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Synthesis of Novel Pentafluorosulfanylfurans. Two Retro-Diels–Alder Approaches

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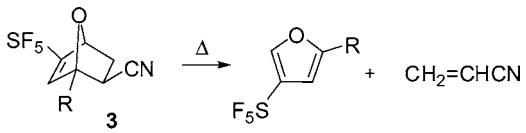
ABSTRACT



The first examples of furan substituted with an SF_5 group are reported. 3-Pentafluorosulfanylfurans were prepared from their respective 2-pentafluorosulfanyl-5-cyano-7-oxabicyclo[2.2.1]hept-2-ene precursors via retro-Diels–Alder reactions. Also, a tandem cycloaddition/retrocycloaddition reaction between 4-phenyloxazole and 1-pentafluorosulfanylhex-1-yne was used to prepare 3-pentafluorosulfanyl-4-butylfuran.

Because of the ever increasing importance of fluorine-containing pharmaceutical and agrochemical products,[1−5] the emergence of a "new" fluorinated substituent attracts special interest because of its potential impact upon the preparation of new biologically active molecules. Although pentafluorosulfanyl-, SF_5-containing compounds have been around for a long time, the SF_5 group appears to have been "newly discovered" by organic chemists, probably because it is only recently that synthetic methodology has been developed to allow reasonably easy preparation of aliphatic and aromatic SF_5 compounds.[6−9] Compounds must be available and their chemistry understood for interest in their commercial potential to grow. This is now happening.

Synthetic methodology in this field has probably been slow to develop because the chemistry of the two most useful sources of the pentafluorosulfanyl group (that is, SF_5Cl and SF_5Br) is limited to free radical chemistry. Recently, new and useful procedures for the preparation of aliphatic and aromatic SF_5 compounds have appeared,[6−10] and this has stimulated commercial interest in compounds containing the SF_5 substituent.[3,11,12]

Heterocyclic compounds containing the SF_5 substituent are a class of compounds that would demand considerable interest with regard to potential biological activity. However, to our knowledge, the only SF_5 heterocyclic compounds that have thus far been reported are the pyrazoles formed by addition of diazomethane to SF_5 acetylene.[13] In this short communication, we wish to report the use of two different retro-Diels−Alder strategies to prepare the first SF_5-substituted furans.

Recognizing the synthetic limitations imposed by the restriction to free radical addition chemistry, we sought an unsaturated precursor that could undergo addition of SF_5Cl

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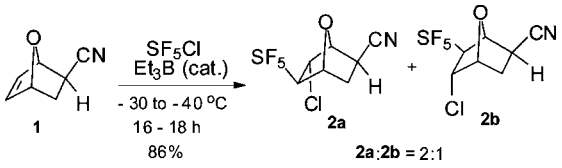
with the adduct being readily converted to an SF_5 furan. Also recognized was the potential exploitation of the known reversibility of furan Diels−Alder reactions in designing a successful synthetic strategy.

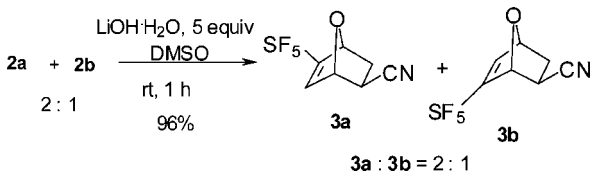
Thus, a procedure was developed that involved addition of SF_5Cl to an appropriate furan Diels−Alder adduct as the first step in a three-step sequence outlined in the series of schemes below, the process culminating in the retro Diels−Alder reaction shown in the third scheme.

After considerable effort to find the most suitable furan adduct for this purpose, the furan-acrylonitrile *exo*-adduct (**1**) was identified as the best overall choice, as it is the only one that provided acceptably good yields for all three steps of the synthesis.[14−16] Using our usual low-temperature Et_3B-initiated free radical chain procedure, SF_5Cl underwent addition to the *exo*-adduct (**1**)[17] to give two regioisomeric adducts in excellent yield. Other furan adducts that were examined included those of ethyl acrylate, ethyl methacrylate, dimethyl maleate, dimethyl fumarate, maleic anhydride, *N*-phenyl maleimide, and dimethyl acetylene-dicarboxylate, of which only the adducts of ethyl acrylate (90%) and dimethyl maleate (∼quantitative) gave yields of greater than 60% for the addition. Unfortunately, unlike the acrylonitrile adduct, neither of these latter two adducts gave acceptable results in the subsequent elimination reaction.

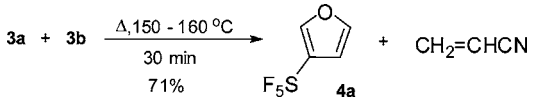


Determining conditions for clean elimination of HCl from these adducts proved challenging because of competitive H−SF_5 elimination from SF_5Cl adducts such as **2a** and **2b** and because of the sensitivity of the products **3a** and **3b** to the basic reaction conditions. Typical elimination conditions using EtO^-/EtOH or HO^-/EtOH which have proved satisfactory for conversion of $RCHClCH_2SF_5$ to $RCH{=}CHSF_5$ proved too harsh. Amine bases, such as Et_3N or DBU, were also unsatisfactory. In the end, it was found that conditions involving use of alkali metal hydroxides in DMSO at room temperature were most effective, with $LiOH{\cdot}H_2O$ providing the fastest and cleanest conversions. Thus, when the mixture of **2a** and **2b** was subjected to this optimized procedure, the isomeric pair of alkenes, **3a** and **3b**, was formed in excellent yield. These isomeric alkenes could be separated by silica gel chromatography and individually characterized.

Finally, when a mixture of **3a** and **3b** was heated for 30 min at 150−160 °C, the expected retro-Diels−Alder reaction led to formation of 3-pentafluorosulfanylfuran in 71% yield



(overall yield = 59% from the initial Diels−Alder adduct). All new products were fully characterized.[18]



This sequence could be repeated starting from 2-methylfuran to prepare 2-methyl-4-pentafluorosulfanylfuran (**4b**) in an overall yield of 67% from the initial Diels−Alder adduct.[19] In this case, the addition step proceeded in 90% yield to give largely (4:1) the 6-cyano regioisomer, with the elimination also proceeding cleanly to give a 95% yield (see Supporting Information).

An alternative synthetic approach utilized the tandem Diels−Alder/retro-Diels−Alder reaction sequence that occurs when one heats an SF_5 acetylene compound with 4-phenyloxazole. The use of 4-phenyloxazole to synthesize furans via such a tandem sequence is well-known,[20−24] and SF_5 acetylene has been shown to be reactive as a dienophile/dipolarophile.[13]

Indeed, in practice, the reaction of 1-pentafluorosulfanylhex-1-yne[10] (**5**) with 4-phenyloxazole provided an excellent

(14) Acrylonitrile-furan *exo*-adduct (**1**) was prepared in 25% yield (along with 25% of the *endo*-adduct) via a modification of previous methods.[15,16]

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(17) In general, the *exo*-adducts gave higher yields than the *endo*-adducts in the free radical chain addition reaction with SF_5Cl. The *exo*- and *endo*-adducts could be readily separated by silica gel chromatography

(18) **2a**: ^{1}H NMR, δ 2.10−2.38 (m, 2H, −CH2−), 3.53 (dd, J = 8.7, 5.1 Hz, 1H, −CH(CN)), 3.74−3.90 (m, 1H, −CH(SF_5)), 4.76 (dd, J = 5.1 Hz, 1H, −CHCl), 4.96 (d, J = 5.3 Hz, 1H, bridgehead−CH), 5.27 (d, J = 5.3 Hz, 1H, bridgehead−CH); ^{19}F NMR, δ +58.9 (d, J = 152 Hz, 4F), +81.5 (pent, J = 152 Hz, 1F). **2b**: ^{1}H NMR, δ 2.10−2.38 (m, 1H), 2.77 (dd, J = 13.5, 9.0 Hz, 1H), 2.91 (dd, J = 9.0, 3.9 Hz, 1H, CHCN), 3.74−3.90 (m, 1H, $CHSF_5$), 4.72 (t, J = 5.1 Hz, 1H, CHCl), 4.87 (t, J = 5.3 Hz, 1H, bridgehead−CH), 5.32 (s, 1H, bridgehead−CH); ^{19}F NMR, δ +59.6 (d, J = 153 Hz, 4F), 81.3 (pent, J = 153 Hz, 1F). Anal. (mixture of **2a** and **2b**) calcd for $C_7H_7F_5ClNOS$: C, 29.64; H, 2.49; N, 4.94. Found: C, 29.95; H, 2.29; N, 4.71. **3a**: ^{1}H NMR, δ 2.11 (dd, J = 12.0, 8.4 Hz, 1H, $-CH_2-$), 2.29 (dt, J = 12.0, 4.0 Hz, 1H, $-CH_2-$), 2.67 (dd, J = 8.4, 4.0 Hz, 1H, −CH(CN)), 5.36 (s, 1H, bridgehead−CH−), 5.37 (d, J = 4.0 Hz, 1H, bridgehead−CH−), 6.74 (s, 1H, $-CH{=}C(SF_5)-$); ^{19}F NMR, δ +65.9 (d, J = 161 Hz, 4F), +80.2 (pent, J = 161 Hz, 1F); ^{13}C NMR, δ 27.6, 31.5, 79.1, 81.9, 120.5, 135.0, 161.2. Anal. Calcd for $C_7H_6F_5NOS$: C, 34.01; H, 2.45; N, 5.67. Found: C, 33.93; H, 2.26; N, 5.36. **3b**: ^{1}H NMR, δ 1.99 (dd, J = 12.0, 8.7 Hz, 1H, $-CH_2-$), 2.26−2.40 (m, 1H, $-CH_2-$), 2.78 (dd, J = 8.7, 3.9 Hz, 1H, −CH(CN)−), 5.32 (bs, 1H, bridge−CH−), 5.44 (s, 1H, bridge−CH−), 6.87 (s, 1H, $-CH{=}C(SF_5)-$); ^{19}F NMR, δ +66.2 (d, J = 161 Hz, 4F), +80.2 (pent, J = 161 Hz, 1F); ^{13}C NMR, δ 28.2, 31.1, 79.0, 81.8, 120.5, 139.0, 157.8. Anal. Calcd for $C_7H_6F_5NOS$: C, 34.01; H, 2.45; N, 5.67. Found: C, 34.03; H, 2.23; N, 5.44. **4a**: ^{1}H NMR, δ 6.67 (m, 1H), 7.42 (s, 1H), 7.84 (s, 1H); ^{19}F NMR, δ +70.4 (d, J = 165 Hz, 4F), +82.4 (pent, J = 165 Hz, 1F); HRMS, calcd For $C_4H_3F_5OS$, $[M]^+$ = 193.9841; found, 193.9850.

(19) **4b**: ^{1}H NMR, δ 2.29 (s, 3H), 6.25 (m, 1H), 7.65 (s, 1H); ^{19}F NMR, δ +69.9 (d, J = 163 Hz, 4F), +83.1 (pent, J = 163 Hz, 1F). Anal. Calcd for $C_5H_5F_5OS$: C, 28.85; H, 2.42. Found: C, 29.00; H, 2.19.

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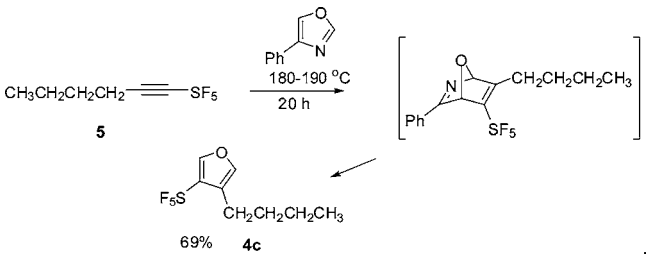

direct process for the synthesis of 3-pentafluorosulfanyl-4-butylfuran (**4c**).[25,26]

Thus, working within the confines of the requisite free radical chemistry exhibited by SF_5Cl and working around the steric and electronic mechanism-related challenges posed by SF_5 substituents, it was possible to devise two successful approaches to the synthesis of furans substituted with SF_5 at the 3-position. It is believed that both of these synthetic strategies will prove to have some generality and that they should therefore be suitable for the synthesis of a variety of multisubstituted SF_5-bearing furans. Work continues on this and related synthetic strategies for other SF_5-substituted heterocycles.

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Supporting Information Available: General experimental information; full experimental procedures and characterization data for the preparation of **4a**−**4c**; and NMR spectra of furans **4a** and **c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Not having been isolated or observed indirectly, the regiochemistry of the intermediate Diels−Alder adduct cannot be known.

(26) **4c**: ^{1}H NMR, δ 0.95 (t, J = 7.3 Hz, 3H), 1.46 (m, 2H), 1.50−1.64 (m, 2H), 2.53 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 0.9 Hz, 1H), 7.79 (s, 1H); ^{19}F NMR, δ +73.4 (d, J = 161 Hz, 4F), +84.2 (pent, J = 161 Hz, 1F); HRMS, Calcd for $C_8H_{11}F_5OS$ $[M + 1]^+$ = 231.0533, found 231.0541.