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New Synthetic Approach to Phenylmethanesulfonamide Derivatives on the Basis of Phenyl-*N*-(2,2,2-trichloroethylidene)-methanesulfonamide

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Abstract—The reaction of *N*,*N*-dichlorophenylmethanesulfonamide with trichloroethylene gave a new representative of highly electrophilic *N*-sulfonyl-substituted polyhalogenated aldehyde imines, phenyl-*N*-(2,2,2-trichloroethylidene)methanesulfonamide. High reactivity of the product was demonstrated by alkylation of toluene, anisole, thiophene, and 2-chlorothiophene.

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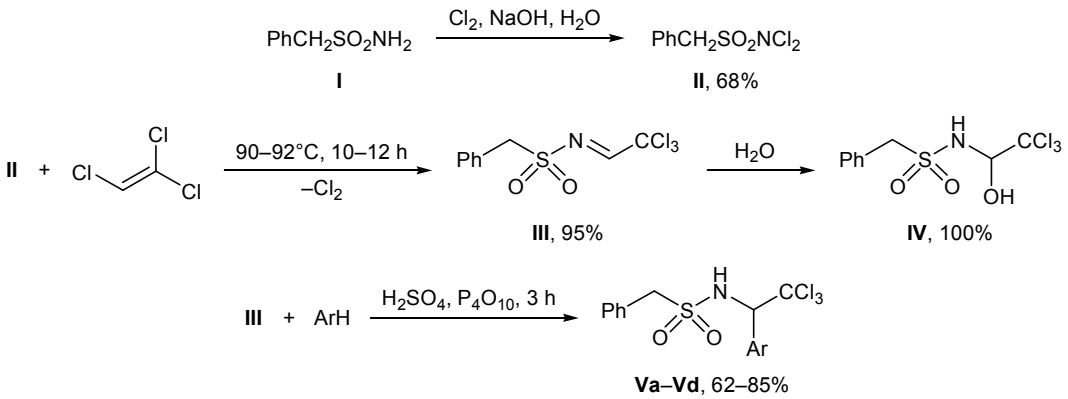
N-(Polyhaloalkylidene) and *N*-(polyhaloalkyl) sulfonamides are convenient reagents for the synthesis of various sulfonamide derivatives, such as *N*-sulfonyl amino acids [1], amidines [2], and heterocyclic compounds [3–7]. One of the most efficient procedures for the preparation of *N*-sulfonyl-substituted polyhaloaldehyde imines is based on reaction of *N*,*N*-dichloro sulfonamides with 1,2-polyhaloethenes [7]. This procedure ensures one-pot preparation of highly reactive *N*-sulfonyl imines in quantitative yield. While continuing studies in this field, we synthesized *N*,*N*-dichlorophenylmethanesulfonamide (**II**) by chlorination of phenylmethanesulfonamide (**I**) and examined the reaction of **II** with trichloroethylene with a view to develop procedures for the preparation of new important reagents and precursors of potential biologically active compounds. Arylmethanesulfonamide derivatives are used in the synthesis of drugs [8, 9] and heterocyclic compounds [10], as well as reagents for sonochemical dealkylation [11]. Therefore, development of methods for the preparation of substituted phenylmethansulfonamide derivatives is an important problem.

N,*N*-Dichloro sulfonamide **II** was synthesized in 68% yield by chlorination of phenylmethanesulfonamide in alkaline solution. The reaction of **II** with trichloroethylene afforded phenyl-*N*-(2,2,2-trichloroethylidene)methanesulfonamide (**III**) in one step with

Scheme 1.



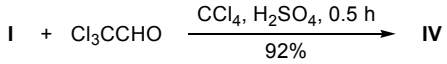
Ar = 4-MeC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), thiophen-2-yl (**c**), 5-chlorothiophen-2-yl (**d**).

a good yield (95%; Scheme 1). Amide **III** was quantitatively converted into phenyl-*N*-(2,2,2-trichloro-1-hydroxyethyl)methanesulfonamide (**IV**) on exposure to air over a period of 24 h or upon treatment with water. These transformations indicate high electrophilicity of the CH=N group activated by strong electron-withdrawing substituents.

Amide **III** is capable of alkylating aromatic and heteroaromatic compounds. Its reaction with toluene, anisole, thiophene, and 2-chlorothiophene under acidic conditions led to the formation of *N*-(1-aryl-2,2,2-trichloroethyl)phenylmethanesulfonamides **Va**–**Vd** in good yield (Scheme 1). When oleum was used as acid catalyst, the reaction was accompanied by tarring and side sulfonation of the aromatic substrate, whereas no compound **V** was formed in the presence of concentrated sulfuric acid. The best yields of **Va**–**Vd** were obtained with the use of a mixture of H_2SO_4 with P_4O_{10}. In this case, the reaction was regioselective, and only *para*-substituted benzene derivatives **Va** and **Vb** and 2- and 2,5-substitured thiophene derivatives **Vc** and **Vd** were obtained.

Orazi et al. [10] described the synthesis of phenylmethanesulfonamide derivatives by its reaction with trichloroacetaldehyde in the presence of an acid. The authors presumed intermediate formation of imine **III**, but no any proof was given. We found that the reaction of phenylmethanesulfonamide (**I**) with trichloroacetaldehyde in carbon tetrachloride in the presence of concentrated sulfuric acid yields hemiaminal **IV** as the only product; no imine **III** was detected by spectral methods under these conditions (Scheme 2).

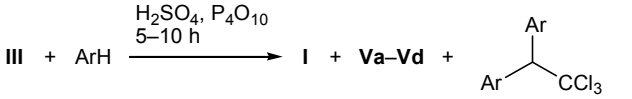
Scheme 2.



The procedures described in [10] led to the formation of mixtures containing *N*,*N*′-(2,2,2-trichloroethane-1,1-diyl)bis(phenylmethanesulfonamide) and cyclic 4-trichloromethyl-3,4-dihydro-1*H*-2λ^6,3-benzothiazine 2,2-dioxide whose ratio depended on the conditions. The approach proposed by us on the basis of transformations of imine **III** is characterized by high chemoselectivity, and neither bisamidoethane nor benzothiazine dioxide was formed.

However, while optimizing the conditions for amidoalkylation of arenes and hetarenes we found that extension of the reaction time over 3 h favors side processes where the sulfonamide fragment acts as nucleofuge. The resulting mixtures of products contained amidoalkyl derivative **Va**–**Vd** (major component) together with phenylmethanesulfonamide (**I**) and 1,1-diaryl-2,2,2-trichloroethane **VIa**–**VId** as by-product whose fraction increased with time (Scheme 3). Compounds **VIa**–**VId** were not isolated as individual substances, and they were identified in the reaction mixtures by ^{1}H NMR. The ^{1}H NMR spectra contained singlets at δ 4.5–4.8 ppm due to CH proton and signals from aromatic protons with a double intensity ratio. The formation of diaryltrichloroethanes and diaryldichloroethanes was observed by us previously in the amidoalkylation with *N*-(polychloroethylidene) sulfonamides [12, 13].

Scheme 3.



Ar = 4-MeC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), thiophen-2-yl (**c**), 5-chlorothiophen-2-yl (**d**).

Phenylmethanesulfonamide derivatives **II**–**V** were isolated as colorless crystalline substances which were readily soluble in polar organic solvents and insoluble in water. Their structure was confirmed by spectral data and elemental analyses. Methylene proton signals in the ^{1}H NMR spectra of **IV** and **Va**–**Vd** appeared as an *AB* pattern. The NH–CH fragment gave rise to two doublets with a coupling constant ^3J of 9.5–10.5 Hz (an exception was compound **Va** which was characterized by a singlet due to fast H–D exchange involving the NH group). Aromatic protons in the benzene ring of **Va** and **Vb** were represented by an *AA′BB′* pattern, indicating *para*-substitution. The ^{13}C NMR spectra of **II**–**IV** and **Va**–**Vd** were fully consistent with the assumed structures.

To conclude, we have developed a procedure for the preparation of a new representative of highly electrophilic electron-deficient imines, phenyl-*N*-(2,2,2-trichloroethylidene)methanesulfonamide (**III**), by reaction of *N*,*N*-dichlorophenylmethanesulfonamide (**II**) with trichloroethylene. High reactivity of compound **III** makes it promising as reagent for the synthesis of various phenyl-*N*-(trichloroethyl)methanesulfonamide derivatives.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker IFS-25 spectrometer. The ^{1}H and ^{13}C NMR spectra

were measured on a Bruker DPX-400 instrument at 400.61 and 100.13 MHz, respectively, using tetramethylsilane as internal reference. Phenylmethanesulfonamide (**I**) was synthesized as described in [10].

***N*,*N*-Dichlorophenylmethanesulfonamide (II).** Phenylmethanesulfonamide (**I**), 1.71 g (10 mmol), was added under stirring to a solution of 0.80 g (20 mmol) of sodium hydroxide in 20 ml of water, gaseous chlorine was passed through the resulting solution until its absorption ceased, and the mixture was kept for 2 h at room temperature. The precipitate was filtered off, washed with cold water until the absence of chloride ions in the washings, dried, and recrystallized from chloroform. Yield 1.63 g (68%), mp 75–76°C. IR spectrum, ν, cm^{-1}: 3086–3010 (C–H_{arom}), 2957–2851 (C–H_{aliph}), 1376, 1172 (SO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 4.86 s (2H, CH_2), 7.48–7.54 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 52.4 (CH_2); 125.2, 129.3, 129.9, 132.3 (C_6H_5). Found, %: C 34.87; H 2.81; Cl 30.09; N 5.58; S 12.87. $C_7H_7Cl_2NO_2S$. Calculated, %: C 35.02; H 2.94; Cl 29.53; N 5.83; S 13.35.

Phenyl-*N*-(2,2,2-trichloroethylidene)methanesulfonamide (III). A mixture of 2.40 g (10 mmol) of dichloro amide **II** and 10.50 g (80 mmol) of trichloroethylene was heated for 10–12 h under reflux in an argon atmosphere until chlorine no longer evolved (iodine–starch test), and the solvent was distilled off under reduced pressure. Yield 2.85 g (95%), mp 128–130°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 4.47 s (2H, CH_2), 7.25–7.38 m (5H, C_6H_5), 8.11 s (1H, N=CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 58.1 (CH_2); 90.8 (CCl_3); 125.9, 126.2, 128.5, 130.6 (C_6H_5), 166.5 (C=N). Found, %: C 35.83; H 2.62; Cl 35.48; N 4.53; S 10.43. $C_9H_8Cl_3NO_2S$. Calculated, %: C 35.96; H 2.68; Cl 35.38; N 4.66; S 10.67.

Phenyl-*N*-(2,2,2-trichloro-1-hydroxyethyl)-methanesulfonamide (IV). *a*. Compound **III**, 1.50 g (5 mmol) was kept for 24 h on exposure to air. Yield 1.59 g (100%).

b. A solution of 1.71 g (10 mmol) of phenylmethanesulfonamide (**I**), 2.21 g (15 mmol) of trichloroacetaldehyde, and 0.3 ml of concentrated sulfuric acid in 30 ml of anhydrous CCl_4 was vigorously stirred for 30 min. The precipitate was filtered off, washed with water, and dried in air. Yield 2.93 g (92%), mp 93–95°C. IR spectrum, ν, cm^{-1}: 3512 (OH), 3205 (NH), 3089–3033 (C–H_{arom}), 2973–2886 (C–H_{aliph}), 1314, 1157 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.64 s (1H, OH), 4.42 m (2H, CH_2, *AB* pattern), 5.22 d (1H, NCH, ^3J = 10.5 Hz), 7.38 m (5H, C_6H_5), 8.39 d (1H, NH, ^3J = 10.5 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 59.8 (CH_2); 85.7 (NCH); 102.0 (CCl_3); 128.2, 128.4, 129.5, 130.9 (C_6H_5). Found, %: C 33.75; H 3.21; Cl 33.59; N 4.58; S 10.37. $C_9H_{10}Cl_3NO_3S$. Calculated, %: C 33.93; H 3.16; Cl 33.38; N 4.40; S 10.06.

Phenyl-*N*-[2,2,2-trichloro-1-(4-methylphenyl)-ethyl]methanesulfonamide (Va). A mixture of imine **III** [prepared from 2.40 g (10 mmol) of **II**], 1 ml of 96% H_2SO_4, and 0.5 g of P_4O_{10} in 10 ml of toluene was stirred for 3 h. The mixture was evaporated, and the residue was washed with water until neutral washings, 20% aqueous ammonia (30 ml), and water again, dried, and recrystallized from acetone–CCl_4 (1:10 by volume). Yield 3.18 g (81%), mp 181–183°C. IR spectrum, ν, cm^{-1}: 3254 (NH), 1338, 1153 (SO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.38 s (3H, CH_3), 4.12 m (2H, CH_2, *AB* pattern), 5.30 s (1H, CH), 7.08, 7.20 m (4H, C_6H_4, *AA′BB′*); 7.18 m, 7.27 m, and 7.63 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9 (CH_3), 60.4 (CH_2), 72.5 (CH), 102.7 (CCl_3); 126.8, 128.4, 128.7, 128.9, 129.4, 130.41, 133.0, 139.8 (C_{arom}). Found, %: C 48.87; H 4.08; Cl 27.21; N 3.42; S 8.24. $C_{16}H_{16}Cl_3NO_2S$. Calculated, %: C 48.93; H 4.11; Cl 27.08; N 3.57; S 8.16.

Phenyl-*N*-[2,2,2-trichloro-1-(4-methoxyphenyl)-ethyl]methanesulfonamide (Vb). A mixture of imine **III** [prepared from 2.40 g (10 mmol) of **II**], 1 ml of 96% H_2SO_4, 0.5 g of P_4O_{10}, and 3 ml of anisole in 10 ml of CCl_4 was stirred for 3 h and was then treated as described above for **Va**. Yield 3.38 g (83%), mp 154–157°C. IR spectrum, ν, cm^{-1}: 3257 (NH), 1337, 1168 (SO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.89 s (3H, CH_3), 4.15 m (2H, CH_2, *AB*), 5.25 d (1H, CH, ^3J = 9.8 Hz), 5.74 d (1H, NH, ^3J = 9.8 Hz), 6.90, 7.41 m (4H, C_6H_4, *AA′BB′*); 7.14 m, 7.30 m, and 7.57 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 54.6 (CH_3), 59.9 (CH_2), 70.8 (CH), 101.0 (CCl_3); 113.1, 130.1, 133.2, 159.9 (C_6H_4); 126.4, 127.6, 128.3, 130.6 (C_6H_5). Found, %: C 47.23; H 3.88; Cl 26.17; N 3.55; S 7.93. $C_{16}H_{16}Cl_3NO_3S$. Calculated, %: C 47.02; H 3.95; Cl 26.02; N 3.43; S 7.85.

Compounds **Vc** and **Vd** were synthesized in a similar way.

Phenyl-*N*-[2,2,2-trichloro-1-(thiophen-2-yl)ethyl]-methanesulfonamide (Vc) was synthesized from 2.40 g (10 mmol) of **II** and 3 ml of thiophene using 1 ml of 96% H_2SO_4 and 0.5 g of P_4O_{10}. Yield 2.37g (62%), mp 125–127°C. IR spectrum, ν, cm^{-1}: 3250

(NH), 1335, 1168 (SO_2). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 4.51 s (2H, CH_2), 5.49 d (1H, CH, ^3J = 9.5 Hz); 7.04 m, 7.36 m, and 7.40 m (3H, thiophene); 7.22 d (1H, NH, ^3J = 9.5 Hz), 7.35 m and 7.47 m (5H, C_6H_5). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 60.6 (CH_2), 66.7 (CH), 100.8 (CCl_3); 128.2, 128.8, 128.9, 129.1, 130.7, 130.9, 131.0, 144.1 (C_{arom}). Found, %: C 40.73; H 3.08; Cl 27.17; N 3.51; S 16.33. $C_{13}H_{12}Cl_3NO_2S_2$. Calculated, %: C 40.58; H 3.14; Cl 27.64; N 3.64; S 16.67.

Phenyl-*N*-[2,2,2-trichloro-1-(5-chlorothiophen-2-yl)ethyl]methanesulfonamide (Vd) was synthesized from 2.40 g (10 mmol) of **II** and 3 ml of 2-chlorothiophene using 1 ml of 96% H_2SO_4 and 0.5 g of P_4O_{10}. Yield 3.55 g (85%), mp 133–134°C. IR spectrum, ν, cm^{-1}: 3257 (NH), 1335, 1163 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.26 m (2H, CH_2, *AB*), 5.47 d (1H, CH, ^3J = 9.6 Hz), 5.60 d (1H, NH, ^3J = 9.6 Hz); 6.84 m, 7.05 m, and 7.20 m (5H, C_6H_5); 6.89 m and 6.99 m (2H, thiophene, *AB*). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 60.1 (CH_2), 68.1 (CH), 99.8 (CCl_3); 124.8, 127.5, 128.7, 136.6 (thiophene); 125.1, 128.2, 130.2, 135.2 (C_6H_5). Found, %: C 37.13; H 2.55; Cl 33.90; N 3.18; S 15.53. $C_{13}H_{11}Cl_4NO_2S_2$. Calculated, %: C 37.25; H 2.65; Cl 33.83; N 3.34; S 15.30.

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