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Condensation of Trifluoromethanesulfonamide with Paraformaldehyde and Oxamide

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Abstract—Depending on the conditions, three-component condensation of trifluoromethanesulfonamide with paraformaldehyde and oxamide led to the formation of linear products, *N*-mono- and *N*,*N*′-bis[(trifluoromethylsulfonyl)aminomethyl]oxamide, bis[(trifluoromethylsulfonyl)aminomethyl] ethanedioate, as well as of hydrolysis and cyclization product, *N*-(4,5-dioxo-1,3-oxazolidin-3-ylmethyl)trifluoromethanesulfonamide.

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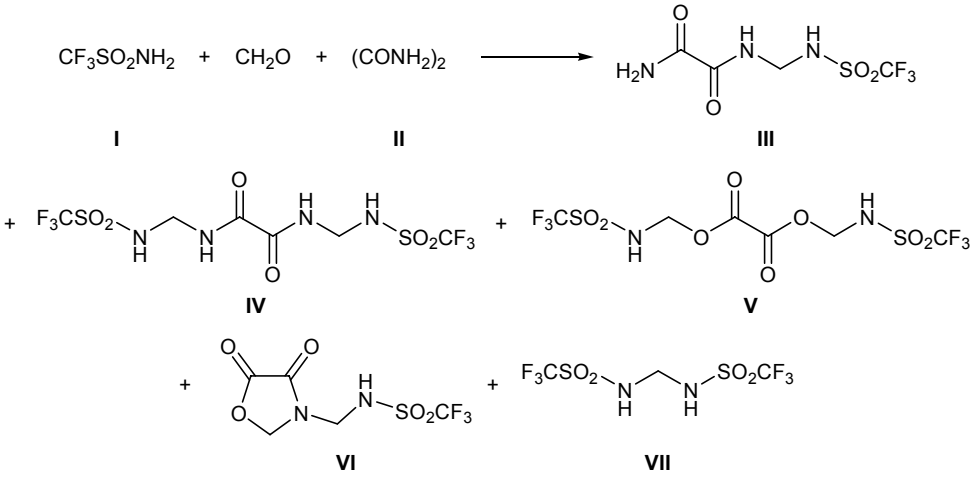
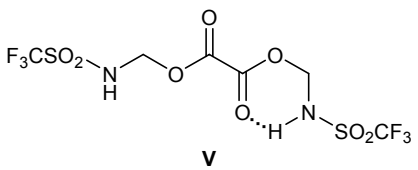
We previously studied the condensation of trifluoromethanesulfonamide $CF_3SO_2NH_2$ with paraformaldehyde and three-component condensations of trifluoromethanesulfonamide with paraformaldehyde and various amides. Depending on the conditions, these reactions led to the formation of various linear and cyclic products [1–4]. In particular, the results of condensations of dicarboxylic acid amides of the general formula $H_2NCO(CH_2)_nCONH_2$ as amide component with paraformaldehyde and trifluoromethanesulfonamide were determined by the number of methylene groups in the initial amide. When $n = 1$, the product was spirocyclic 4,10-bis(trifluoromethylsulfonyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,7-dione [3], while amides possessing two methylene groups ($n = 2$) gave rise to either linear *N*,*N*-bis[(trifluoromethylsulfonyl)aminomethyl]succinamide or heterocyclization product, *N*-[(trifluoromethylsulfonyl)-aminomethyl]succinimide, depending on the conditions [4]. In the present work we examined the three-component condensation of sulfonamide **I** with paraformaldehyde and the simplest dicarboxylic acid amide, oxamide (**II**, $n = 0$). We expected formation of linear condensation products at one (**III**) or both amide groups (**IV**) and, probably (by analogy with our previous results), heterocyclization products.

Scheme 1.



The reaction was carried out in concentrated sulfuric acid or in ethyl acetate in the presence of sulfuric acid. As we showed previously, different condensation products can be formed in these media [2]. In fact, by varying the conditions, we succeeded in isolating *N*-[(trifluoromethylsulfonyl)aminomethyl]oxamide (**III**), *N*,*N*′-bis[(trifluoromethylsulfonyl)aminomethyl]-oxamide (**IV**), bis[(trifluoromethylsulfonyl)aminomethyl] ethanedioate (**V**), and heterocyclization product, *N*-(4,5-dioxo-1,3-oxazolidin-3-ylmethyl)trifluoromethanesulfonamide (**VI**) (Scheme 1). In addition, *N*,*N*′-methylenedi(trifluoromethanesulfonamide) (**VII**) and oxamide hydrolysis and alcoholysis products (in the reaction carried out in ethyl acetate), oxalic acid and diethyl oxalate, were detected. The products were separated by column chromatography on silica gel, and their structure was determined on the basis of their IR, Raman, and ^{1}H and ^{13}C NMR spectra. Monosubstituted product **III** displayed in the ^{1}H NMR spectrum a doublet from methylene protons and four NH signals with equal intensities: two singlets due to primary amino group $CONH_2$, a triplet from the secondary amide group, and a broadened singlet due to sulfonamide group, the latter being located most downfield. The ^{13}C NMR spectrum of **III**, apart from signals belonging to the methylene carbon atom and CF_3 group (quartet), contained two signals typical of amide carbonyl carbon atoms. Unlike compound **III**, in the ^{1}H NMR spectrum of symmetric disubstitution product **IV** we observed a signal from the methylene protons and two NH signals, one of which being a triplet (NHCO), and the other, a broadened singlet ($NHSO_2$). Correspondingly, the ^{13}C NMR spectrum of **IV** contained signals from the CH_2 and CF_3 groups and only one signal due to amide carbonyl carbon atom. Despite formally symmetric structure, compound **V** showed in the ^{1}H NMR spectrum two signals from nonequivalent NH protons as broadened singlets with equal intensities (1H) at δ ~10 and 13 ppm. The IR and Raman spectra indicated that one NH proton in structure **V** is involved in intramolecular hydrogen bond and that the other NH proton participates in intermolecular hydrogen bond. This followed from the presence in the IR spectrum of a narrow peak at 3314 cm^{-1} (ν_{NH}, intramolecular hydrogen bond) and a broadened ν_{NH} band in the region 3020–3120 cm^{-1} (intermolecular hydrogen bond). These data are consistent with the low-frequency shift of the ν_{NH} band of trifluoromethanesulfonamide fragment upon formation of intermolecular hydrogen bond, as reported in [5]. The IR spectrum of **V** also contained an absorption band at 1722 cm^{-1} due to asymmetric stretching vibrations ν_{as}(C=O) of the dicarbonyl fragment, whereas the corresponding symmetric vibrations ν_s(C=O) were active in the Raman spectrum (1672 cm^{-1}).



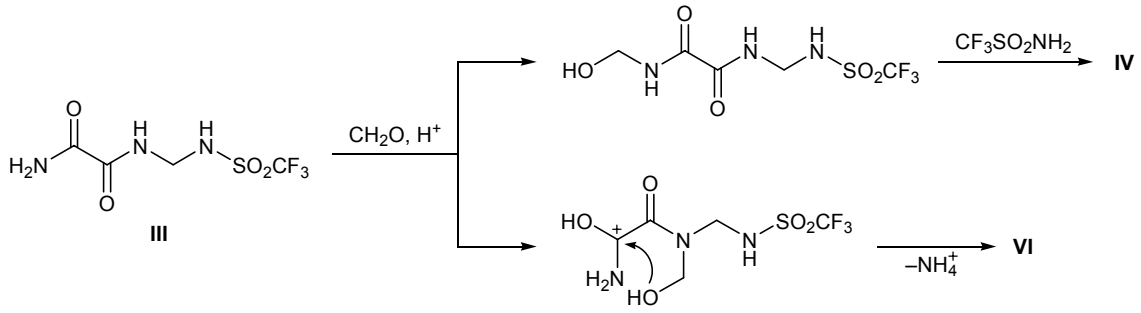
V

In the mass spectra of **III**–**V** we observed characteristic fragment ion peaks with *m*/*z* 162 ($CF_3SO_2NHCH_2$), 133 (CF_3SO_2), 78 (NSO_2), and 69 (CF_3).

The structure of heterocyclic compound **VI** is confirmed by the presence in its ^{1}H NMR spectrum of signals from two nonequivalent methylene groups and a very broad NH signal. The ^{13}C NMR spectrum of **VI** contained two signals from methylene carbon atoms (δ_C 50 and 76 ppm) [1], two carbonyl carbon signals, and a quartet from the CF_3 group, and one signal was observed in the ^{19}F NMR spectrum of this compound. Two carbonyl stretching vibrations bands ($\nu_{C=O}$ 1736 and 1812 cm^{-1}) and one ν_{NH} band at 3200 cm^{-1} were present in the IR spectrum of **VI**. The NCH_2N and OCH_2N proton signals in the ^{1}H NMR spectrum were assigned on the basis of the ^{1}H–^{13}C HSQC spectrum [6], where δ/δ_C cross peaks were observed at 5.45/76 and 4.86/50 ppm. The molecular ion peak of **VI** was detected only in the negative ion mass spectrum, and its relative intensity was as low as 2%. Fragmentation of the molecular ion of **VI** involves cleavage of the CH_2–NH bond with charge localization on the trifluoromethanesulfonamide fragment. The precise *m*/*z* value of the $[M + Na]^+$ ion in the TOF ESI mass spectrum of **VI** corresponds to the formula $C_5H_5F_3N_2NaO_5S$, which is consistent with the assumed structure.

The ratio of the condensation products strongly depends on the reaction conditions. When the reaction was carried out in ethyl acetate in the presence of sulfuric acid, after removal of compound **VII** and unreacted trifluoromethanesulfonamide by washing the reaction mixture with diethyl ether–hexane (1:6) and of diethyl oxalate by distillation, we isolated compounds **IV** and **VI** at a ratio of ~6:1. By carrying out the condensation in sulfuric acid at room temperature we succeeded in raising the yield of heterocyclic product **VI** and isolating monosubstituted compound **III**. In this case the ratio **VI**:**III** was 3:1. Compound **III** was formed as the major product in the condensation of

Scheme 2.



trifluoromethanesulfonamide with paraformaldehyde and oxamide in sulfuric acid when the reaction time was 40 min (room temperature). Under more severe conditions, i.e., in sulfuric acid at elevated temperature, the major product was oxazolidinedione **VI**. However, when a mixture of oxamide and trifluoromethanesulfonamide in sulfuric acid was preliminarily heated until complete dissolution and paraformaldehyde was then added, we obtained bis[(trifluoromethylsulfonyl)aminomethyl] ethanedioate (**V**).

These findings led us to conclude that monosubstitution product **III** is formed initially. The subsequent hydroxymethylation of **III** with paraformaldehyde either at the primary amide group, followed by condensation with the second trifluoromethanesulfonamide molecule, or at the secondary amide group, followed by heterocyclization, yields disubstitution product **IV** or 3-substituted 4,5-dioxo-1,3-oxazolidine **VI**, respectively (Scheme 2). Compound **VI** was also obtained as the major product by heterocyclization of oxamide with paraformaldehyde and *N*,*N*′-methylenedi(trifluoromethanesulfonamide) (**VII**) prepared by condensation of trifluoromethanesulfonamide with paraformaldehyde [1].

EXPERIMENTAL

The IR spectrum of compound **V** was recorded on a Bruker Vertex 70 spectrometer with Fourier transform, and the Raman spectrum of **V** was obtained on a Varian 3100 FT-IR instrument. The NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 (^{1}H), 100 (^{13}C), and 376 MHz (^{19}F); the chemical shifts were determined relative to tetramethylsilane (^{1}H, ^{13}C) and CCl_3F (^{19}F). The mass spectra (electron impact, 70 eV) were recorded on a Trace DSQ II instrument (Thermo Fisher Scientific GmbH, Dreieich, Germany) with direct sample admission into the ion source. The high-resolution mass spectrum (positive electrospray ionization) was obtained on a Micromass Q-TOF$_{micro}$ mass spectrometer (Waters, Manchester, UK); a sample (20 μl/min) was introduced with the aid of a Harvard syringe pump (capillary entrance voltage 3.2 kV, cone voltage 20–25 V). The elemental composition was determined by measuring the precise molecular weight with an accuracy of ±3 ppm using H_3PO_4 as reference. The progress of reactions was monitored by TLC on silica gel 60 F-254 plates using hexane–diethyl ether (1 : 2) as eluent.

Condensation of trifluoromethanesulfonamide with paraformaldehyde and oxamide in ethyl acetate–sulfuric acid. Oxamide, 2 g (22 mmol), trifluoromethanesulfonamide, 7.45 g (50 mmol), and paraformaldehyde, 1.5 g (50 mmol), were mixed with 42 ml of ethyl acetate, and 14 ml of 92% sulfuric acid was added dropwise. The mixture was stirred for 2 days at room temperature, poured into a mixture of ice with sodium chloride, and extracted with ethyl acetate (3 × 70 ml). The extract was dried over $MgSO_4$, the solvent was distilled under reduced pressure, and the residue (~9 g) was washed with a mixture of diethyl ether–hexane (1 : 6) to remove unreacted trifluoromethanesulfonamide and *N*,*N*′-methylenedi(trifluoromethanesulfonamide) (~6.4 g). Diethyl oxalate was removed from the residue by vacuum distillation. The still residue (~900 mg) contained (according to the ^{1}H and ^{13}C NMR data) 50% of diethyl oxalate, 40% of *N*,*N*′-bis[(trifluoromethylsulfonyl)aminomethyl]-oxamide (**IV**), and 10% of *N*-(4,5-dioxo-1,3-oxazolidin-3-ylmethyl)trifluoromethanesulfonamide (**VI**). By column chromatography (diethyl ether–hexane, 1 : 2; diethyl ether) we isolated 300 mg of compound **VI** and 50 mg of **IV**.

Condensation of trifluoromethanesulfonamide with paraformaldehyde and oxamide in sulfuric acid. *a*. A mixture of 2 g (22 mmol) of oxamide and 1.5 g (50 mmol) of paraformaldehyde was added to 7.45 g (50 mmol) of trifluoromethanesulfonamide in 95% sulfuric acid. The mixture was stirred for 2 days

at room temperature, poured into a mixture of ice with sodium chloride, and extracted with diethyl ether with addition of propan-2-ol (3×70 ml), The extract was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue (7.5 g) was washed with diethyl ether–hexane (1:6). The undissolved material (~700 mg) contained (according to the NMR data) 75% of compound **VI** and 25% of **III**. By column chromatography we isolated 50 mg of **III**.

b. A mixture of 3 g (34 mmol) of oxamide, 10.15 g (68 mmol) of trifluoromethanesulfonamide, and 2.04 g (68 mmol) of paraformaldehyde in 120 ml of 92% sulfuric acid was stirred for 40 at room temperature. The mixture was then poured into a mixture of ice with sodium chloride, the precipitate (580 mg) was filtered off and washed with diethyl ether–hexane (1:6), and the undissolved material was recrystallized from methanol. The aqueous filtrate was extracted with ethyl acetate (4×80 ml), the extract was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue (9.5 g) was washed with diethyl ether–hexane (1:6). The undissolved residue (2.5 g) contained 80% of compound **III** and 20% of **IV**; it was subjected to column chromatography (diethyl ether–hexane, 3:1; diethyl ether–hexane–acetone, 2:3:1), and compound **III** thus isolated was recrystallized from methanol. Yield 2 g (24%).

c. A mixture of 0.5 g (5.7 mmol) of oxamide, 2.12 g (14.2 mmol) of trifluoromethanesulfonamide, and 0.43 g (14.2 mmol) of paraformaldehyde in 20 ml of concentrated sulfuric acid was stirred for 4–5 h at 60°C and for 1 h at 90–95°C. The mixture was cooled and poured into a mixture of ice with sodium chloride, the precipitate was filtered off, and the filtrate was extracted first with diethyl ether–hexane (1:6) to remove unreacted trifluoromethanesulfonamide and compound **VII** and then with diethyl ether–propan-2-ol to isolate compound **VI** (major product). The extracts were dried over $MgSO_4$, the solvent was removed, and crude product **VI** (0.56 g) was purified by recrystallization from propan-2-ol.

d. A mixture of 1 g (11.4 mmol) of oxamide and 5.08 g (34.1 mmol) of trifluoromethanesulfonamide in 50 ml of concentrated sulfuric acid was stirred at 60°C until it became homogeneous. The mixture was cooled to room temperature, and 1.02 g (34.1 mmol) of paraformaldehyde was added in small portions (the mixture thickened and was diluted with 20 ml of concentrated sulfuric acid). The mixture was then stirred for 10 h at room temperature, for 30 min at 60°C (until the precipitate dissolved completely), and for 2 h at 90°C, cooled, poured into ice water, and extracted with diethyl ether–propan-2-ol. The extract was dried over $MgSO_4$, the solvent was removed, and the residue, compound **V** (3.16 g), was purified by column chromatography using hexane–diethyl ether (6:1 to 1:3) as eluent.

Reaction of oxamide with *N*,*N*′-methylenedi(trifluoromethanesulfonamide) (VII) and paraformaldehyde. Paraformaldehyde, 0.1 g (3.2 mmol), was added to a solution of 0.14 g (1.6 mmol) of oxamide in 5 ml of concentrated sulfuric acid, the mixture was heated until it became homogeneous and cooled to room temperature, and 0.5 g (1.6 mmol) of compound **VII** was added under vigorous stirring. The mixture was heated for 2–3 h at 60–90°C until compound **VII** disappeared (TLC), cooled, poured into a mixture of ice with sodium chloride, and extracted with diethyl ether–propan-2-ol. The extract was dried over $MgSO_4$ and evaporated to obtain ~0.5 g of a colorless crystalline substance which contained (according to the NMR data), heterocyclic compound **VI** and a small impurity of trifluoromethanesulfonamide.

***N*-[(Trifluoromethylsulfonyl)aminomethyl]oxamide (III).** White crystals, mp 240–242°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.55 d (2H, NCH_2N, J = 6.4 Hz), 7.86 s and 8.16 s (1H each, $CONH_2$), 9.34 t (1H, NHCO, J = 5.6 Hz), 10.13 br.s (1H, $NHSO_2$). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 48.08 (NCN), 119.32 q (CF_3, J = 321.14 Hz), 160.65 s (NH_2C=O), 161.35 s (NHC=O). ^{19}F NMR spectrum (CD_3CN): δ_F –77.89 ppm. Found, %: C 19.50; H 2.71; F 23.31. $C_6H_6F_3N_3O_4S$. Calculated, %: C 19.28; H 2.43; F 22.87.

***N*,*N*′-Bis[(trifluoromethylsulfonyl)aminomethyl]oxamide (IV).** White crystals, mp 215–217°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.57 d (4H, NCH_2N, J = 6.23 Hz), 9.54 t (2H, NHCO, J = 6.35 Hz), 10.18 br.s (2H, $NHSO_2$). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 48.05 (NCN), 119.42 q (CF_3, J = 321.8 Hz), 159.63 s (C=O). ^{19}F NMR spectrum (CD_3CN): δ_F –77.89 ppm. Found, %: C 18.00; H 2.56; F 27.77; N 12.73. $C_6H_8F_6N_4O_6S_2$. Calculated, %: C 17.57; H 1.97; F 27.78; N 13.66.

Bis[(trifluoromethylsulfonyl)aminomethyl] ethanedioate (V). Colorless needles, mp 102–103°C. IR spectrum (KBr), ν, cm^{-1}: 3314, 3071, 2999, 2970, 1722, 1426, 1378, 1270, 1231, 1202, 1154, 1115, 923, 898, 679, 607, 507, 404. Raman spectrum, ν, cm^{-1}: 3312, 2997, 2970, 1672, 1423, 1371, 1227, 1152, 909, 764, 566, 390, 335, 313. ^{1}H NMR spectrum

(DMSO-d_6), δ, ppm: 3.90 s (4H, CH_2), 10.0 br.s (1H, NH), 12.9 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 44.03 (NCO), 119.41 q (CF_3, J = 321.8 Hz), 169.72 s (CO). Found, %: C 18.05; H 1.49; F 27.18; N 6.49; S 15.57. $C_5H_5F_3N_2O_5S$. Calculated, %: C 17.48; H 1.47; F 27.65; N 6.80; S 15.56.

***N*-(4,5-Dioxo-1,3-oxazolidin-3-ylmethyl)trifluoromethanesulfonamide (VI).** Colorless crystals, mp 198–200°C (sublimes). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 4.86 s (2H, NCH_2N), 5.45 s (2H, OCH_2N), 6.64 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 49.88 (NCN), 75.93 (NCO), 119.36 q (CF_3, J = 321.6 Hz), 152.05, 159.22 s (CO). ^{19}F NMR spectrum (DMSO-d_6): δ_F –77.99 ppm. Mass spectrum, m/z (I_{rel}, %): 262 (2) $[M]^+$, 148 (55) $[CF_3SO_2NH]^+$, 133 (100) $[CF_3SO_2]^+$, 92 (28) $[SO_2NCH_2]^+$, 69 (6) $[CF_3]^+$. High-resolution mass spectrum: found for $[M + Na]^+$: m/z 525.0347; calculated for $C_5H_5F_3N_2O_5SNa$: 525.0353. Found, %: C 22.70; H 1.72; N 10.70; S 12.08. $C_5H_5F_3N_2O_5S$. Calculated, %: C 22.91; H 1.92; N 10.69; S 12.23.

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