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Oxymethylation of Trifluoromethanesulfonamide with Paraformaldehyde in Ethyl Acetate

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Abstract—Acid-catalyzed reaction of trifluoromethanesulfonamide with paraformaldehyde in ethyl acetate led to the formation of oxymethylated products that did not form in the reaction carried out in sulfuric acid. Following products were obtained: 5-trifluoromethylsulfonyl-1,3-dioxazinane, 3,7-bis-(trifluoromethylsulfonyl)-1,5,3,7-dioxadiazocane, and a complex of trifluoromethanesulfonamide with 2,4,8,10-tetraoxospiro[5,5]undecene, 1:1. The spiroring resulted from the cyclization of pentaerythritol under the action of formaldehyde. The pentaerythritol formed in its turn by oxymethylation of the methyl group of ethyl acetate with paraformaldehyde followed by the reduction of the COOEt group into CH_2OH by the formaldehyde.

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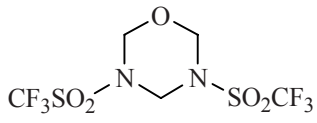
We showed formerly that the reaction of trifluoromethanesulfonamide $CF_3SO_2NH_2$ (**I**) with paraformaldehyde in sulfuric acid led to the formation of linear and cyclic condensation products **II–V** [1].

$CF_3SO_2NHCH_2NHSO_2CF_3$

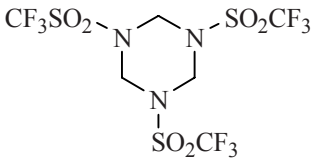
II

$CF_3SO_2N(CH_2NHSO_2CF_3)_2$

III

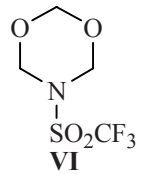


IV

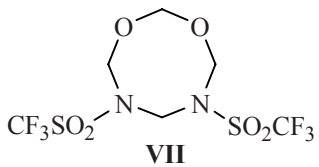


V

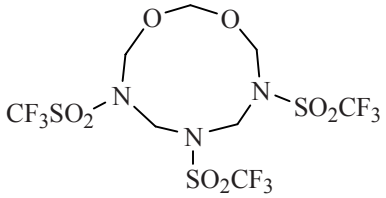
In reaction of compound **II** with paraformaldehyde in a mixture ethyl acetate–sulfuric acid at heating formed according to NMR data cyclic compounds **VI–VIII** whose structure was established from the analysis of ^1H, ^{13}C, and ^{19}F NMR spectra registered from the fractions enriched with the corresponding components by means of column chromatography [1].



VI



VII



VIII

Compound **VI** was assigned the dioxazinane structure based on the presence in its ^1H and ^{13}C spectra of signals indicating NCH_2O (3.7 and 71 ppm) and OCH_2O (4.7 and 95 ppm) groups in the ratio 2:1 [1]. However in the spectra of six-membered rings **IV** and **V** these groups

appeared close to each other and in a far weaker field, ~5.3 ppm [1], and this fact induced us to investigate the structure of the previously obtained compound in more detail.

To this end we studied the reaction of amide **I** with paraformaldehyde in ethyl acetate in the presence of sulfuric acid. It turned out that under mild conditions (20°C, 6 h) just 5-trifluoromethylsulfonyl-1,3-dioxazinane (**VI**) was the main product. This is indicated by the appearance in the ^{1}H NMR spectrum of two singlets at 5.3 and 5.2 ppm in a ratio 2:1, and in the ^{13}C NMR spectrum, of the corresponding signals at 79 and 95 ppm; the obtained values of the chemical shifts were close to the analogous figures for heterocycle **IV**. The ^{1}H NMR spectrum of dioxazinane **VI** is temperature-dependent* in the fashion characteristic of the six-membered heterocycles similarly to that we have previously observed for its close analogs **IV** [2] and **V** [3].

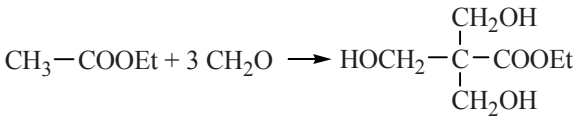
5-Trifluoromethylsulfonyl-1,3-dioxazinane (**VI**) for spectral measurements was isolated by vacuum distillation. According to ^{1}H, ^{13}C, and ^{19}F NMR data it contained an impurity of trifluoromethanesulfonamide, and also of a compound of unestablished structure containing an ethyl and a trifluoromethanesulfonyl groups and a fragment OCN (δ 78.8 ppm).

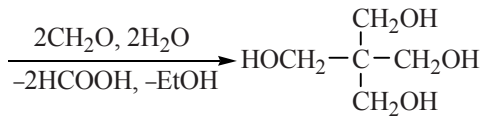
Under more severe conditions (80°C, 3 h) the trifluoromethanesulfonamide formed a complex with 2,4,8,10-tetra-oxospiro[5,5]undecene, 1:1 (**IX**). Complex **IX** was isolated by column chromatography on silica gel. Its structure was confirmed by the presence in the ^{1}H NMR spectrum of signals from NH_2, CCH_2O, and OCH_2O in a ratio 2:4:8, and in the ^{13}C NMR spectrum, of signals corresponding to CF_3, CCO, OCO, and quaternary carbon atom; the final proof of the structure was obtained by X-ray diffraction analysis (see the table).

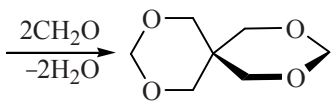
Just the presence in the ^{1}H NMR spectrum of complex **IX** of signals at 3.7 and 4.7 ppm in a ratio 2:1, and in the ^{13}C NMR spectrum the corresponding signals at ~71 and 95 ppm and also of a quartet from CF_3 group, all the signals virtually coinciding with those in the ^{13}C NMR spectrum of dioxazinane **VI**, was the reason of the erroneous conclusion on formation of compound **VI** in [1].

The formation of a spirocyclic complex **IX** was unexpected for neither of the reagents contained a quaternary carbon atom. We suggested that complex **IX** formed through cyclization of pentaerythritol under the action of formaldehyde. The pentaerythritol, in its turn, formed (analogously to its industrial production by reaction of formaldehyde with acetaldehyde) by triple aldol condensation of formaldehyde with the activated methyl group of ethyl acetate followed by reduction of the ester group in the intermediate ethyl 3-hydroxy-2,2-bis(hydroxymethyl)propionate and oxidation of the formaldehyde.

We put to test this assumption by performing a reaction of paraformaldehyde with excess ethyl acetate at gradual addition of concn. H_2SO_4; the reaction mixture was maintained for 24 h at room temperature and then heated for 7 h at 80°C. Intermittently a sampling of the reaction mixture was done, the sample was poured into water, extracted with ethyl acetate, the extract was dried, the solvent was removed, and the residue was analyzed by NMR. The main signals in the ^{1}H NMR spectrum were the peaks of 2,4,8,10-tetraoxospiro[5,5]undecane: singlets at 3.7 and 4.7 ppm in the ratio ~2:1, and in the ^{13}C NMR spectrum, the resonances at ~71 and 95 ppm in the ratio 2:1, and also a signal of a quaternary carbon at 34.4 ppm. As far as we know this is the first example of ester group COOR reduction into alcohol CH_2OH group effected by formaldehyde.



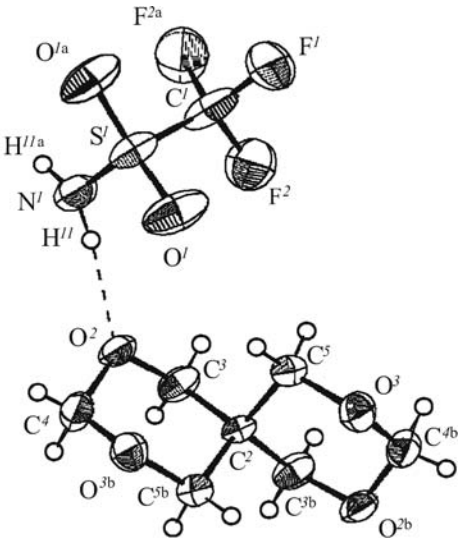




A complex was described in the literature of trifluoromethanesulfonamide with a heterocyclic base, tetrahydro-*N*-(4*H*-1,2,4-triazol-4-yl)-2*H*-pyran-2-imine, also 1:1, with H-bonds betweent the protons of trifluoromethanesulfonamide and atoms N^1 and N^2 of the triazole ring of the heterocycle of the length 1.84–2.13 E [4]. With the less basic analog of this heterocycle, tetrahydro-2*H*-pyran-2-one *N*-methyl-*N*-phenylhydrazone trifluoromethanesulfonamide did not form an adduct [4].

* The comprehensive description of the results of experimental and theoretical conformation study of compound **VI** by means of dynamic NMR and quantum chemistry will be published elsewhere.

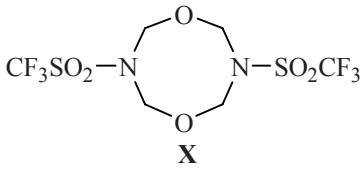
Bond lengths (*l*), bond (φ) and torsion (θ) angles in complex **IX**



IX

Bond	*l*, Å	Bond	*l*, Å
S^1–N^1	1.561(5)	C^2–C^3 (C^2–C^{3b})	1.525(4)
S^1–C^1	1.766(7)	C^2–C^5 (C^2–C^{5b})	1.521(4)
S^1–O^1 (O^{1a})	1.413(3)	O^2–C^3	1.437(4)
F^1–C^1	1.393(9)	O^2–C^4	1.404(4)
F^2–C^1	1.302(5)	O^3–C^{4b}	1.400(5)
N^1–H^{11} (N^1–H^{11a})	1.01(4)	O^3–C^5	1.431(4)
		NH? O	1.94(3)
Angle	φ, deg	Angle	φ, deg
$N^1S^1C^1$	102.5(3)	$C^3O^2C^4$ ($C^{4b}O^3C^5$)	110.3(3)
$N^1S^1O^1$ (O^{1a})	109.99(17)	$C^3C^2C^{3b}$ (C^5)	109.8(3)
$C^1S^1O^1$ (O^{1a})	105.45(18)	$C^3C^2C^{5b}$ ($C^{3b}C^2C^5$)	108.28(19)
$O^1S^1O^{1a}$	121.5(2)	$C^{3b}C^2C^{5b}$	109.78(17)
$S^1N^1H^{11}$ (H^{11a})	126(2)	$O^2C^3C^2$	110.0(3)
$H^{11}NH^{11a}$	97(3)	$O^2C^4O^{3b}$	111.6(3)
$C^5C^2C^{5b}$	110.9(3)	$O^3C^5C^2$	110.7(2)
		N–H? O	150.54
Angle	θ, deg	Angle	θ, deg
$N^1S^1C^1F^1$	180.00	$O^{1a}S^1C^1F^2$ ($O^1S^1C^1F^{2a}$)	179.4(4)
$O^1S^1C^1F^2$	50.9(5)	$C^3C^2C^5O^3$ ($C^{3b}C^2C^3O^2$)	172.4(3)
$N^1S^1C^1F^2$	64.3(4)	$C^{4b}O^3C^5C^2$	57.8(3)
$O^1S^1C^1F^1$	64.87(16)	$C^{3b}C^2C^5O^3$	52.6(3)
$C^4O^2C^3C^2$	58.2(3)	$C^{5b}C^2C^5O^3$	68.0(3)
$C^3O^2C^4O^{3b}$	63.7(4)	$C^{5b}C^2C^3O^2$	52.6(3)
$C^{5b}O^{3b}C^4O^2$	63.3(4)	$C^5C^2C^3O^2$	68.7(3)

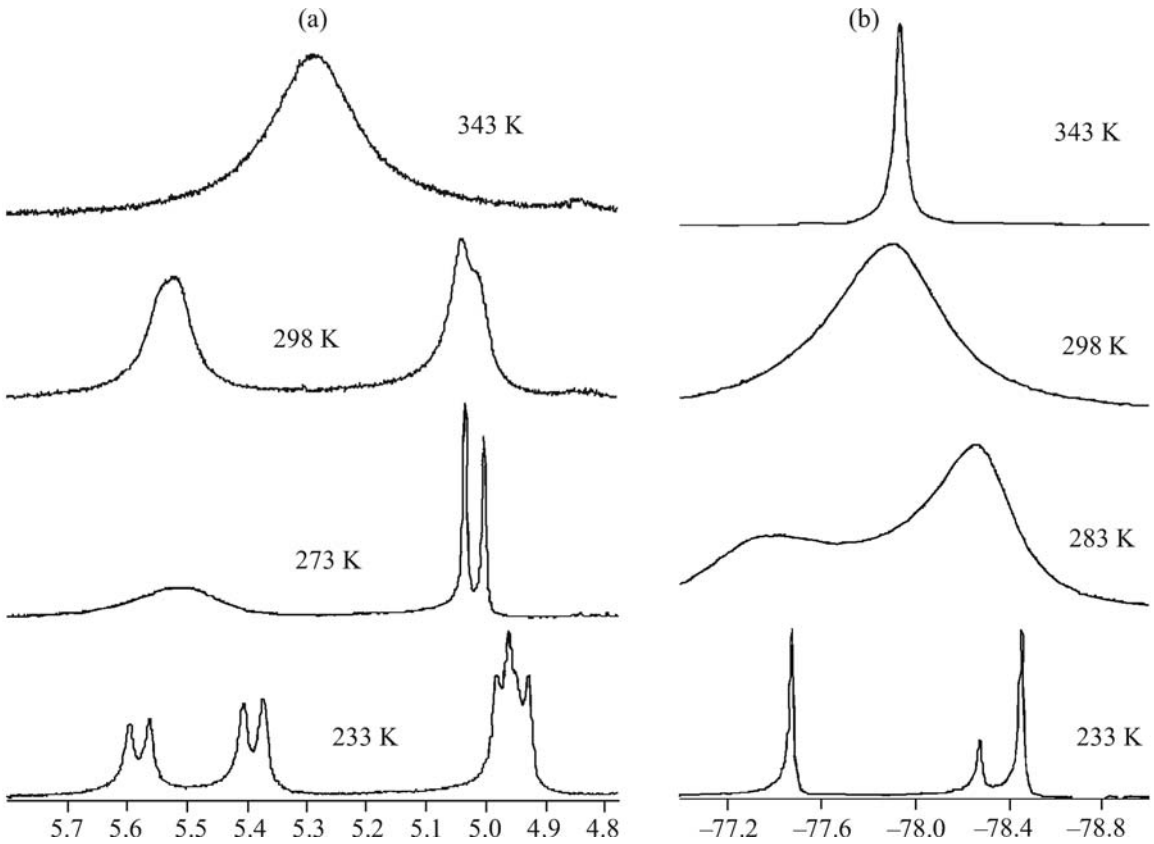
By means of the column chromatography we also separated the isomer of compound **VII**, 3,7-bis(trifluoromethylsulfonyl)-1,5,3,7-dioxadiazocane (**X**).



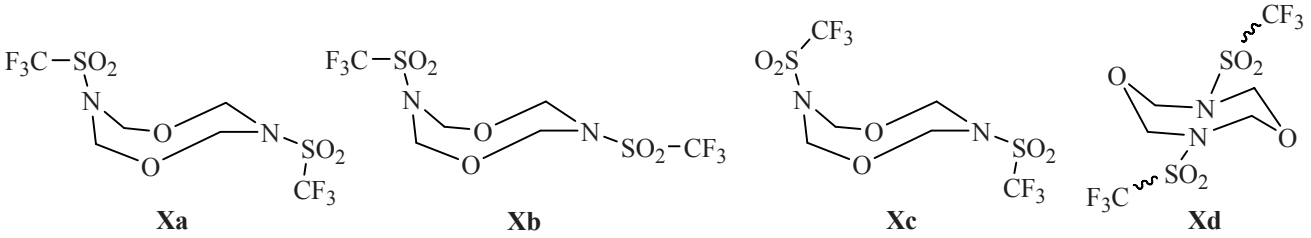
X

Its ^{1}H NMR spectrum at 25°C contains two broadened signals at ~5.0 and 5.5 ppm and a single signal in the ^{13}C NMR spectrum corresponding to both proton peaks at ~84 ppm, in the region characteristics of NCH_2O groups. The temperature dependence of ^{1}H and ^{19}F NMR spectra of compound **X** was investigated (see the figure). ^{19}F NMR spectrum at –40°C indicates the presence of two conformers in a ratio ~6:1,; therewith in the major conformer the trifluoromethyl groups are nonequivalent, whereas in the minor conformer they are equivalent.

A multitude of conformers is presumable for compound **X**, but according to the published data the most stable for the eight-memebered rings are boat-chair conformers [5]. Calculations on the level B3LYP/6-311G(d,p) showed that the lowest minimum on the potential energy surface corresponds to the 3,7-boat-chair conformer **Xa** with nonequivalent CF_3 groups: one exocyclic and one endocyclic. For the six-membered rings **IV** and **V** that we previously have investigated the most stable conformers also possess CF_3 groups of different orientation [2, 3, 6]. Evidently just to this conformer belong two signals in the low-temperature ^{19}F NMR spectrum at –77.5 and –78.5 ppm. Conformer **Xb** is placed by 0.83 kcal mol^{-1} higher on the energy scale, and presumably the minor signal in the ^{19}F NMR spectrum at –78.3 ppm corresponds to two exocyclic CF_3 groups of this conformer. The energy difference between the major and minor conformers estimated from the experimental ratio of signals intensity in the ^{19}F NMR



Temperature dependence of ^{1}H (a) and ^{19}F (b) NMR spectra of 3,7-bis(trifluoro-methylsulfonyl)-1,5,3,7-dioxadiazocane (**X**) in acetonitrile-d_3.



Xa **Xb** **Xc** **Xd**

spectrum by an equation $\Delta E = -RT \ln K$ at T 233 K was 0.83 kcal mol^{-1} and exactly coincided with the calculated value.

The energy of conformer **Xc** with both endocyclic CF_3 groups exceeds that of conformer **Xa** by 3.5 kcal mol^{-1}. Conformer 1,5-boat-chair **Xd** notwithstanding the orientation of the CF_3 groups is also less feasible by the energy compared with **Xa** (by 1.3–2.7 kcal mol^{-1}).

EXPERIMENTAL

NMR spectra were registered on a spectrometer Bruker DPX-400 at operating frequencies 400 (^{1}H), 100 (^{13}C), and 376 MHz (^{19}F), internal reference HMDS, chemical shifts are reported with respect to TMS (^{1}H, ^{13}C) and CCl_3F (^{19}F). The reaction progress was monitored by TLC on plates with silica gel 60 F-254, eluent hexane–ether, 1:2.

X-ray diffraction analysis was performed on a diffractometer IPDS-2 (Stoe) at 293 K, graphite monochromator, MoK_α radiation. Crystals orthorhombic (from a mixture ether–hexane), $C_8H_{14}F_3NO_6S$, space group Ama2, Z 4, a 19.0293(6), b 12.0000(12), c 5.616(3) E, V 1282.4(7) E^3, ρ 1.602 g/cm^3. The cell parameters were estimated from 4038 reflections with $2.1 < \theta < 25.0°$. The structure was solved by the direct method [7] and refined in the full-matrix least-squares method in the anisotropic approximation for nonhydrogen atoms and in isotropic approximation for hydrogen atoms [8]. The final values of divergence factors are R 0.0399, R_w 0.1070 for 971 reflections with $I > 2\sigma(I)$. Quantum-chemical calculations are carried out with the use of GAUSSIAN-98 software [9].

Reaction of trifluoromethanesulfonamide with CH_2O in ethyl acetate. To a mixture of 5 g (0.034 mol) of trifluoromethanesulfonamide (**I**) and 8 g (0.268 mol)of paraformaldehyde in 75 ml of ethyl acetate at vigorous stirring was slowly added 24 ml of concn. H_2SO_4, and the mixture was stirred at room temperature for 6 h. According to NMR data under these conditions the main reaction product was 5-trifluoro-methylsulfonyl-1,3-dioxazinane (**VI**). A half of the reaction mixture was separated, poured into ice water, thrice extracted with ethyl acetate, the extract was washed with $NaHCO_3$ solution and dried with $MgSO_4$. On removing the solvent the residue (about 7 g) was distilled in a vacuum. We obtained 3.14 g of colorless liquid of bp 73–75°C (3 mm Hg) containing by GLC data three principal components. We failed to obtain pure 5-trifluoromethylsulfonyl-1,3-dioxazinane (**VI**) by repeated distillation or fractionation. The sample used for spectral measurements contained ~70% of target compound **VI**, ~20% of trifluoromethylsulfonamide, and ~10% of an impurity of unknown structure.

The remaining reaction mixture was gradually heated from 20 to 80°C within 6 h, then it was cooled, poured into ice water, thrice extracted with ethyl acetate, the extract was washed with $NaHCO_3$ solution and dried with $MgSO_4$, the solvent was removed, part of the residue (1 g) was subjected to column chromatography on silica gel using eluents of growing polarity: hexane–ether, 2: 1 (360 ml), 1: 1 (100 ml), 1:2 (100 ml), 1: 3 (100 ml), hexane–ether–acetone, 1:2:1 (360 ml). From the fractions obtained we succeeded to isolate complex **IX** characterized by X-ray diffraction analysis, and compound **X** identified by means of NMR spectroscopy.

5-Trifluoromethylsulfonyl-1,3-dioxazinane (VI). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 5.16 s (2H, OCH_2O), 5.26 s (4H, OCH_2N). ^{13}C NMR spectrum (CD_3CN), δ, ppm: 78.95 (OCN), 95.28 (OCO). ^{19}F NMR spectrum (CD_3CN), δ, ppm: –77.77 br.s.

Complex 2,4,8,10-tetraoxospiro[5,5]undecene–trifluoromethanesulfonamide (IX). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 3.72 s (8H, OCH_2C), 4.76 s (4H, OCH_2O), 6.66 br.s (2H, NH_2). ^{13}C NMR spectrum (CD_3CN), δ, ppm: 34.44 (CCC), 70.80 (OCC), 95.02 (OCO), 120.64 q (CF_3, J 318.8 Hz). ^{19}F NMR spectrum (CD_3CN), δ, ppm: –78.99.

3,7-Bis(trifluoromethylsulfonyl)-1,5,3,7-dioxadiazocane (X). ^{1}H NMR spectrum (CD_3CN), δ, ppm:

4.98, 5.49 m (CH_2). ^{13}C NMR spectrum (CD_3CN), δ, ppm: 84.40 (CH_2), 120.34 q (CF_3, J 323.4 Hz). ^{19}F NMR spectrum (CD_3CN), δ, ppm: –77.87 br.s.

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