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Formation of 2,6-Diphenyl-1,4-bis(trifluoromethylsulfonyl)piperazine in the Reaction of Styrene with Trifluoromethylsulfonylnitrene

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Abstract—The reaction of styrene with trifluoromethylsulfonylnitrene generated in the system *t*-BuOCl–NaI led to the formation of trifluoro-*N*-[2-phenyl-2-(trifluoromethylsulfonylamino)ethyl]methanesulfonamide $CF_3SO_2NHCH(Ph)CH_2NHSO_2CF_3$, 2-iodo-1-phenylethanol, and heterocyclization product, 2,6-diphenyl-1,4-(trifluoromethylsulfonyl)piperazine. The latter is regioisomeric to 2,5-diphenyl-1,4-(trifluoromethylsulfonyl)-piperazine obtained previously by analogous reaction in the system *t*-BuOCl–NaI·2H_2O.

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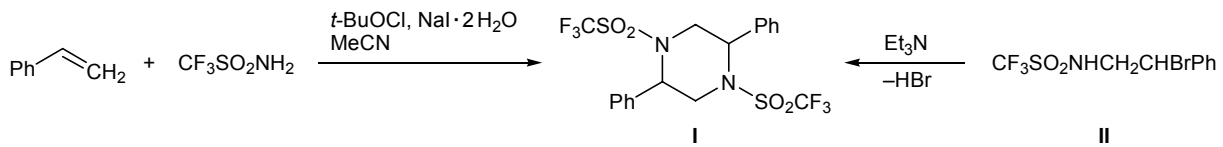
We recently studied the reaction of styrene with trifluoromethylsulfonylnitrene CF_3SO_2N**:** generated from trifluoromethanesulfonamide in the system *t*-BuOCl–NaI·2H_2O and obtained 2,5-diphenyl-1,4-bis(trifluoromethylsulfonyl)piperazine (**I**) together with other products. The structure of compound **I** was determined by X-ray analysis, and a probable mechanism of its formation was proposed [1]. Unexpectedly, compound **I** was also obtained by dehydrobromination of *N*-(2-bromo-2-phenylethyl)trifluoromethanesulfonamide (**II**) by the action of triethylamine [2] (Scheme 1).

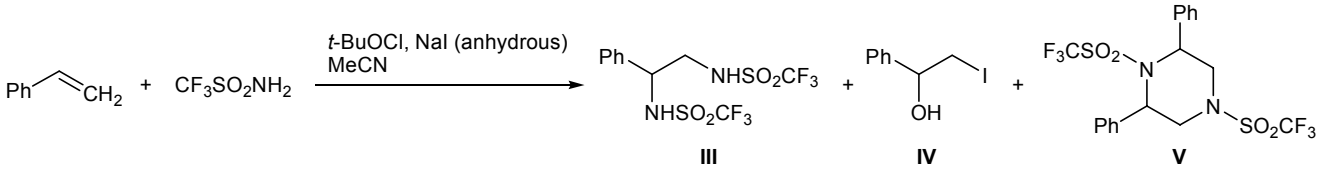
Compound **I** was not the major product in the reaction of styrene with trifluoromethylsulfonylnitrene; apart from **I**, trifluoro-*N*-[2-phenyl-2-(trifluoromethylsulfonylamino)ethyl]methanesulfonamide (**III**) and 2-iodo-1-phenylethanol (**IV**) were formed [1]. With a view to obtain the corresponding aziridine [3] we modified the system *t*-BuOCl–NaI·2H_2O and used anhydrous sodium iodide. The reaction occurred in a way similar to that reported previously [1], i.e., with formation of compounds **III** and **IV** as products of opening of the aziridine ring in the primary addition product of trifluoromethylsulfonylnitrene to styrene. However, the third isolated compound (**V**) differed from piperazine **I** obtained previously. Its ^{1}H NMR spectrum contained signals from aromatic protons and an *ABX* spin pattern, but the H_A signal was displaced by 0.3 ppm upfield, and the H_B and H_X signals were located in a weaker field (by 0.2 and 0.1 ppm, respectively) relative to the corresponding signals in the spectrum of **I**. In the ^{13}C NMR spectrum of compound **V** the CH carbon atom resonated in a stronger field (by 5 ppm), and the most important difference from the spectrum of **I** was the presence of two signals assignable to CF_3 group. Correspondingly, two different signals were observed in the ^{19}F NMR spectrum of **V**. The above data allowed us to assign compound **V** the structure of 2,6-diphenyl-1,4-bis(trifluoromethylsulfonyl)piperazine (Scheme 2).

Apart from the presence of signals from two magnetically nonequivalent trifluoromethyl groups in the NMR spectra, the unsymmetrical structure of compound **V** was confirmed by the mass spectral data. The exact molecular weights of **I** and **V** coincide with each

Scheme 1.



Scheme 2.

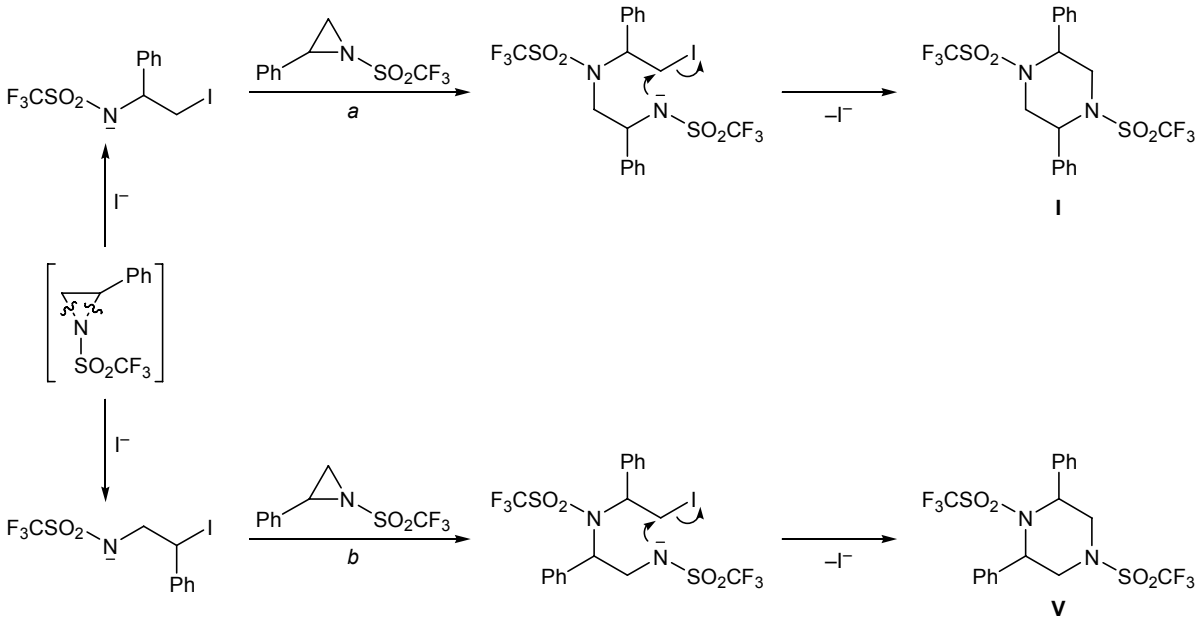


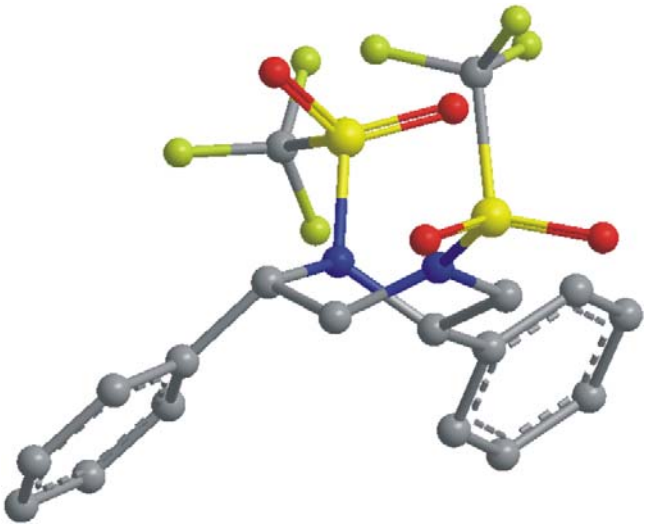
other, i.e., these compounds are isomers. Fragmentation patterns of the molecular ions of **I** and **V** are also similar, but the mass spectrum of **V** contained a fragment ion peak with *m*/*z* 194 which was absent in the spectrum of compound **I**. This ion has the structure $[PhCH{=}N{=}CHPh]^+$; obviously, it cannot be formed from isomer **I**.

The mechanism of formation of compound **I** in the reaction of styrene with trifluoromethylsulfonylnitrene involves double opening of the three-membered ring in intermediate 1-(trifluoromethylsulfonyl)-2-phenylaziridine [1] (Scheme 3). If cleavage of the aziridine ring occurs each time via dissociation of the N–CH_2 bond [4–6] and nucleophile addition to the unsubstituted carbon atom (path *a* in Scheme 3), symmetric piperazine **I** is formed [1]. If cleavage of the N–CH(Ph) bond occurs at one step (path *b*), as in the reaction of structurally related 1-(4-methylphenylsulfonyl)-2-phenylaziridine with Me_3SiN_3 [6], isomeric unsymmetrically substituted piperazine **V** is obtained.

Analysis of recently published data on reactions of *N*-sulfonylaziridines with nucleophiles [4–21] showed that the main factors determining the reaction direction are electronic properties of the substituent in the aziridine ring and the nature of nucleophile. Steric factor and reaction conditions also play a definite role [7]. For example, 2-aryl-1-(4-methylphenylsulfonyl)aziridines react with C-, O-, S-, and Hlg-nucleophiles either exclusively or preferentially at the N–C^2 bond [8–10, 14–17], whereas the N–C^3 bond is cleaved in 2-alkyl-1-(4-methylphenylsulfonyl)aziridines [18–21]. An exception is the reaction of 1-(4-methylphenylsulfonyl)-2-phenylaziridine with benzenethiol [17], which afforded isomeric products resulting from opening of the aziridine ring at the N–C^2 and N–C^3 bonds at a ratio of 1 : 1. In the reactions with indium halides, the above ratio of regioisomers decreases as the size of the halogen atom rises [19]. The reaction with participation of $NaI \cdot 2H_2O$ (path *a* in Scheme 3) involves opening of the aziridine ring by the action of a large solvated iodide ion and sterically hindered nitrogen-centered nucleophile $[CF_3SO_2NCH(Ph)CH_2I]^-$, which is likely to occur at the N–C^3 bond at each step; as a result, isomer **I** is formed. In the reaction with anhydrous sodium iodide (path *b*), attack by less bulky unsolvated iodide ion can be directed at C^2 to produce isomeric anion $[CF_3SO_2NCH_2CH(Ph)I]^-$ and then isomer **V**.

Scheme 3.





2,5-*Twist* conformation of the piperazine ring in molecule **V**, optimized by the B3LYP/6-311G** method.

According to the X-ray diffraction data and quantum-chemical calculations, the piperazine ring in molecule **I** has 2,5-*twist* rather than *chair* conformation due to the presence of two neighboring bulky groups [1]. Even stronger steric strain might be expected for compound **V** where bulky substituents are attached to three contiguous atoms. In fact, B3LYP/6-311G** calculations (see figure) also predicted 2,5-*twist* conformation of the piperazine ring in isomer **V**, the total energy of **V** being higher by 6.1 kcal/mol than that of **I**.

As we noted previously [1], elemental analysis and routine NMR spectroscopy cannot distinguish between aziridines and piperazines formed by their dimerization [22]; for this purpose, X-ray analysis or at least measurement of direct carbon–proton coupling constants $^1J_{CH}$ is necessary. The failure to isolate aziridines in the reaction of styrene with trifluoromethylsulfonylnitrene in this and previous [1] works prompted us to reproduce the syntheses of aziridines via reactions of styrene with methanesulfonamide and 4-methylbenzenesulfonamide, rigorously following the conditions reported in [3].

In the ^{13}C NMR spectrum of the crude product obtained in the reaction of styrene with 4-methylbenzenesulfonamide we observed signals assignable to the target aziridine (δ_C 35.86 and 41.18 ppm), but its amount was estimated at a trace level (~5%). The major signals were observed at δ_C 30.53 and 51.29 ppm, and they had similar intensities and were assigned to CH and CH_2 carbon atoms. In the proton-coupled ^{13}C NMR spectrum, the CH signal was split into a doublet with $^1J_{CH}$ = 154.4 Hz, and the CH_2 signal was split into 8 lines due to coupling with diastereotopic methylene protons ($^1J_{CH}$ = 142.2, 144.0 Hz) and CH proton ($^2J_{CH}$ = 4.1 Hz). The observed direct coupling constants $^1J_{CH}$ are much smaller than those typical of aziridines (>170 Hz [23]). Likewise, the ^{13}C NMR spectrum of the crude product obtained by aziridination of styrene with methanesulfonamide according to [3] contained multiplet signals with coupling constants $^1J_{CH}$ of 155–157 Hz. These findings indicate the necessity of more thorough examination of the conditions for aziridination of alkenes in the system sulfonamide–*tert*-butyl hypochlorite–sodium iodide.

EXPERIMENTAL

The IR spectrum of compound **V** was recorded on a Bruker Vertex 70 spectrometer with Fourier transform. The NMR spectra were measured from solutions in CD_3CN on a Bruker DPX 400 spectrometer at 400 (^1H), 100 (^{13}C), and 376 MHz (^{19}F); the chemical shifts were determined relative to tetramethylsilane (^1H, ^{13}C) and CCl_3F (^{19}F). The mass spectra (electron impact, 70 eV) were obtained on a GC-MS TRACE DSQ II instrument (Thermo Fisher Scientific GmbH) with direct sample admission into the ion source. The high-resolution mass spectrum was recorded on a Waters Micromass Q-TOF$_{micro}$ spectrometer (positive electrospray); a sample was introduced using a Harvard syringe pump (20 μl/min); capillary entrance voltage 3.2 kV, cone voltage 20–25 V. The elemental compositions were determined from the precise molecular weights with an accuracy of <3 ppm; H_3PO_4 was used as reference. The progress of reactions and separation of products were monitored by TLC on silica gel 60 F-254 plates using hexane–diethyl ether (1:2) as eluent.

Reaction of trifluoromethylsulfonylnitrene with styrene. *tert*-Butyl hypochlorite, 6.5 g (0.06 mmol), was added dropwise to a solution of 3 g (0.02 mmol) of trifluoromethanesulfonamide, 2.09 g (0.02 mmol) of styrene, and 9 g (0.06 mmol) of anhydrous sodium iodide in 120 ml of acetonitrile. The mixture was stirred for 12 h at –10°C in the dark under nitrogen, treated with 120 ml of a 0.3 M solution of $Na_2S_2O_3$, and extracted with a mixture of acetonitrile and ethyl acetate. The extract was dried over $CaCl_2$, the solvent was distilled under reduced pressure, and the residue, ~4.5 g of a liquid tarry material, was subjected to column chromatography on silica gel (grain size 0.063–0.200 mm). The column was eluted with hexane to

remove tars and separate a mixture of compounds **IV** and **V** from compound **III**. Compounds **IV** and **V** were separated by repeated chromatography on silica gel (grain size 0.015–0.040 mm) using hexane as eluent.

Trifluoro-*N*-[2-phenyl-2-(trifluoromethylsulfonylamino)ethyl]methanesulfonamide (III). Yield 2 g (50%), colorless crystals. The melting points and IR and NMR spectra of **III** coincided with the data reported by us previously [1].

2-Iodo-1-phenylethanol (IV) was isolated as an oily substance with crystalline inclusions. Its NMR spectra were identical to those reported previously [1].

2,6-Diphenyl-1,4-bis(trifluoromethylsulfonyl)-piperazine (V). Yield 0.4 g (8%), colorless crystals, mp 199–202°C (from hexane). IR spectrum, ν, cm^{-1}: 3059, 3021, 1955, 1605, 1501, 1470, 1453, 1395, 1375, 1229, 1176, 1151, 1051, 956, 875, 742, 709, 692, 674, 605. ^{1}H NMR spectrum, δ, ppm: 3.73 d.d (1H, CH_2, J = 13.8, 3.6 Hz), 4.62 d (1H, CH_2, J = 13.8 Hz), 5.42 d (1H, PhC**H**, J = 3.6 Hz), 7.05 m (3H, *m*-H, *p*-H), 7.25 m (2H, *o*-H). ^{13}C NMR spectrum, δ_C, ppm: 48.47 (CH_2, $^1J_{CH}$ = 145.57 Hz), 56.5 (CH, $^1J_{CH}$ = 141.89 Hz), 121.05 q (1-CF_3, J_{CF} = 324.22 Hz), 121.14 q (4-CF_3, J_{CF} = 322.38 Hz), 128.41 (C^o), 128.78 (C^p), 128.96 (C^m), 136.58 (C^i). ^{19}F NMR spectrum, δ_F, ppm: –76.11 (4-CF_3), –73.98 (1-CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 502 (16) $[M]^+$, 369 (8) $[M - CF_3SO_2]^+$, 235 (20) $[369 - CF_3SO_2H]^+$, 194 (13) $[(PhCH)_2N]^+$, 117 (14) $[194 - Ph]^+$, 104 (85) $[PhCHN]^+$, 91 (28) $[PhCH_2]^+$, 77 (16) $[Ph]^+$, 69 (37) $[CF_3]^+$, 41 (100) $[C_2H_3N]^+$. Found: *m*/*z* 502.0461 $[M]^+$. $C_{18}H_{16}F_6N_2O_4S_2$. Calculated: *M* 502.0450.

Reactions of methylsulfonylnitrene and 4-methylphenylsulfonylnitrene with styrene. *tert*-Butyl hypochlorite, 3.24 g (0.03 mmol), was added dropwise to a solution of 0.01 mmol of methanesulfonamide or 4-methylbenzenesulfonamide, 1.04 g (0.01 mmol) of styrene, and 5.55 g (0.03 mmol) of sodium iodide in 100 ml of acetonitrile. The mixture was stirred for 12 h at room temperature in the dark under nitrogen, treated with 100 ml of a 0.3 M solution of $Na_2S_2O_3$, and extracted with chloroform. The extract was dried over $CaCl_2$, the solvent was distilled off under reduced pressure, and the residue, ~3 g of a liquid tarry material, was purified by column chromatography on silica gel (grain size 0.063–0.200 mm) using hexane as eluent. The products were analyzed by NMR spectroscopy.

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