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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Cascade Transformations of Trifluoromethanesulfonamide in Reaction with Formaldehyde

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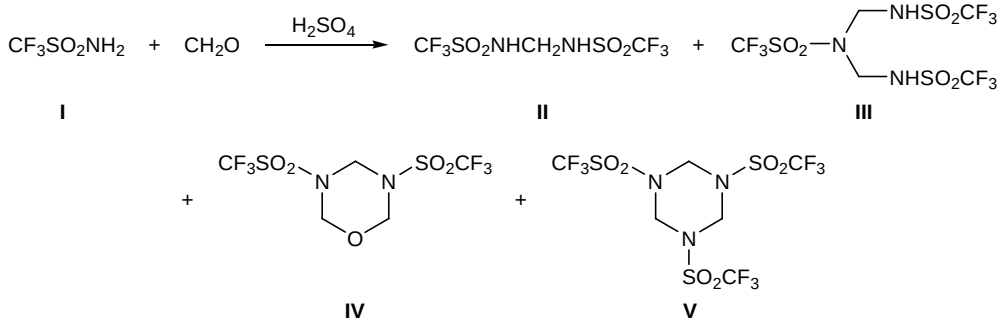
Abstract—Trifluoromethanesulfonamide reacts with paraformaldehyde in acid medium to give both open-chain and cyclic condensation products: bis(trifluoromethylsulfonylamino)methane, *N*,*N*-bis(trifluoromethylsulfonylaminomethyl)trifluoromethanesulfonamide, 5-(trifluoromethylsulfonyl)dihydro-1,3,5-dioxazine, 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine, 1,3,5-tris(trifluoromethylsulfonyl)hexahydro-1,3,5-triazine, 5,7-bis(trifluoromethylsulfonyl)-1,3,5,7-dioxadiazocane, and 5,7,9-tris(trifluoromethylsulfonyl)-1,3,5,7,9-dioxatriazecane. Amidoalkylation of acetonitrile in the system trifluoromethanesulfonamide–paraformaldehyde–phosphoric acid leads to formation of *N*-(trifluoromethylsulfonylaminomethyl)acetamide.

Condensations involving formaldehyde molecules play an important role in synthetic organic chemistry. These include coupling of formaldehyde with acetylene (Favorskii reaction), alkenes (Prins), nitroalkanes (Henry), phenols (Lederer–Manasse), aldehydes and ketones (Tollens), ketones and amines (Mannich), and amines and formic acid (Eschweiler–Clarke). Primary amines readily react with formaldehyde to give symmetric 1,3,5-trialkylhexahydrotriazines [1]. Carboxamides and sulfonamides with formaldehyde give rise to hydroxymethylation products [2]; owing to reduced basicity of amides, these reactions are carried out in H_2SO_4 to generate hydroxymethyl cation $HOCH_2^+$. The basicity of the nitrogen atom in the molecule of trifluoromethansulfonamide is much weaker than in alkane- or arenesulfonamides; therefore, it was difficult to expect *a priori* whether the corresponding hydroxymethylation products will be formed from trifluoromethansulfonamide under analogous conditions. It is known that trifluoromethanesulfonamide does not add even to highly electrophilic carbonyl group in trichloroacetaldehyde while carboxamides and sulfonamides react with the same reagent without additional activation [3]. Taking into account the above stated, in continuation of our studies on the chemistry of trifluoromethanesulfonamides [4–6], in the present work we examined reactions of trifluoromethanesulfonamide with formaldehyde under various conditions.

Orazi and Corral [7] reported on the formation of N-sulfonyl-substituted dihydro-1,3,5-dioxazines, tetra-

Scheme 1.



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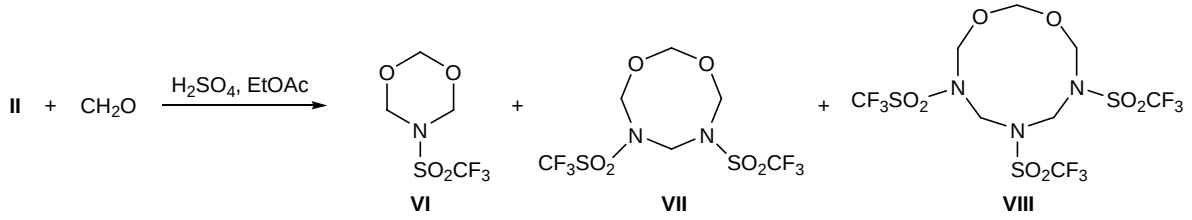
Scheme 2.

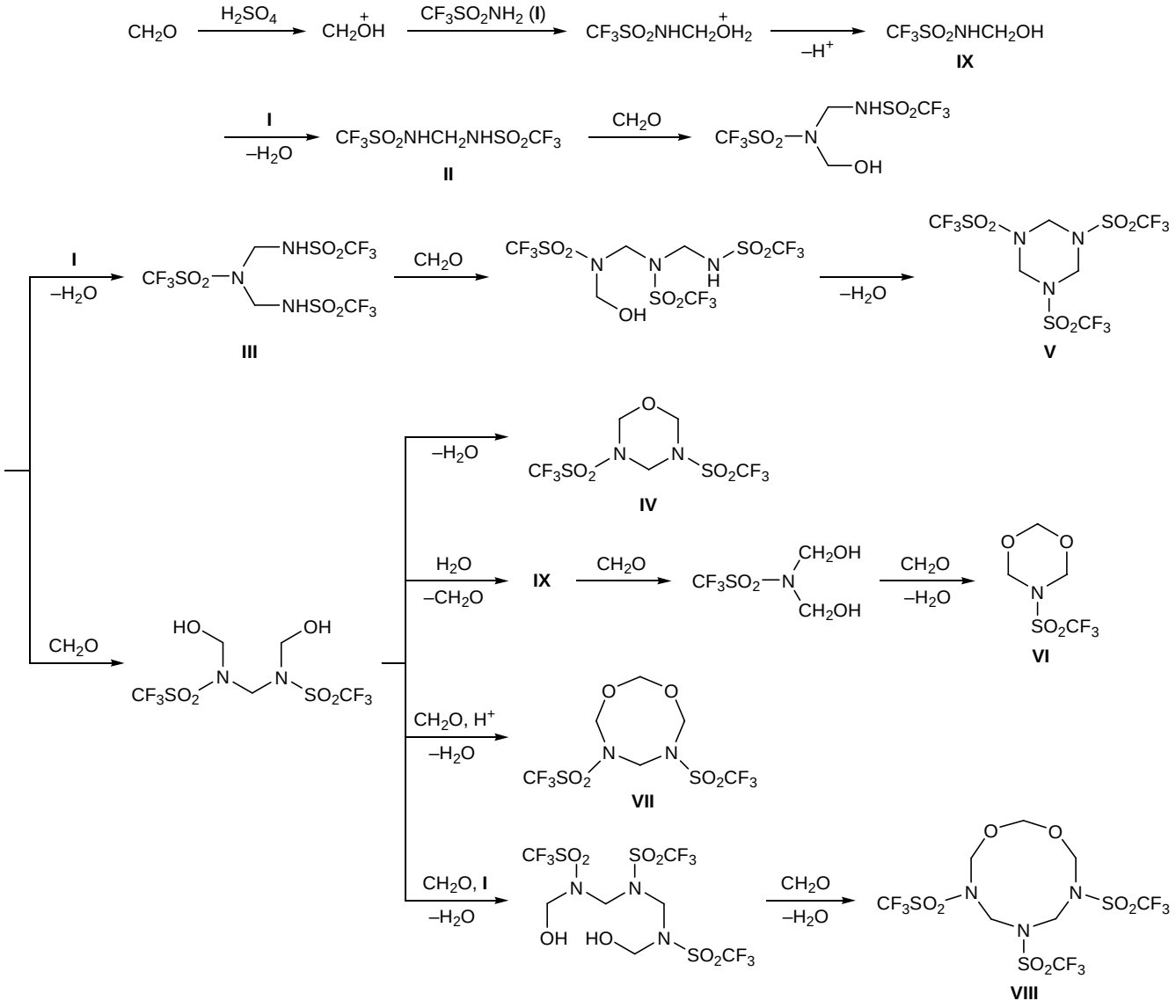


hydro-1,3,5-oxadiazines, and hexahydro-1,3,5-triazines in reactions of 1,3,5-trioxane (as a source of formaldehyde) with alkane- and arenesulfonamides. We found that trifluoromethanesulfonamide (**I**) reacts with paraformaldehyde in sulfuric acid at various temperatures and reactant ratios to produce a number of open-chain and cyclic condensation products. In particular, we isolated and identified bis(trifluoromethylsulfonylamino)methane (**II**), *N*,*N*-bis(trifluoromethylsulfonylaminomethyl)trifluoromethanesulfonamide (**III**), 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine (**IV**), and 1,3,5-tris(trifluoromethylsulfonyl)hexahydro-1,3,5-triazine (**V**) (Scheme 1). It should be noted that no linear products like **II** and **III** were detected in [7]; on the other hand, we did not identify 5-(trifluoromethylsulfonyl)dihydro-1,3,5-dioxazine (**VI**) among the products, though aromatic analogs of **VI** were isolated in [7]. We isolated compound **VI** together with other condensation products in the reaction of bis(trifluoromethylsulfonylamino)methane (**II**) with paraformaldehyde and sulfuric acid in ethyl acetate, which was carried out by slowly heating the reaction mixture from room temperature to 85°C. Apart from compound **VI**, eight- and ten-membered cyclic products, 5,7-bis(trifluoromethylsulfonyl)-1,3,5,7-dioxadiazocane (**VII**) and 5,7,9-tris(trifluoromethylsulfonyl)-1,3,5,7,9-dioxatriazecane (**VIII**), were formed (Scheme 2). An analog of **II**, 1,3-dinitro-1,3-diazapropane $O_2NNHCH_2NHNO_2$ was reported in [8] to undergo cyclization by the action of paraformaldehyde and sulfuric acid in ethyl acetate to afford eight-membered 5,7-dinitro-1,3,5,7-dioxadiazocane.

The product ratio depends on the reaction conditions. At a trifluoromethanesulfonamide-to-paraformaldehyde ratio of 2:1 at room temperature (under these conditions, amide **I** does not dissolve in sulfuric acid, and the reaction is heterogeneous), the major product was bis(trifluoromethylsulfonylamino)methane (**II**), and cyclic 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine (**IV**) was also obtained. On heating to 40°C, amide **I** dissolves in sulfuric acid almost completely, and *N*,*N*-bis(trifluoromethylsulfonylaminomethyl)trifluoromethanesulfonamide (**III**) is formed together with compounds **II** and **IV**. Amide **III** was obtained as the only open-chain product when the ratio **I**–CH_2O was 4:3, and the reaction time was 4 h at 40°C and 20 h at room temperature; pure compound **III** was isolated after separation of a small impurity of cyclic product **IV** which is insoluble in hexane–diethyl ether. Raising the temperature to 60–70°C, the reactant ratio remaining the same (**I**:CH_2O = 4:3), leads to formation of symmetric hexahydrotriazine derivative **V**. Cyclic products **IV** and **V** were separated from open-chain amides **II** and **III** by treatment with a hexane–diethyl ether mixture in which the cyclic products are insoluble. Individual compounds **IV**–**VIII** were isolated by column chromatography.

The structure of the products was proved by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis (we failed to obtain analytically pure samples of compounds **VI**–**VIII** even by column chromatography). The ^1H NMR spectrum of **II** contained two signals with similar intensities: a triplet at δ 4.7 ppm from the methylene protons and a broadened (due to exchange) triplet at δ 7.8 ppm from the NH protons. Under conditions of fast exchange (in the presence of traces of an acid), the NH signal becomes strongly broadened, and the CH_2 signal degenerates to a singlet. In the ^1H NMR spectrum of amide **III** we also observed a broadened triplet from the NH proton (δ 7.8 ppm), but the methylene proton signal appeared as a doublet with a twice as high intensity. Compound **III** showed in the ^{13}C NMR spectrum a signal from the methylene carbon atom, which was displaced downfield by ~5 ppm relative to the corresponding signal of **II**, and two quartets from the CF_3 groups at about δ_C 120 ppm with an intensity ratio of 1:2. The downfield CF_3 signal belongs to the CF_3SO_2NH group, and the upfield, to CF_3SO_2N. The structure of **IV** follows from the absence in the ^1H NMR spectrum of NH signal and the presence of two singlets from CH_2 groups at δ 5.4 and 5.3 ppm at a ratio of 2:1. The ^{13}C NMR spectrum of **IV** contained two signals at δ_C 61 and 79 ppm (intensity ratio 1:2) and one quartet from the CF_3

Scheme 3.



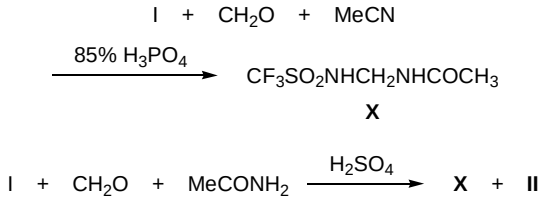
group. In the ^{19}F NMR spectrum of **IV** only one signal was present. Symmetric hexahydro-1,3,5-triazine **V** showed in the ^{1}H NMR spectrum at room temperature one broadened singlet from the methylene protons; at reduced temperature, this signal is transformed into separate signals belonging to axial and equatorial protons. Splitting of signals is also observed in the ^{13}C and ^{19}F NMR spectra recorded at reduced temperature (the results of dynamic NMR study on the conformational behavior of compound **V** will be reported elsewhere).

Dioxazine **VI** gives rise to two singlets from the methylene groups at δ 3.7 (NCH_2O) and 4.7 ppm (OCH_2O) (intensity ratio 2:1) in the ^{1}H NMR spectrum; the corresponding carbon signals in the ^{13}C NMR spectrum are located at δ_C 70.8 and 95.0 ppm. The ^{1}H NMR spectrum of eight-membered cyclic product **VII** contained three singlets at δ 3.7 (NCH_2O), 4.0 (NCH_2N), and 4.7 ppm (OCH_2O) at a ratio of 2:1:1, and the corresponding signals in the ^{13}C NMR spectrum appeared at δ_C 69.9, 64.0, and 94.8 ppm, respectively. The ^{1}H and ^{13}C NMR signals were assigned using the two-dimensional ^{1}H–^{13}C HETCOR spectrum. The ten-membered cyclic structure of compound **VIII** was assigned on the basis of characteristic chemical shifts of protons and carbon nuclei in the NCH_2O, NCH_2N, and OCH_2O groups. Like compound **VII**, the ^{1}H NMR spectrum of **VIII** contained three singlets at δ 3.8, 4.1, and 4.8 ppm, but with an intensity ratio of 2:2:1; these data indicate the presence of

two NCH_2O groups, two NCH_2N groups, and one OCH_2O group. The corresponding signals in the ^{13}C NMR spectrum of **VIII** (δ_C 69.5, 63.5, and 94.8 ppm) had the same intensity ratio.

The reaction under study is likely to begin with addition of trifluoromethanesulfonamide (**I**) to formaldehyde molecule activated by protonation with sulfuric acid. *N*-Hydroxymethyl derivative $CF_3SO_2NHCH_2OH$ (**IX**) thus formed is involved in consecutive condensations with further molecules of trifluoromethanesulfonamide and formaldehyde to produce the set of identified linear and cyclic products (Scheme 3). We failed to isolate pure *N*-hydroxymethyltrifluoromethanesulfonamide (**IX**); nevertheless, its formation is beyond doubt, for one-pot process with participation of trifluoromethanesulfonamide, paraformaldehyde, and acetonitrile in 85% orthophosphoric acid or of trifluoromethanesulfonamide, paraformaldehyde, and acetamide in concentrated sulfuric acid gives mixed *N*-(trifluoromethylsulfonylaminomethyl)acetamide (**X**) (Scheme 4). Obviously, the reaction involves intermediate formation of hydroxymethyl derivative **IX**, hydrolysis of acetonitrile to acetamide, and amidomethylation of the latter with intermediate **IX** according to Tscherniac–Einhorn. This reaction sequence is confirmed by the formation of amide **X** from trifluoromethanesulfonamide, acetamide, and paraformaldehyde in sulfuric acid. In the latter case, the yield of **X** was greater than in the reaction with acetonitrile, and a small amount (about 20%) of linear condensation product **II** was formed. Compound **II** can readily be separated by treatment with hexane–diethyl ether.

Scheme 4.



EXPERIMENTAL

The NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400, 100, and 376 MHz for ^1H, ^{13}C, and ^{19}F, respectively, using hexamethyldisiloxane as internal reference; the chemical shifts are given relative to tetramethylsilane (^1H, ^{13}C) and CCl_3F (^{19}F). The progress of reactions was monitored by TLC on silica gel (60F-254 plates) using hexane–diethyl ether (1:2) as eluent.

Reaction of trifluoromethanesulfonamide with paraformaldehyde. *a*. Paraformaldehyde, 0.6 g (0.02 mol of CH_2O), was added in small portions under vigorous stirring to a suspension of 6 g (0.04 mol) of finely powdered trifluoromethanesulfonamide in 40 ml of concentrated sulfuric acid. The mixture was stirred for 1 h at room temperature and poured into ice water, and the finely crystalline precipitate was filtered off, washed with ice water, and dried in air. We thus obtained 3.0 g of a mixture of bis(trifluoromethylsulfonylamino)methane (**II**) and 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine (**IV**). The product was treated with diethyl ether–hexane (2:1), and the undissolved material was filtered off and washed with hexane to isolate 0.8 g of 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine (**IV**). The filtrate was evaporated to obtain 2.2 g of bis(trifluoromethylsulfonylamino)methane (**II**) which was purified by recrystallization from benzene.

Compound **II**. mp 120°C (decomp.). ^1H NMR spectrum (CD_3CN), δ, ppm: 4.71 s (2H, CH_2), 7.76 br.s (2H, NH). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 53.22 (CH_2), 120.34 q (CF_3, J_{CF} = 319.9 Hz). ^{19}F NMR spectrum (CD_3CN): δ_F –79.31 ppm. Found, %: C 12.08; H 1.34; N 9.18; S 20.98. $C_3H_4F_6N_2O_4S_2$. Calculated, %: C 11.62; H 1.30; N 9.03; S 20.67.

Compound **IV**. mp 150°C (sublimes). ^1H NMR spectrum (CD_3CN), δ, ppm: 5.28 s (4H, NCH_2O), 5.39 s (2H, NCH_2N). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 61.33 (NCH_2N), 79.42 (NCH_2O), 120.24 q (CF_3, J_{CF} = 320.5 Hz). ^{19}F NMR spectrum (CD_3CN): δ_F –78.09 ppm. Found, %: C 17.16; H 1.58; N 8.35; S 18.42. $C_5H_6F_6N_2O_5S_2$. Calculated, %: C 17.05; H 1.72; N 7.95; S 18.20.

b. The reaction was carried out as described above in *a*, but the suspension of trifluoromethanesulfonamide in H_2SO_4 was heated to 40°C, and the mixture became almost homogeneous. After addition of paraformaldehyde, the mixture was stirred for 2 h at 40°C and was treated as described above. After separation of compound **IV** which is insoluble in hexane–diethyl ether, we obtained an approximately equimolar mixture of bis(trifluoromethylsulfonylamino)methane (**II**) and *N*,*N*-bis(trifluoromethylsulfonylaminomethyl)trifluoromethanesulfonamide (**III**). When the reactant ratio trifluoromethanesulfonamide–paraformaldehyde was 4:3 and the mixture was kept for 4 h at 40°C and for 20 h at room temperature, separation of product **IV** left pure compound **III**.

Compound **III**. mp 136°C. ^1H NMR spectrum (CD_3CN), δ, ppm: 4.99 d (4H, CH_2, J = 6.4 Hz),

7.86 br.t (2H, NH). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 57.89 (CH_2), 120.21 q (CF_3SO_2N, J_{CF} = 321.3 Hz), 120.50 q (CF_3SO_2NH, J_{CF} = 320.0 Hz). ^{19}F NMR spectrum (CD_3CN), δ_F, ppm: –76.42 (1F), –78.06 (2F). Found, %: C 13.38; H 1.31; F 35.95; N 9.35; S 20.41. $C_5H_6F_9N_3O_6S_3$. Calculated, %: C 12.74; H 1.28; F 36.28; N 8.92; S 20.41.

c. The reaction was carried out as described above in *b*, but the ratio trifluoromethanesulfonamide–paraformaldehyde was 4:3 and the mixture was heated at 60–70°C. The mixture was poured into water, and the precipitate was treated as described above. The material insoluble in hexane–diethyl ether (1.26 g) was 1,3,5-tris(trifluoromethylsulfonyl)hexahydro-1,3,5-triazine (**V**) which was recrystallized from isopropyl alcohol–hexane, and the soluble portion was a mixture of amides **II** and **III**.

Compound **V**. mp 217–218°C. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 5.36 br.s (CH_2). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 61.86 (CH_2), 120.16 q (CF_3, J_{CF} = 320.5 Hz). ^{19}F NMR spectrum (CD_3CN): δ_F –78.06 ppm. Found, %: C 14.97; H 1.40; F 36.17; N 8.79; S 19.50. $C_6H_6F_9N_3O_6S_3$. Calculated, %: C 14.91; H 1.25; F 35.38; N 8.69; S 19.90.

Reaction of bis(trifluoromethylsulfonylamino)-methane (II) with paraformaldehyde. A solution of 1.16 g of paraformaldehyde (0.038 mol of CH_2O) in a mixture of 4.2 ml of concentrated sulfuric acid and 12.6 ml of ethyl acetate was cooled to 15°C, 2 g (0.006 mol) of compound **II** was added in small portions under vigorous stirring, and the mixture was stirred for 5 h at room temperature, for 4 h at 35°C, and for 8 h while gradually raising the temperature to 85°C. The mixture was cooled, poured into ice water, and extracted with three portions of ethyl acetate. The extract was dried over $MgSO_4$ and evaporated, and the residue (2.4 g) was subjected to column chromatography on silica gel using hexane–diethyl ether (3:1) as eluent to isolate compounds **VI**, **VII**, and **VIII**.

5-(Trifluoromethylsulfonyl)tetrahydro-1,3,5-dioxazine (VI). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 3.72 s (2H, NCH_2), 4.76 s (1H, OCH_2O). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 70.80 (NC), 95.02 (OCO), 121.41 q (CF_3, J_{CF} = 318.4 Hz). ^{19}F NMR spectrum (CD_3CN): δ_F –80.50 ppm.

5,7-Bis(trifluoromethylsulfonyl)-1,3,5,7-dioxadiazocane (VII). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.66 s (4H, OCH_2N), 4.02 s (2H, NCH_2N), 4.68 s (2H, OCH_2O). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 64.04 (NCN), 69.92 (NCO), 94.77 (OCO), 120.73 q (CF_3, J_{CF} = 319.2 Hz). ^{19}F NMR spectrum (CD_3CN): δ_F –80.53 ppm.

5,7,9-Tris(trifluoromethylsulfonyl)-1,3,5,7,9-dioxatriazecane (VIII). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.77 s (4H, OCH_2N), 4.08 s (4H, NCH_2N), 4.78 s (2H, OCH_2O). ^{13}C NMR spectrum (CD_3CN), δ_C, ppm: 63.52 (NCN), 69.50 (NCO), 94.81 (OCO), 120.73 q (CF_3, J_{CF} = 319.2 Hz).

***N*-(Trifluoromethylsulfonylaminomethyl)acetamide (X).** *a*. Acetonitrile, 2.8 ml, was added dropwise under stirring to a mixture of 10 ml of 85% H_3PO_4, 3 g (0.02 mol) of trifluoromethanesulfonamide, and 1.33 g of paraformaldehyde (0.044 mol of CH_2O). The mixture was heated to 65–70°C, and it then spontaneously warmed up to 93°C. The mixture was stirred for 4 h at 90–95°C, cooled, poured into 100 ml of ice water containing 20 ml of concentrated aqueous ammonia, adjusted to neutral pH value, and extracted with diethyl ether (3×20 ml). The extracts were combined, washed with a saturated solution of sodium chloride, and dried over $MgSO_4$, the solvent was removed, and the residue was recrystallized from hexane–isopropyl alcohol (10:1). Yield 36%, mp 123–124°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 2.03 s (3H, CH_3), 4.61 m (2H, CH_2), 6.46 br.s (1H, $NHSO_2$), 7.14 br.s (1H, NHCO); in acetone-d_6: 1.95 s (3H, CH_3), 4.65 m (2H, CH_2), 8.19 s (1H, $NHSO_2$), 8.76 s (1H, NHCO). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 22.47 (CH_3), 49.42 (CH_2), 120.61 q (CF_3, J = 320.5 Hz), 171.61 (C=O). ^{19}F NMR spectrum (acetone-d_6): δ_F –78.26 ppm. Found, %: C 22.16; H 3.08; F 25.29; N 12.52. $C_4H_7F_3N_2O_3S$. Calculated, %: C 21.82; H 3.20; F 25.89; N 12.72.

b. Paraformaldehyde, 0.6 g (0.02 mol of CH_2O), was added in small portions under vigorous stirring at room temperature to a mixture of 3 g (0.02 mol) of trifluoromethanesulfonamide and 1.18 g (0.02 mol) of acetamide in 50 ml of concentrated sulfuric acid. During the addition, the mixture gradually thickened. It was heated to 60°C, stirred for 30 min at that temperature, for 1 h at 70, and for 1 h at 80°C, cooled, poured into ice water, and extracted with diethyl ether (2×20 ml) and ethyl acetate (1×20 ml). The extracts were combined and dried over $MgSO_4$, and the solvent was removed. According to the ^{1}H NMR data, the residue, 3.11 g, was a mixture of compounds **II** and **X** at a ratio of 1:4; yield of crude **X** 65%. Compound **X** was purified by treatment with hexane–diethyl ether (where product **II** is soluble), the undissolved colorless material was filtered off, washed with hexane, and

dried. Yield of pure amide **X** 1.42 g (32%). It was identical to a sample prepared as described above in *a* in the melting point and NMR spectra.

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