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Synthesis and Structure of 4-Trifluoromethylsulfonamidotrichloroethyl-5-chloropyrazoles

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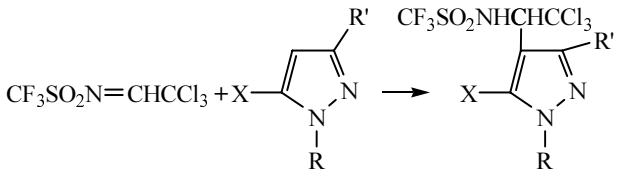
Abstract—Reactions of trifluoromethanesulfonic acid N-(2,2,2-trichloroethylidene)amide with 1,3-dialkyl-5-chloropyrazoles and 1-phenyl-3-methylpyrazole afforded 4-(amidotrichloroethyl)-substituted pyrazole derivatives. 4-Chloropyrazoles were not involved into this process. The structure of compounds synthesized was studied by means of IR and NMR spectroscopy. The presence of intra- and intermolecular hydrogen bonds was revealed by a decrease in the absorption frequencies and a complicated form of ν(NH) and $\nu_{as}(SO_2)$ absorption bands in the IR spectra, and also in splitting of signals in ^1H and ^{13}C NMR spectra.

In the framework of development of convenient synthetic approaches to biologically active azole derivatives and in continuation of systematic investigation of reactivity, in particular, the activity in amidoalkylation of acyl-, arene-, and perfluoroalkylsulfonyl imines of polyhaloaldehydes [1–3] we report here on the study of reactions of trifluoromethanesulfonic and 4-chlorobenzenesulfonic acids *N*-(2,2,2-trichloroethylidene)-amides with N-substituted 4- and 5-chloropyrazoles. The reactions of pyrazoles amidoalkylation are virtually unstudied [1] except for published examples of trichloroamidoethylation of 1-alkyl(aryl)-3-alkyl(phenyl)-pyrazol-5-ones with ethoxycarbonyl-, acetyl-, and benzoyl imines of chloroal [4] and reactions of 1,3,5-trimethylpyrazole and 1-heptyl-3-methylpyrazol-5-one with chloral 4-chlorophenylsulfonyl imine [2]. No studies were as yet performed concerning the amidoalkylation of halopyrazoles that had become accessible when we had developed their preparation from halovinyl ketones and alkylhydrazines or 1,1-dimethylhydrazine [5, 6]. At the same time these processes permit preparation of compounds combining in their structure pharmacophor groups: pyrazole ring, amido, polyhalomethyl, sulfonyl groups etc.

On the other hand we deemed it important to reveal the difference in the amidoalkylating activity of chloral arylsulfonyl-and trifluoromethanesulfonyl imines whose convenient preparation methods from *N,N*-dichlorosulfonamides and trichloroethylene we had developed formerly [1, 3]. The reaction of trifluoromethanesulfonic acid *N,N*-dichloroamide with 1,2-polychloroethenes is nowadays the only possible preparation method for highly electrophilic polychloroaldehyde imines containing a trifluoromethylsulfonyl group [1, 3]. The high activity of these compounds, promising for the synthesis of a number of functionalized derivatives of arenesulfonamides and trifluoromethanesulfonamides, was demonstrated formerly by examples of their reactions with O-, N-nucleophiles, and in the process of C-amidoalkylation of aromatic and heterocyclic compounds [1, 3, 7].

We established in the present study that trifluoromethanesulfonic acid, *N*-(2,2,2-trichloroethylidene)amide (**I**) reacted at room temperature without catalysts with 1,3-dialkyl-5-chloropyrazoles **IIa–IIc** affording in plausible yields the corresponding 4-amidotrichloroethyl-substituted azole derivatives **IIIa–IIIc**. The reaction of imine **I** with 1-phenyl-3-methylpyrazole (**IId**) resulted specifically in compound **IIId**.



X = Cl, R = R' = Me (**a**); R = Et, R' = Me (**b**); R = Me, R' = *i*-Pr (**c**); X = H, R = Ph, R' = Me (**d**).

We failed to bring into reaction with imine **I** 1-Ethyl-3-propyl- (**IV**) and 1-heptyl-3-methyl-4-chloropyrazole.

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The attempt to activate the process by heating or use of Lewis acids resulted only in tarring of the reaction mixture. This fact is apparently due to the reduced electron density in the position *5* of the 4-chloropyrazole ring as compared to the position *4* in 5-chloropyrazole [8, 9].

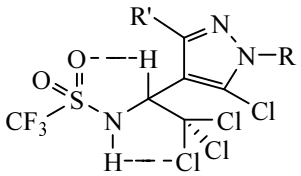
Arenesulfonic acids trichloroethylideneamides are less active in reactions with pyrazoles. For instance, chloral 4-chlorophenylsulfonyl imine reacted with 1,3,5-trimethylpyrazole only in the presence of $BF_3 \cdot OEt_2$ or at prolonged heating of the reaction mixture at 80°C [2].

We failed to develop proper conditions for involving chloral 4-chlorophenylsulfonyl imine into reaction either with 5-chloropyrazoles **IIa–IId** or with the N-substituted 4-chloropyrazoles both without catalysts and in the presence of Lewis acids. This is apparently due to less electron-withdrawing character and larger size of the arenesulfonyl substituent compared to the triflate one resulting in reduced electrophilicity of the azomethine group and in decreased sterical availability of the reaction sites.

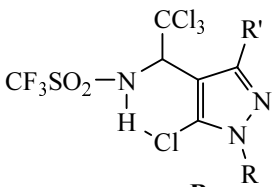
The structure of compounds synthesized was proved by their IR and NMR spectra. It was found that 4-amidotrichloroethyl-substituted pyrazoles **IIIa–IIId** are capable of forming in chlorohydrocarbon solutions strong intermolecular and intramolecular hydrogen bond leading to complications in the IR and NMR spectra of compounds **IIIa–IIId**.

Thus in the IR spectra of compounds **IIIa–IIId** in $CHCl_3$ solution (*C* 0.08–0.10 mol l^{-1}) two components of ν(NH) are present of very low frequencies (~3150 and ~3350 cm^{-1}) indicating associated state of molecules with the NH groups involvement. Therewith the parallel changes in the stretching vibration band with the lowest frequency ν(NH) (~3150 cm^{-1}) and the low-frequency component of the doublet $\nu_{as}(SO_2)$ (1375, 1382 cm^{-1}) both sensitive to dilution and heating permit to assign these bands to occurrence of intermolecular hydrogen bonds of S=O···H–N type. At the concentration of about $2 \cdot 10^{-4}$ mol l^{-1} (cell thickness 50 mm) in the IR spectra of compounds **IIIa–IIId** the absorption at 3150 and 1375 cm^{-1} corresponding to intermolecular hydrogen bonds virtually disappeared. In the IR spectrum the high-frequency component $\nu_{as}(SO_2)$ 1382 cm^{-1} is observed and also sufficiently low-frequency second band ν(NH) ~3350 cm^{-1} of complicated pattern.

The steady low value of frequency ν(NH) and the asymmetrical form of the band in question at 3350 cm^{-1} (shoulder at 3390 cm^{-1}) even in very diluted solutions evidence the possibility of intramolecular hydrogen bonds formation in the molecules of compounds **IIIa–IIId** involving the NH groups. The most probable is the formation of a five-membered quasicycle **A** due to the intramolecular hydrogen bond including NH···Cl–C (CCl_3) groups. Just this type of H-bonding we formerly had found in similar in structure N-2,2,2-trichloroethyl-substituted trifluoromethanesulfonamides [10]. Actually, at heating the solutions of amidoalkylated pyrazoles **IIIa–IIId** in pentachloroethane and chlorobenzene we observed typical spectral changes suggesting that they corresponded to degradation of the intramolecular hydrogen bonds NH···Cl: the intensity of the components in the complex ν(NH) band underwent redistribution in favor of the high-frequency component, and the form of the ν(C–Cl) band became simpler. For trifluoromethanesulfonamides **IIIa–IIIc** the possibility should be taken into account of intramolecular hydrogen bonds formation of the type NH···Cl–C=C (of pyrazole ring) **B**.



A



B

The more detailed investigation of the existing types of the intramolecular hydrogen bonds including quantum-chemical calculations and graphical procedures for processing the complex bands of associates we plan to perform later and publish the results in the next communication.

The presence of strong intermolecular hydrogen bonds in the solutions of amidoalkylated pyrazoles in solvents of low polarity leads to certain singular features in the ^1H and ^{13}C NMR. For instance, at registering the ^1H NMR spectra of compounds **IIIa** and **IIIb** in $CDCl_3$ at room temperature the signal from the methyl groups in position *3* of pyrazole rings appeared as two broadened singlets with the integral intensity ratio ~1:2.5. The fragment NH–CH of amidoalkylated substituent appeared as two groups of signals: two doublets in the downfield region (6.03–6.36 ppm) belonging to proton in the NH group, and two doublets at 5.18–5.27 ppm (CH). The ratio of the integral intensities of the signals within each group of doublets is the same as with the methyl group signals and equals to 1:2.5. Likewise, in the ^{13}C NMR spectra the resonances from groups 3-CH_3, CCl_3, CH and C atoms of the pyrazole ring appear as two sets of signals. On heating the solution to 50°C or at registering the spectra in a highly polar solvent (DMSO) the ^1H NMR

spectra appear in a pattern classical for amidotrichloroethyl-substituted arenes and hetarenes [3]: two doublets corresponding to the NH–CH fragment (J_{NH-CH} 10–11 Hz) (or in event of deuteroexchange two broadened singlet or just CH singlet), and the signals of protons from the other substituents with the appropriate integral intensities; in the ^{13}C NMR spectra an only signal corresponds to each carbon atom.

In compound **IIIc** a chemical nonequivalence of the methyl groups belonging to the isopropyl substituents was observed as showed the presence of two doublets in ^1H NMR spectrum and of two signals in the ^{13}C NMR spectrum. This is apparently due to hampered rotation of the isopropyl group around the C^3–CH bond caused by strong steric hindrances created by trichloroethyl or trifluoromethenesulfonamide fragments.

The synthesized compounds **IIIa–IIId** are colorless or lightly colored crystalline substances soluble in organic solvents and alkali, insoluble in water.

Thus the chloral trifluoromethylsulfonyl imine unlike its aromatic analog reacts with N-(alkyl)-substituted 5-chloropyrazoles and *N*-phenyl-3-methylpyrazole giving 4-amidotrichloroethyl-substituted pyrazoles. 1-Ethyl-3-propyl- and 1-heptyl-3-methyl-4-chloropyrazoles were not involved into analogous reactions due to reduced electron density in the position *5* of the pyrazole ring.

EXPERIMENTAL

^1H, ^{13}C, and ^{19}F NMR spectra were registered on a spectrometer Bruker DPX-400 (at 400.13, 101.61, and 376.3 MHz respectively) from solutions in $CDCl_3$. The chemical shifts were measured from internal references TMS (^1H and ^{13}C) and CCl_3F (^{19}F) with an accuracy of 0.01 ppm. The values of the coupling constants (J_{HH} and J_{CF}) were determined with an accuracy of 0.1 Hz. A mass spectrum was obtained on a mass spectrometer Shimadzu GC-17/ GCMS-QP5050-1. IR spectra were recorded on a double-beam spectrophotometer Specord 75IR from KBr pellets and solutions in $CHCl_3$, C_2HCl_5, and C_6H_5Cl. The dependence of the spectra on concentration was measured in cells of the thickness from 0.05 to 50 mm. The absorption bands of vibrations ν(NH), ν(SO_2), and ν(CCl) were registered at a scale 100 cm^{-1}/100 mm. In the experiments anhydrous solvents were used. Temperature dependence was measured with the use of a device manufactured by Karl Zeiss Jena Co equipped with a graduated thermocouple.

Pyrazoles were prepared by known methods: **IIa**, **IIc** [5], **IIb** [6], **IId** [11], **IV** and **V** [12].

1,3-Dimethyl-4-[*N*-(2,2,2-trichloroethyl)trifluoromethylsulfonamido]-5-chloropyrazole (IIIa). To a reaction mixture obtained from 2.18 g (0.01 mol) of trifluoromethanesulfonic acid *N,N*-dichloroamide and 6 ml of freshly distilled anhydrous trichloroethylene as described in [3] cooled to 0°C was added dropwise while stirring 1.3 g (0.01 mol) of 1,3-dimethyl-5-chloropyrazole. The temperature was raised to ambient, and the mixture was kept in a closed reactor for 7 days. Then the solvent was evaporated in a vacuum, the residual oily substance was poured into a cold hexane, the separated precipitate was filtered off and recrystallized from hexane. The product was additionally purified by dissolving in 15 ml of 10% water solution of NaOH, the solution was filtered, and the filtrate was acidified with 10% HCl solution till the end of precipitation. The precipitate was separated, washed with water, and dried. Yield 2.45 g (60%), mp 123–125°C. IR spectrum (KBr), ν, cm^{-1}: 1140, 1195, 1230, 1380 (CF_3SO_2), 3270 (NH). ^1H NMR spectrum, δ, ppm: 2.30 s (0.9H, C^3–CH_3) and 2.41 s (2.1H, C^3–CH_3), 3.81 s (3H, N^1–CH_3), 5.18 d (0.7H, CH–CCl_3, $^3J_{CH-NH}$ 10.3 Hz) and 5.26 d (0.3H, CH–CCl_3, $^3J_{CH-NH}$ 8.2 Hz), 6.03 d (0.3H, NH, $^3J_{CH-NH}$ 8.2 Hz) and 6.30 d (0.7H, NH, $^3J_{CH-NH}$ 10.3 Hz). ^1H NMR spectrum (50°C), δ, ppm: 2.32 br.s (3H, C^3–CH_3), 3.81 s (3H, N^1–CH_3), 5.20 br.s (1H, CH–CCl_3), 6.30 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 12.86 and 15.08 (C^3–$\underline{CH}_3$), 36.33 (N^1–CH_3), 65.80 and 66.22 ($\underline{CH}$–CCl_3), 100.86 and 101.04 (CCl_3), 108.63 and 108.79 (C^4), 114.25, 117.44, 120.63, 123.81 (CF_3, $^1J_{C-F}$ 320.7 Hz), 125.58 and 129.52 (C^5), 145.54 and 148.54 (C^3). ^{19}F, δ, ppm: –77.29 C (CF_3). Mass spectrum, *m/z* (I_{rel}, %): 409 (0.4) [*M*], 292 (100) [*M* – CCl_3], 157 (31.3) [*M* – CF_3SO_2H – CCl_3], 69 (63.3) [CF_3], 66 (12.9), 42 (12.7). Found, %: C 22.86; H 1.90; Cl 35.52; N 9.95; S 7.78. $C_8H_8Cl_4F_3N_3O_2S$. Calculated, %: C 23.59; H 1.98; Cl 34.38; N 10.32; S 7.86.

1-Ethyl-3-methyl-4-[*N*-(2,2,2-trichloroethyl)-trifluoromethylsulfonamido]-5-chloropyrazole (IIIb) was prepared in the same way as **IIIa**. Yield 2.0 g (48%), mp 103–106°C. IR spectrum (KBr), ν, cm^{-1}: 1140, 1190, 1220, 1375 (CF_3SO_2), 2950, 2990 (CH), 3280 (NH). ^1H NMR spectrum, δ, ppm: 1.40 t (3H, CH_3, Et, ^3J 7.2 Hz), 2.30 s (2.1H, C^3–CH_3) and 2.42 s (0.9H, C^3–CH_3), 4.15 q (2H, CH_2, Et, ^3J 7.2 Hz), 5.18 d (0.7H, CH–CCl_3, $^3J_{NH-CH}$ 9.7 Hz) and 5.27 br.s (0.3H, CH), 6.15 br.s (0.3H, NH) and 6.36 d (0.7H, NH, $^3J_{NH-CH}$ 9.7 Hz). ^1H NMR spectrum (50°C), δ, ppm: 1.41 t (3H, CH_3, Et, ^3J 7.2 Hz), 2.33 br.s (3H, C^3–CH_3), 4.14 q (2H, CH_2, Et, ^3J 7.2 Hz), 5.23 br.s (1H, CH–CCl_3), 6.26 br.s

(1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.13 and 15.38 (C^{3}–$\underline{CH}_3$), 14.75 (CH_3, Et), 44.67 (CH_2, Et), 66.00 and 66.31 ($\underline{CH}$–CCl_3), 101.21 (CCl_3), 108.66 (C^{4}), 114.41, 117.60, 120.79. 123.98 (CF_3, $^{1}J_{C–F}$ 320.9 Hz), 124.62 (C^{5}), 148.77 (C^{3}). Found, %: C 24.78; H 2.32; Cl 32.88; N 9.78; S 7.66. $C_9H_{10}Cl_4F_3N_3O_2S$. Calculated, %: C 25.55; H 2.38; Cl 33.52; N 9.93; S 7.58.

1-Methyl-3-isopropyl-4-[*N*-(2,2,2-trichloroethyl)-trifluoromethylsulfonamido]-5-chloropyrazole (IIIc) was prepared in the same way as **IIIa**. Yield 3.5 g (80%), mp 164°C. IR spectrum (KBr), ν, cm^{-1}: 1145, 1195, 1225, 1380 (CF_3SO_2), 2980 (CH), 3300 (NH). ^{1}H NMR spectrum, δ, ppm: 1.18 d (3H, CH_3, *i*-Pr, ^{3}J 6.7 Hz), 1.30 d (3H, CH_3, *i*-Pr, ^{3}J 6.8 Hz), 3.05–3.13 m (1H, CH, *i*-Pr), 3.82 s (3H, N^{1}–CH_3), 5.28 d (1H, CH–CCl_3, ^{3}J 10.4 Hz), 6.35 d (1H, NH, ^{3}J 10.4 Hz). ^{13}C NMR spectrum, δ, ppm: 21.01 (CH_3, *i*-Pr), 23.68 (CH_3, *i*-Pr), 26.48 (CH, *i*-Pr), 36.70 (N^{1}–CH_3), 65.40 and 66.56 ($\underline{CH}$–CCl_3), 101.05 (CCl_3), 106.95 (C^{4}), 117.57, 120.76, 123.95, 124.91 (CF_3, $^{1}J_{C–F}$ 320.6 Hz), 124.91 (C^{5}), 157.58 (C^{3}). Found, %: C 27.05; H 2.69; Cl 31.72; N 9.50; S 7.25. $C_{10}H_{12}Cl_4F_3N_3O_2S$. Calculated, %: C 27.48; H 2.77; Cl 32.44; N 9.61; S 7.33.

1-Phenyl-3-methyl-4-[N-(2,2,2-trichloroethyl)-trifluoromethylsulfonamido]pyrazole (IIId) was prepared in the same way as **IIIa.** Yield 2.92 g (67%), mp 96–98°C. IR spectrum (KBr), ν, cm^{-1}: 1140, 1195, 1225, 1385 (CF_3SO_2), 2970 (CH), 3295 br.s (NH). ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 5.24 d (1H, CH, $^{3}J_{CH–NH}$ 9.9 Hz), 6.16 d, (1H, NH, $^{3}J_{CH–NH}$ 9.9 Hz), 7.30 t (1H), 7.44 t (2H), 7.63 d (2H, C_6H_5), 8.05 s (1H, C^{5}–H). ^{13}C NMR spectrum, δ, ppm: 12.19 (CH_3), 65.52 ($\underline{CH}$–CCl_3), 100.77 (CCl_3), 114.44, 117.63, 120.82, 124.01 (CF_3, $^{1}J_{C–F}$ 320.9 Hz), 115.64 (C^{4}), 119.26 ($C^{7,11}$), 125.93 (C^{5}), 127.14 (C^{9}), 129.65 ($C^{8,10}$), 139.54 (C^{6}), 149.75 (C^{3}). Found, %: C 34.95; H 2.57; Cl 23.72; N 9.58; S 7.42. $C_{13}H_{11}Cl_3F_3N_3O_2S$. Calculated, %: C 35.76; H 2.54; Cl 24.36; N 9.62; S 7.34.

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