasingly attracted interest as a novel fluorine-containing substituent. The "discovery" of this substituent by organic, agrochemical, and pharmaceutical chemists has led to a number of recent papers and patents that have confirmed the idea that the SF_5 substituent might indeed provide unique advantages in terms of biological activity.[6−8] According to a SciFinder search, whereas in the eight years prior to 2005 there was an average of only 5−6 patents per year related to biologically active SF_5-containing compounds, since 2005, there has been an average of 25 such patents submitted per year.[9] Research in this area has, however, generally been hampered by a lack of availability of key SF_5-containing building blocks. Recently, the commercial availability of SF_5-benzene derivatives has facilitated exploratory work with these compounds,[10] with the result that most of the encouraging studies mentioned above were carried out using SF_5-aromatics as the building blocks.

Heterocycles are very important potential components of pharmaceuticals However, to our knowledge few heterocycles bearing an SF_5-group are known: furans,[11] pyrazoles,[12] and triazoles.[12] There do not appear to be any mention in the journal literature of ring-substituted SF_5-thiophenes, pyrroles, or pyridines, although there is mention in a patent application of a preparation of SF_5-pyridines[13] and in a patent of SF_5-thienylthiophenes.[14]

The search for synthetic pathways to additional classes of SF_5-heterocycles has therefore become an ongoing goal of our research program. At this time, we would like to report the first general method for preparation of SF_5-substituted pyrrole derivatives, namely 4-(pentafluorosulfanyl)pyrrole-2-carboxylic acids. Most of the well-known methods for preparing pyrroles,[15] such as the Paal−Knorr synthesis, the Knorr synthesis, the Hantzsch synthesis, the van Leusen synthesis, etc., all involve ring formation via condensation reactions via carbanionic intermediates. All such methods have thus far failed when using SF_5-substituted substrates, probably because of the instability of anionic intermediates bearing an α- or β-SF_5 group. For example, in an attempt to utilize a van Leusen approach to prepare SF_5-pyrroles, the reaction of TosMIC with SF_5-substituted α,β-unsaturated ester **1** led only to a fluorine-free product, presumably pyrrole **2**, formed by preferential elimination of SF_5^- rather than loss of Tos^-, which is the usual final, pyrrole-forming step of a van Leusen synthesis (Scheme 1).

There is also no *electrophilic* source of SF_5 (i.e., an SF_5^+ reagent), so one cannot prepare SF_5-pyrroles directly from pyrroles by electrophilic substitution.

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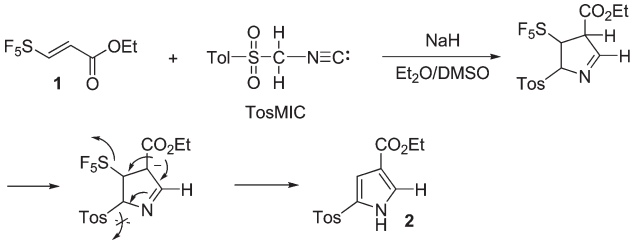
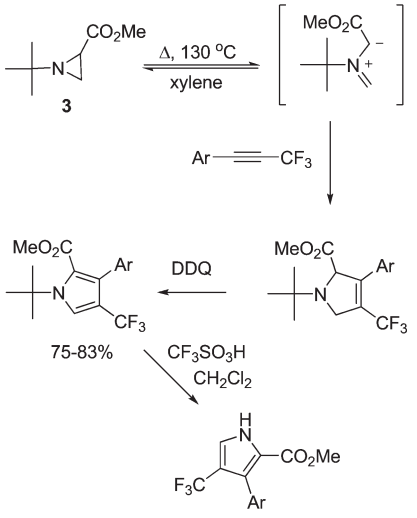
SCHEME 1. Attempted van Leusen Synthesis of SF_5-Pyrroles



SCHEME 2. Azomethine Methodology for Synthesis of Pyrroles



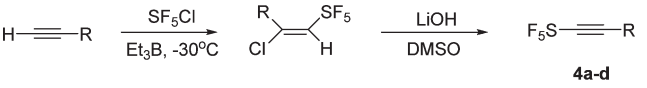
Thus far there has been but one ring-forming approach that has been demonstrated to tolerate SF_5 on the building block, and that is cycloaddition chemistry.[16] Diels−Alder reactions of both SF_5-alkenes[17−19] and SF_5-alkynes,[11] have been reported, as have 1,3-dipolar cycloadditions of the alkynes.[12,18] A Diels−Alder approach was used in our preparation of SF_5-furans.[11]

The 1,3-dipolar cycloaddition of azomethine ylides to SF_5-alkynes, followed by oxidation of the intermediate pyrrolines, appeared to be a reasonable approach to the synthesis of SF_5-pyrroles, such a method having been successfully implemented by La Porta and co-workers in their preparation of (trifluoromethyl)pyrroles from trifluoromethyl alkynes (Scheme 2).[20]

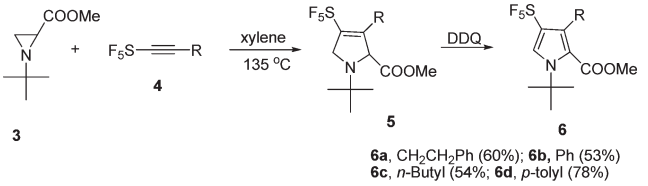
One advantage of this specific aziridine precursor is the ability to readily remove the *tert*-butyl group from the pyrrole nitrogen.

The required analogous pentafluorosulfanyl alkynes, **4**, were readily available by the addition of SF_5Cl to terminal

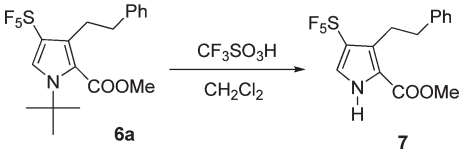
SCHEME 3. Preparation of SF_5-Alkynes



SCHEME 4. Preparation of SF_5-Pyrroles



SCHEME 5. Removal of *tert*-Butyl Group



alkynes, followed by base-catalyzed elimination of HCl (Scheme 3),[21−23] and when such alkynes were allowed to react with aziridine ester **3** as depicted in Scheme 4, SF_5-substituted pyrrolines, **5**, were obtained. Although crude pyrroline **5b** was isolated and characterized, and its regiochemistry of cycloaddition determined, generally the pyrrolines were not fully characterized but were simply isolated and immediately subjected to oxidation by DDQ to form the *tert*-butyl pyrroles **6** (53 to 78% yield), which were themselves fully characterized.

To demonstrate the efficacy of the procedure, the *tert*-butyl group of pyrrole **6a** was cleanly removed by treatment with catalytic quantities of triflic acid in methylene chloride to produce pyrrole **7** in a nonoptimized yield of 72% (Scheme 5).

The procedure reported in this paper for the first time makes a wide variety of SF_5-substituted pyrrole building blocks available for potential incorporation into possible bioactive compounds.

Experimental Section

NMR spectra were obtained in $CDCl_3$ using TMS and $CFCl_3$ as the internal standards for $^1H/^{13}C$ NMR and ^{19}F NMR respectively; melting points were uncorrected. Aziridine **3** and SF_5-alkyne starting materials **4b** and **4c** were prepared according to the previous literature.[20,21]

Procedure for Preparation of Alkynes 4a and 4d[21]. Into a flask equipped with a dry ice reflux condenser were added at −40 °C 20 mL of anhydrous hexane, alkyne (3−4 mmol), and SF_5Cl (1.2 equiv). The solution was stirred at this temperature for 10 min, and Et_3B (0.1 equiv, 1 M in hexane) was added slowly using a syringe. The solution was stirred for 1 h at −30 °C, and then warmed to rt. The mixture was quenched with aqueous $NaHCO_3$, and the organic phase was dried with $MgSO_4$. After removing the solvent, 20 mL of DMSO was added to the residue along with 5 equiv of LiOH. The solution was stirred at rt for 2 h, after which the mixture was poured into ice water and neutralized with 2 M HCl. The product was extracted with ether twice, dried with $MgSO_4$, and finally purified by column chromatography.

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Data for 4a (43%). ^{1}H NMR: δ 2.55−2.62 (m, 2H), 2.85−2.90 (t, J = 10 Hz, 2H), 7.18−7.33 (m, 5H). ^{13}C NMR: δ 20.4, 33.5, 127.0, 128.5, 128.8, 139.2. ^{19}F NMR: δ +77.4(m, 1F), +82.6 (d, J = 160 Hz, 4F).

Data for 4d (45%). ^{1}H NMR: δ 2.40 (s, 3H), 7.20−7.22 (d, J = 7.8 Hz, 2H), 7.44−7.47 (d, J = 7.8 Hz, 2H). ^{13}C NMR: δ 21.9, 129.7, 132.7, 142.1. ^{19}F NMR: δ +77.3 (p, J = 162 Hz, 1F), +83.05 (d, J = 177 Hz, 4F).

Procedure for Preparation of Pyrroles 6a−d. A mixture of **3** (2.05 mmol, 3 equiv), **4** (0.68 mmol, 1 equiv), and 2.5 mL of xylene was heated at about 130−140 °C for 24 h (monitored by NMR). Product **5** was separated from excess **3** by flash chromatography, and then 5 mL of CCl_4 and 310 mg of DDQ were added to the crude **5** at rt, and the mixture was stirred for 3 h (monitored by TLC). The solvent was then removed by distillation, and the residue submitted to column chromatography to obtain **6** as a white solid.

Although the intermediate dihydropyrroles were not generally isolated but were directly converted to the respective pyrroles by treatment with DDQ, the structure of one dihydropyrrole intermediate, **5b**, was demonstrated unambiguously by NMR analysis prior to its oxidative conversion to pyrrole **6b**.

Methyl 1-*tert*-Butyl-4-pentafluorosulfanyl-3-phenyl-2,5-dihydro-2*H*-pyrrole-2-carboxylate, 5b. ^{1}H NMR: δ 1.12 (s, 9H), 3.48 (s, 3H), 4.18 (dd, J = 14.1, 5.1 Hz, 1H), 4.35 (dd, J = 14.1. 6.6 Hz, 1H), 4.70 (m, 1H), 7.10 (m, 2H), 7.34 (m, 3H). ^{13}C NMR: δ 25.0, 51.2, 53.4, 54.6 (C-5), 72.6 (C-2), 126.4, 127.1, 127.6, 131.1, 139.7 (C-3), 147.4 (SF_5−C), 171.4 (C=O). ^{19}F NMR: δ +67.2 (d, J = 148 Hz, 4F), +76.1 (m, 1F).

Methyl 1-*tert*-Butyl-4-pentafluorosulfanyl-3-(2-phenylethyl) pyrrole-2-carboxylate, 6a. (60%) mp 115−117 °C. ^{1}H NMR: δ 1.67 (s, 9H), 2.77−2.83 (dd, J = 6.6 and 4.5 Hz, 2H), 2.96−3.02 (dd, J = 6.6 and 4.5 Hz, 2H), 3.91 (s, 3H), 7.21−7.34 (m, 6H). ^{13}C NMR: δ 28.8, 30.7, 37.9, 52.2, 60.0, 121.4 (m), 123.1 (m), 126.2, 127.1 (m), 128.5, 128.6, 135.0 (m), 142.2, 163.6. ^{19}F NMR: δ +88.7 (m, 1F), +74.3 (d, J = 150 Hz, 4F). HRMS: calcd for $C_{18}H_{22}F_5NO_2S$, 411.1291; found, 411.1277. Anal. Calcd for $C_{18}H_{22}F_5NO_2S$: C, 52.55; H, 5.39; N, 3.40. Found: C, 52.73; H, 5.42; N, 3.28.

Methyl 1-*tert*-Butyl-4-pentafluorosulfanyl-3-phenylpyrrole-2-carboxylate, 6b. (53%) mp 108−110 °C. ^{1}H NMR: δ 1.66 (s, 9H), 3.34 (s, 3H), 7.18−7.31 (m, 6H). ^{13}C NMR: δ 30.7, 52.0, 59.8, 121.7 (m), 122.7 (m), 126.9 (m), 127.4, 127.4, 130.1, 134.3, 135.2 (m), 163.9. ^{19}F NMR: δ +87.4 (m, 1F), +75.4 (d, J = 153 Hz, 4F). HRMS: calcd for $C_{16}H_{18}F_5NO_2S$, 383.0978; found, 383.0973. Anal. Calcd for $C_{16}H_{18}F_5NO_2S$: C, 50.13; H, 4.73; N, 3.65. Found: C, 50.42; H, 4.61; N, 3.36.

Methyl 1-*tert*-Butyl-4-pentafluorosulfanyl-3-butylpyrrole-2-carboxylate, 6c. (54%) mp 41−44 °C. ^{1}H NMR: δ 0.88−0.93 (t, J = 14.4 Hz, 3H), 1.13−1.50 (m, 4H), 1.64 (s, 9H), 2.63−2.69 (t, J = 15.9 Hz, 2H), 3.86 (s, 3H), 7.26(s, 1H). ^{13}C NMR: δ 14.0, 23.3, 25.9, 30.8, 33.8, 52.1, 59.7, 121.1 (m), 122.7 (m), 128.1 (m), 134.9 (m), 163.7. ^{19}F NMR: δ +88.8 (m, 1F), +74.3 (d, J = 155 Hz, 4F). HRMS: calcd for $C_{14}H_{22}F_5NO_2S$, 363.1291; found, 363.1316. Anal. calcd for $C_{14}H_{22}F_5NO_2S$: C, 46.27; H, 6.10; N, 3.85. Found: C, 46.39; H, 6.40; N, 3.93.

Methyl 1-*tert*-Butyl-4-pentafluorosulfanyl-3-p-tolylpyrrole-2-carboxylate, 6d. (78%) mp 114−116 °C. ^{1}H NMR: δ 1.68 (s, 9H), 2.36 (s, 3H), 3.41(s, 3H), 7.12 (s, 4H), 7.33 (s, 1H). ^{13}C NMR: δ 21.4, 30.7, 52.1, 59.7, 121.5 (m), 122.7 (m), 126.8 (m), 128.2, 130.0, 131.1, 135.3 (m), 137.0, 164.1. ^{19}F NMR: δ +87.6 (p, J = 152 Hz, 1F), +75.4 (d, J = 152 Hz, 4H). HRMS: calcd for $C_{17}H_{20}F_5NO_2S$, 397.1135; found, 397.1120. Anal. calcd for $C_{17}H_{20}F_5NO_2S$: C, 51.38; H, 5.07; N, 3.52. Found: C, 51.40; H, 5.25; N, 3.30.

Procedure for Removal of *tert*-Butyl Group. Methyl 4-Pentafluorosulfanyl-3-(2-phenylethyl)pyrrole-2-carboxylate, 7. Two drops of CF_3SO_3H was added to a flask containing 80 mg of **6a** and 2 mL of CH_2Cl_2 at rt, and the mixture was stirred for about 2 h (monitored by TLC). The mixture was purified directly by column chromatograph to obtain **7** as a white solid (78%): mp 165−167 °C. ^{1}H NMR: δ 2.78−2.84 (dd, J = 8.1 and 4.2 Hz, 2H), 3.16−3.22 (dd, J = 8.1 and 4.2 Hz, 2H), 3.92 (s, 3H), 7.19−7.34 (m, 6H), 9.34 (s, 1H). ^{13}C NMR: δ 28.4, 37.5, 52.1, 118.8 (m), 122.0 (m), 126.2, 128.0 (m), 128.6, 128.6, 138.5 (m), 142.1, 161.3. ^{19}F NMR: δ +88.9 (p, J = 148 Hz, 1H), +73.6 (d, J = 148 Hz, 4H). HRMS: calcd for $C_{14}H_{14}F_5NO_2S$, 355.0665; found, 355.0648. Anal. calcd for $C_{14}H_{14}F_5NO_2S$: C, 47.32; H, 3.97; N, 3.94. Found: C, 47.04; H, 3.68; N, 3.86.

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Supporting Information Available: ^{1}H, ^{13}C and ^{19}F NMR spectra of compounds **4a** and **d**, **5b**, **6a**−**d** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.