Synthesis of new CF_3-containing 3,4-dihydro-2*H*-pyrans

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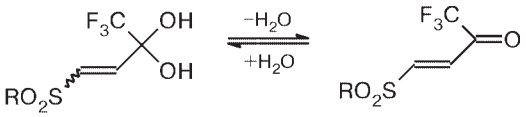
The reactions of vinyl sulfides with β-sulfonylvinyl trifluoromethyl ketones afforded CF_3-containing 3,4-dihydro-2*H*-pyrans. An attempt to synthesize 1,1,1-trifluoro-3-(methylthio)but-3-en-2-one resulted in its dimerization into a CF_3-containing 3,4-dihydro-2*H*-pyran.

Key words: trifluoromethyl ketone, vinyl sulfides, 3,4-dihydro-2*H*-pyrans, the hetero-Diels—Alder reaction.

The hetero-Diels—Alder reaction is a well known method of preparing dihydro-2*H*-pyrans.[1] However, the syntheses of their fluorine-containing derivatives have been described only in a few papers,[2—4] though these compounds possess considerable synthetic potential[5,6] and are of interest as biologically active substances.[7]

The present paper is devoted to the study of reactions of easily accessible and stable sulfones **1a**,**b** with vinyl sulfides. Earlier, we have investigated the reactions of sulfones **1a**,**b** with various nucleophiles[8] and their Diels—Alder reactions with dienes.[9]

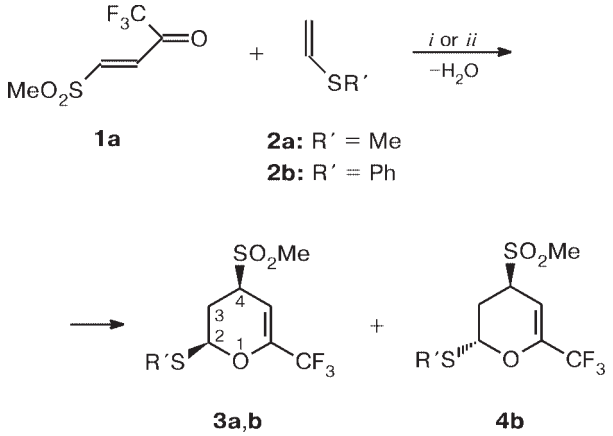
It should be noted that the *gem*-diol and ketone forms of sulfones **1a**,**b** in solutions are in equilibrium; thus we assumed that these compounds can function as heterodienes in the Diels—Alder reaction with inverted electronic demands.



1a: R = Me, *E*
1b: R = Ph, *E*/*Z* 7/2

E

Addition of vinyl sulfides **2a**,**b** to a solution of sulfones **1a**,**b** in methylene chloride at room temperature was accompanied by considerable heat evolution. In the case of less sterically hindered sulfide **2a**, the reaction yielded a mixture of all the four possible stereo- and regioisomeric cycloadducts, while a bulkier phenyl vinyl sulfide **2b** reacts with sulfone **1a** to give a mixture of *cis*- (**3b**) and *trans*-3,4-dihydro-2*H*-pyrans (**4b**); *i.e.*, the reaction is regioselective, but it is not stereoselective. We found that slow addition of vinyl sulfides **2a**,**b** to a solution of sulfone **1a** in methylene chloride at 0 °C affords CF_3-containing 3,4-dihydro-2*H*-pyrans **3a**,**b** as individual regio- and stereoisomers in good yields.



1a

2a: R′ = Me
2b: R′ = Ph

3a,**b**

4b

i. CH_2Cl_2, 25 °C. *ii*. CH_2Cl_2, 0 °C.

The expected products of the reactions of sulfone **1b** with vinyl sulfides **2a**,**b** were detected only using chromatography; apparently, the phenylsulfonyl group is easily split off from the resulting cycloadducts to cause them to polymerize. No target products were obtained in the reactions with vinyl ethers, which is probably associated with their high capability for polymerization.

To study the spatial structures of pyrans **3** and **4**, we performed quantum-mechanical calculations of the conformational behavior of pyrans **3a**,**b** and **4b** using the DFT method (the PBE96 functional,[10] the TAINA program[11]) (Fig. 1).

For *cis*-pyrans **3a**,**b**, a difference between the energies of their most stable conformers is 2.8—2.9 kcal mol^{-1}. Note that, in full agreement with the literature data, in both cases the $(SO_2Me)_{eq}/(SR)_{eq}$ conformers with the equatorial SO_2Me and SR groups were found to be the most stable.[3] Moreover, such a conformation also corresponds to the longest distance between two bulky SR and SO_2Me groups (Fig. 2).

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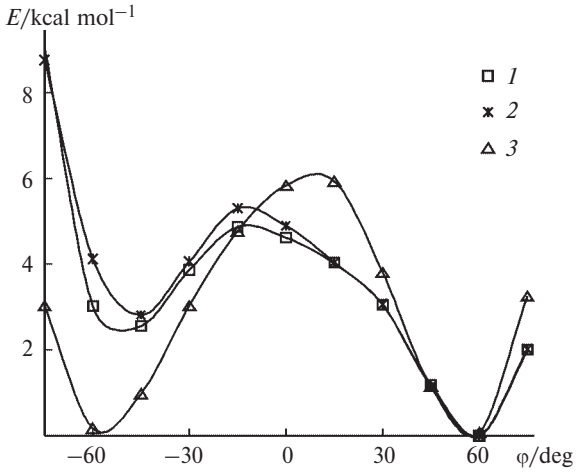
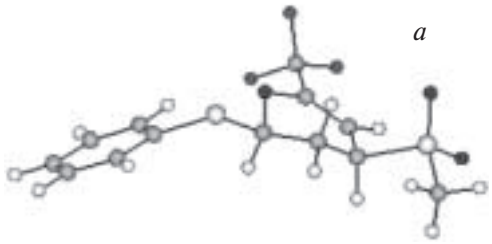
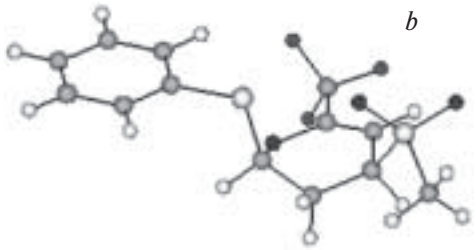


Fig. 1. Diagram of the relative conformation energies (*E*) for pyrans (*1*) **3a**, (*2*) **3b**, and (*3*) **4b**; φ is the O—C(2)—C(3)—C(4) torsion angle.



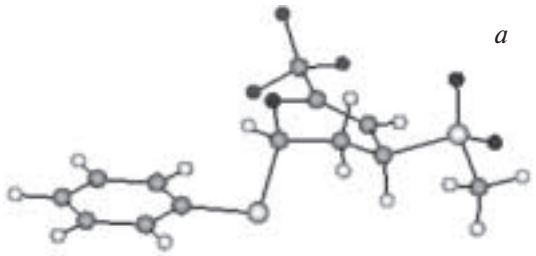
$(SO_2Me)_{eq}/(SPh)_{eq}$-*cis*-**3b**



$(SO_2Me)_{ax}/(SPh)_{ax}$-*cis*-**3b**

Fig. 2. General view of the conformers of *cis*-**3b** containing (*a*) the equatorial and (*b*) axial SO_2Me and SPh groups.

It turned out that both conformers of *trans*-pyran **4b** differ in conformation energy only by 0.1 kcal mol^{-1}, and the transition barrier energy is ~6.5 kcal mol^{-1} (Fig. 3).



$(SO_2Me)_{eq}/(SPh)_{ax}$-*trans*-**4b**

$(SO_2Me)_{ax}/(SPh)_{eq}$-*trans*-**4b**

Fig. 3. General view of the conformers of *trans*-**4b** containing (*a*) the equatorial and (*b*) axial SO_2Me group and (*a*) the axial and (*b*) equatorial SPh group.

Torsion angles between the characteristic hydrogen atoms in conformers **3a**,**b** and **4b** are given in Table 1.

The spatial structures of pyrans **3** and **4** can unambiguously be determined from the ^{1}H NMR data and the torsion angles obtained by quantum-mechanical calculations for the conformers of **3** and **4**. A high-field signal (δ 2.20, ddd) in the spectrum of compound **3b** can be assigned to either the $H_a(3)$ or $H_b(3)$ atom; in both cases, all the three coupling constants are high (J = 13.7, 11.3, and 10.8 Hz). The value 13.7—13.8 Hz corresponds to the geminal coupling between $H_a(3)$ and $H_b(3)$ atoms. The two other constants correspond to a large torsion angle between one of the H(3) atoms and the H(2) and H(4) atoms, which is possible only when the latter are arranged diaxially. A signal at δ 2.2 was unambiguously assigned to the axial $H_a(3)$ atom, the PhS and $MeSO_2$ groups being in equatorial positions. While comparing the chemical shifts of signals for the analogous protons in **3a**, one can assign a similar structure to this compound; in addition, the coupling constants ($J_{H(2),H_a(3)}$ = 11.0 Hz, $J_{H(2),H_b(3)}$ = 2.0 Hz, and $J_{H(4),H_b(3)}$ = 6.9 Hz) correlate

Table 1. Torsion angles (φ/deg) in the most stable conformations of **3a**,**b** and **4b**

Angle	**3a**		**3b**		**4b**	
	$(SO_2Me)_{eq}/(SMe)_{eq}$	$(SO_2Me)_{ax}/(SMe)_{eq}$	$(SO_2Me)_{eq}/(SMe)_{eq}$	$(SO_2Me)_{ax}/(SMe)_{eq}$	$(SO_2Me)_{eq}/(SMe)_{ax}$	$(SO_2Me)_{ax}/(SMe)_{eq}$
H(4)—H(3a)	154	92	154	91	159	42
H(4)—H(3b)	34	26	34	27	39	77
H(2)—H(3a)	179	74	178	73	55	178
H(2)—H(3b)	64	42	63	42	62	61

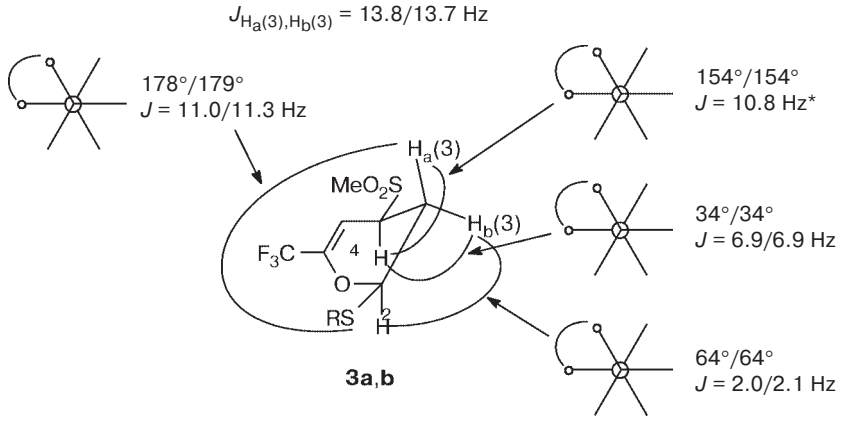


Fig. 4. Torsion angles and spin-spin coupling constants for pyrans **3a**/**3b**.
* For pyran **3b**.

with the analogous constants for compound **3b**. Such a spatial arrangement of the hydrogen atoms, with the torsion angles calculated for the $(SO_2Me)_{eq}/(SR)_{eq}$ conformers of **3a**,**b**, is displayed in Fig. 4.

It should be noted that the results obtained are consistent both with the experimental data reported by other authors and with the empirical Carplus dependences of the coupling constants of the vicinal protons on the torsion angle.[12]

While analyzing the ^{1}H NMR and quantum-mechanical data for compound **4b**, one can not only ascertain that the SPh and SO_2Me groups are *trans*, but even determine which of the conformers is the actual reaction product. First, signals for the hydrogen atoms at the double bond in compounds **3b** and **4b** are characterized by the identical chemical shifts; second, a signal for the H(2) atom in pyran **4b** appears as a doublet (J = 5.9 Hz), and a signal for the H(4) atom as a broadened doublet (J = 12.0 Hz), while the ^{1}H NMR spectrum of compound **3b** shows a complex multiplet for this hydrogen atom. Based on the coupling constants and the torsion angles for conformers of **4b**, one can conclude that the H(2) atom at the phenylthio group occupies an equatorial position, while the H(4) atom at the mesyl group is in an axial position (Fig. 5). Apparently, the $(SO_2Me)_{eq}/(SPh)_{ax}$ conformation is additionally stabilized by an anomeric effect of the heterocyclic oxygen atom on the sulfur atom.[13]

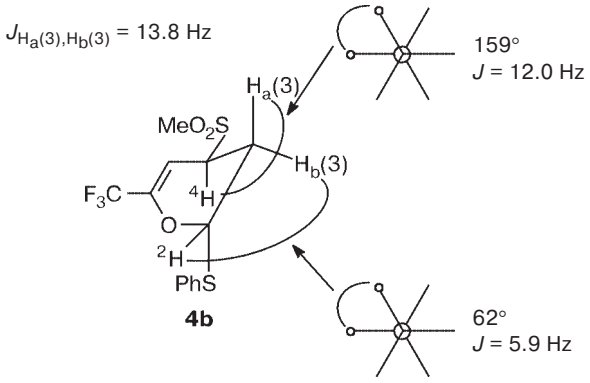
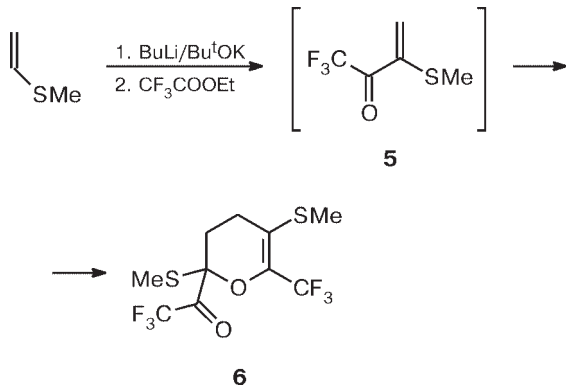


Fig. 5. Torsion angles and spin-spin coupling constants for pyran **4b**.

It is worth noting that the formation of regioisomeric dihydropyrans can completely be excluded since the ^{1}H NMR spectra of compounds **3a**,**b** and **4b** show low-field signals for the H(2) atom at δ 5.1—5.3, which is possible for these structures only when the oxygen and sulfur atoms are both attached to the C(2) atom.

Earlier,[8,9] it has been demonstrated that sulfones **1a**,**b** obtained by the oxidation of the corresponding trifluoromethyl β-RS-vinyl ketones possess high synthetic potential. In connection with this, we attempted to synthesize a new α-(methylthio)vinyl trifluoromethyl ketone (**5**) by the metalation of methyl vinyl sulfide followed by the treatment of the resulting organometallic compound with ethyl trifluoroacetate. However, the expected product **5** completely dimerized during its isolation even at 0 °C within 1 h to give an unknown CF_3CO-containing 3,4-dihydro-2*H*-pyran **6**; a similar phenomenon was noted earlier[14] for nonfluorinated analogs of alkene **5**. Monomeric product **5** was detected only chromatographically.



Hence, the reactions of β-sulfonylvinyl trifluoromethyl ketones **1a**,**b** with vinyl sulfides under mild conditions give new CF_3-containing 3,4-dihydro-2*H*-pyrans in virtually quantitative yields. The compounds obtained are promising starting reagents for the synthesis of biologically active heterocycles. Both aliphatic and aromatic vinyl sulfides can be involved in this reaction. The resulting 1,1,1-trifluoro-3-(methylthio)but-3-en-2-one (**5**) is very unstable and easy to dimerize.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a UR-20 spectrometer (Vaseline oil). TLC was carried out with Silufol UV-254 plates, spots were visualized in an acidified solution of $KMnO_4$ and by the iodine vapor.

Synthesis of 3,4-dihydro-2*H*-pyrans 3a,b (general procedure). The corresponding vinyl sulfide (2 mmol) was added at 0 °C to a solution of sulfone **1a** or **1b** (1 mmol) in 5 mL of methylene chloride. The course of the reaction was monitored by TLC. 3,4-Dihydro-2*H*-pyrans were isolated by column chromatography on silica gel.

***cis*-4-Methylsulfonyl-2-methylthio-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (3a).** Yield 93%, white crystals, m.p. 122—124 °C. IR, ν/cm^{-1}: 1590 (C=C). ^1H NMR ($CDCl_3$), δ: 5.75 (br.s, 1 H, C(5)H); 5.14 (dd, 1 H, C(2)H, J = 11.0 Hz, J = 2.0 Hz); 3.97 (m, 1 H, C(4)H); 2.91 (s, 3 H, SO_2CH_3); 2.68 (br.dd, 1 H, C(3)H, J = 13.8 Hz, J = 6.9 Hz); 2.40 (s, 3 H, SCH_3); 2.39 (m, 1 H, C(3)H). ^{13}C NMR ($CDCl_3$), δ: 147.4 (q, C(6), J = 35.5 Hz); 118.2 (q, CF_3, J = 275.4 Hz); 95.8 (q, C(5), J = 4.3 Hz); 82.0, 57.1, 36.8, 28.2, 13.1. Found (%): C, 34.65; H, 3.93. $C_8H_{11}F_3O_3S_2$. Calculated (%): C, 34.78; H, 4.01.

***cis*-4-Methylsulfonyl-2-phenylthio-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (3b).** Yield 90%, white crystals, m.p. 114—115 °C. IR, ν/cm^{-1}: 1592 (C=C). ^1H NMR ($CDCl_3$), δ: 7.55 (m, 2 H, Ph); 7.43 (m, 3 H, Ph); 5.71 (br.s, 1 H, C(5)H); 5.28 (dd, 1 H, C(2)H, J = 11.3 Hz, J = 2.1 Hz); 3.92 (m, 1 H, C(4)H); 3.00 (s, 3 H, SO_2CH_3); 2.73 (br.dd, 1 H, C(3)H, J = 13.7 Hz, J = 6.9 Hz); 2.20 (ddd, 1 H, C(3)H, J = 13.7 Hz, J = 11.3 Hz, J = 10.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 148.0 (q, C(6), J = 35.7 Hz); 130.0, 131.9, 129.2, 128.8; 119.7 (q, CF_3, J = 272.2 Hz); 97.3 (q, C(5), J = 3.8 Hz); 83.6, 56.6, 37.7, 28.4. Found (%): C, 46.04; H, 3.80. $C_{13}H_{13}F_3O_3S_2$. Calculated (%): C, 46.14; H, 3.87.

The reaction of phenyl vinyl sulfide **2b** with sulfone **1a** at ~25 °C gave a mixture of stereoisomers **3b** : **4b** (70 : 30) as an oil in 81% yield. IR, ν/cm^{-1}: 1590 (C=C). Found (%): C, 46.02; H, 3.77. $C_{13}H_{13}F_3O_3S_2$. Calculated (%): C, 46.14; H, 3.87.

***trans*-4-Methylsulfonyl-2-phenylthio-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (4b).** ^1H NMR ($CDCl_3$), δ: 7.50 (m, 2 H, Ph); 7.41 (m, 3 H, Ph); 5.71 (br.s, 1 H, C(5)H); 5.18 (d, 1 H, C(2)H, J = 5.9 Hz); 3.80 (d, 1 H, C(4)H, J = 12.0 Hz); 3.44 (dd, 1 H, C(3)H, J = 13.8 Hz, J = 6.0 Hz); 3.05 (s, 3 H, SO_2CH_3); 2.56 (m, 1 H, CH(3)). ^{13}C NMR ($CDCl_3$), δ: 148.0 (q, C(6), J = 35.7 Hz); 133.0, 131.8, 129.0, 129.0; 120.1 (q, CF_3, J = 273.9 Hz); 97.5 (q, C(5), J = 3.9 Hz); 92.5, 62.6, 38.0, 32.9.

2,5-Bis(methylthio)-2-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (6). A solution of freshly distilled methyl vinyl sulfide (11 mmol) in 10 mL of THF was added at −100 °C to a solution of BuLi/Bu^{t}OK (10 mmol) in THF. The temperature was elevated to −60 °C, and anhydrous LiBr (10 mol) in 5 mL of THF was added. The reaction mixture was stirred at −50 °C for 10 min and cooled to −100 °C. Then freshly distilled ethyl trifluoroacetate (10 mmol) was slowly added dropwise. The temperature was elevated to −60 °C, and the reaction mixture was diluted with 20 mL of ice water and acidified to pH 3 by slowly adding 10% HCl. The product from the aqueous layer was extracted with ether (3×20 mL), and the ethereal extracts were dried with Na_2SO_4. Column chromatography on silica gel gave 3,4-dihydro-2*H*-pyran **6** as a dark red oil in 82% yield. IR, ν/cm^{-1}: 1596 (C=C), 1655 (C=O). ^1H NMR ($CDCl_3$), δ: 2.70 (m, 2 H, CH_2); 2.44 (m, 1 H, CH_2); 2.29 (s, 3 H, CH_3); 2.24 (m, 1 H, CH_2); 2.02 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 180.7 (q, CO, J = 35.1 Hz); 136.8 (q, C(2), J = 36.0 Hz); 118.5 (q, CF_3, J = 278.5 Hz); 117.1 (q, CF_3, J = 275.5 Hz); 85.7, 81.6, 26.8, 23.7, 15.3, 10.8. Found (%): C, 35.17; H, 2.82. $C_{10}H_{10}F_6O_2S_2$. Calculated (%): C, 35.29; H, 2.96.

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