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Cascade Synthesis of 2-Amino-5-(4-methoxyphenyl)-4-phenyl-1,3-thiazole by Reaction of 4-Chloro-*N*-[2,2-dichloro-1-(4-methoxyphenyl)-2-phenylethyl]benzenesulfonamide with Thiourea

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Abstract—4-Chloro-*N*-[2,2-dichloro-1-(4-methoxyphenyl)-2-phenylethyl]benzenesulfonamide reacted with thiourea on heating in DMF in the presence of sodium carbonate to give 5-(4-methoxyphenyl)-4-phenyl-1,3-thiazole-2-amine. A probable reaction scheme includes cyclization of the initial *N*-dichloroethyl amide to *N*-sulfonyl-2,3-diaryl-2-chloroaziridine which undergoes isomerization with opening of the three-membered ring to 1-arylsulfonylamino-2-chloro-2-(4-methoxyphenyl)-1-phenylethene. The subsequent heterocyclization in the reaction with thiourea is accompanied by aromatization via elimination of the arenesulfonamide fragment.

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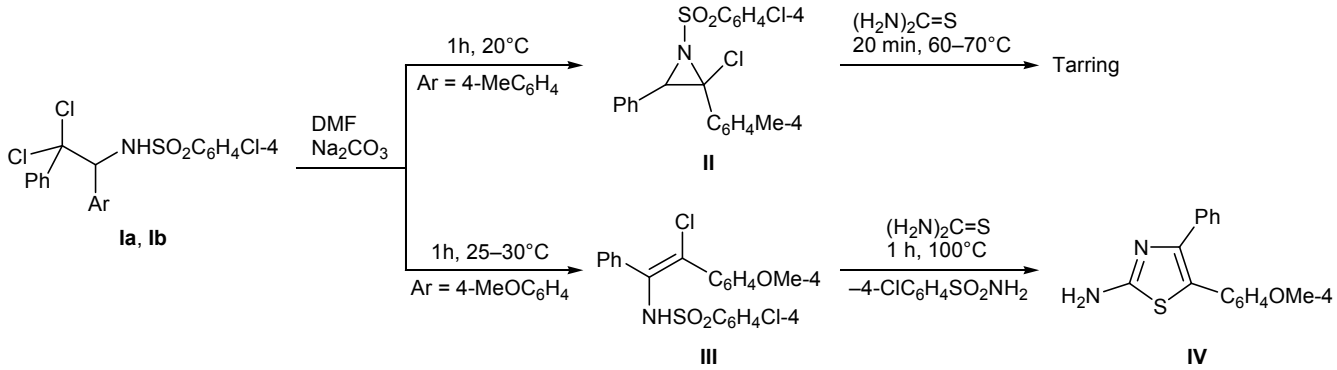
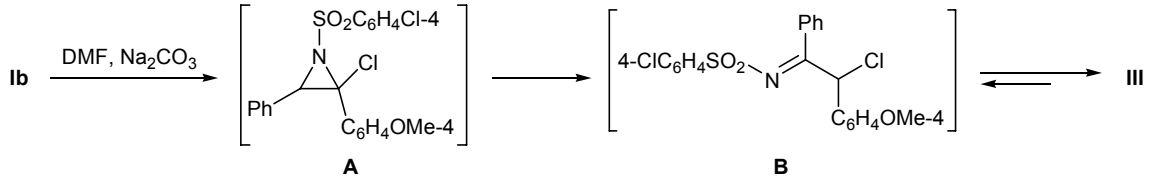
We previously developed convenient methods for C-amidoalkylation of aromatic, functionally substituted aromatic, and heteroaromatic compounds with the use of polychloroacetaldehyde imines as amidoalkylating agents [1–3]. As a result, a wide series of *N*-polychloroethylsulfonamides $RSO_2NHCH(Ar)CCl_2X$ became accessible, and we were able to initiate studies on their biological activity and chemical reactivity. Synthetic importance of *N*-polychloroethylsulfonamides is determined by the presence in their molecules of NH group and polyhalomethyl fragment; it was demonstrated by the preparation on their base of biologically active N-protected amino acids [4], as well as by cascade reactions leading to amidines [5], aminocarbonyl compounds [6], imides [7], macroheterocyclic systems [8], and aziridines [9]. In addition, it was found that reactions of *N*-(1-aryl-2,2,2-trichloroethyl)arenesulfonamides with thioamides in dimethylformamide in the presence of inorganic bases lead to the formation of substituted 1,3-thiazoles [10].

Scheme 1.



Ar = 4-MeC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**).

Scheme 2.



In continuation of our systematic studies on the reactivity of *N*-polychloroethyl sulfonamides with a view to develop approaches to functionalized thiazole systems, in the present work we examined reactions of thiourea with *N*-(1-aryl-2,2-dichloro-2-phenylethyl)-arenesulfonamides **Ia** and **Ib**. The direction of transformation of compounds **Ia** and **Ib** in DMF in the presence of sodium carbonate and thiourea strongly depends on the nature of the aromatic substituent in position *1* of the ethyl fragment. Compound **Ia** having a *p*-tolyl substituent did not react with thiourea at room temperature, but it underwent intramolecular cyclization with formation of 2-chloro-1-(4-chlorophenylsulfonyl)-2-(4-methylphenyl)-3-phenylaziridine (**II**) (Scheme 1). Substituted aziridine **II** failed to react with such ambident N,S-nucleophile as thiourea at room temperature, whereas the reaction at elevated temperature was accompanied by tarring, and we did not succeed in isolating individual products or characterizing them by spectral methods.

Unlike compound **Ia**, sulfonamide **Ib** having a *p*-methoxyphenyl substituent reacted with thiourea under analogous conditions (at room or slightly elevated temperature) to produce 4-chloro-*N*-[2-chloro-2-(4-methoxyphenyl)-1-phenylethenyl]benzenesulfonamide (**III**) which was isolated as individual substance.

Compound **III** is likely to be formed via cyclization to aziridine **A** which is unstable due to electron-donating effect of the 4-methoxyphenyl substituent. Isomerization of aziridine **A** involves opening of the three-membered ring and migration of chlorine to give intermediate Schiff base **B**. Prototropic transformation of the latter yields more stable enamide **III** (Scheme 2).

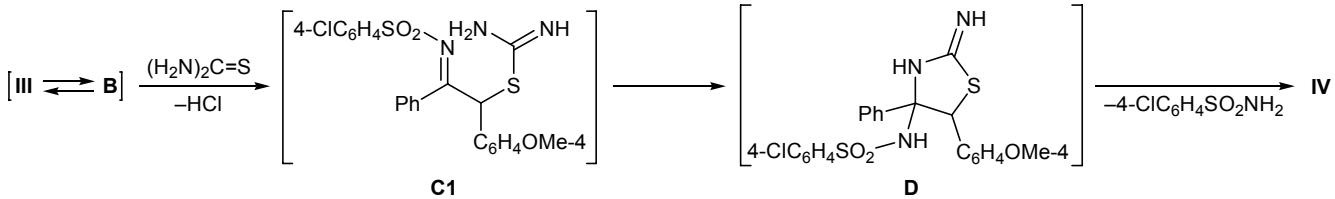
Isomerization of halogen-containing aziridines with ring opening and migration of the halogen atom, which is analogous to the above transformation of chloroaziridine **A**, was discussed in detail in [11, 12], and similar transformations of diarylhaloaziridines were noted in review [13]. In the present work we found that heating of a mixture containing compound **Ib** and thiourea in DMF in the presence of sodium carbonate at 100°C resulted in the formation of 5-(4-methoxyphenyl)-4-phenyl-1,3-thiazol-2-amine (**IV**) as final product (Scheme 1).

Presumably, enamide **III** generated *in situ* reacts as tautomer **B** with thiourea which acts as sulfur-centered nucleophile and replaces the chlorine atom to give intermediate substitution product **C1**. Intramolecular heterocyclization of the latter yields thiazolidine **D** which undergoes aromatization to produce final aminothiazole **IV** via elimination of 4-chlorobenzenesulfonamide molecule and tautomerization (Scheme 3). On the other hand, addition of thiourea as nitrogen-centered nucleophile at the C=N carbon atom of Schiff base **B** cannot be ruled out. Intermediate adduct **C2** undergoes intramolecular cyclization to thiazolidine **D** with subsequent aromatization (Scheme 4). Analogous formation of thiazoles from adducts structurally related to **C2** [addition products of thioamides to dichloro(phenyl)acetaldehyde imines] was reported in [14]. Enamide **III** did not react with thiourea at room temperature and was recovered from the reaction mixture.

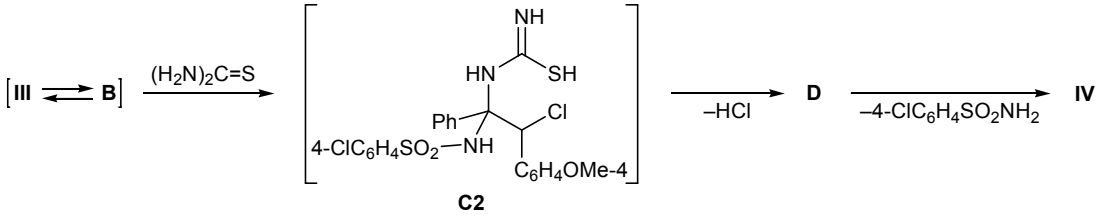
Chloroaziridine **II** was synthesized by us previously [9], and its structure was proved by X-ray analysis. The spectral parameters and melting point of a sample of **II** obtained in the present work were identical to those given in [9].

The ^{1}H and ^{13}C NMR and IR spectra and elemental composition of compound **III** were consistent with the assumed structure. The configuration of the double

Scheme 3.



Scheme 4.



C=C bond in molecule **III** was unambiguously determined by two-dimensional NMR spectroscopy using HMBC $^{1}H–^{13}C$ correlation technique (optimized for J_{CH} = 10 Hz, which corresponds to coupling through three bonds). The NH proton in the sulfonamide group gave a cross peak with C^2 in the ethylene fragment (δ_C 126.67 ppm). The same carbon atom (C^2) displayed coupling with *ortho*-protons in the *p*-methoxyphenyl group. This pattern could be observed only when the arylsulfonylamino and *p*-methoxyphenyl groups are attached to different carbon atoms. Furthermore, *ortho*-protons in the phenyl ring showed a cross peak with C^1 in the ethylene fragment (δ_C 139.94 ppm). According to the NOESY data, the lack of dipole–dipole interaction between protons in the phenyl and *p*-methoxyphenyl rings indicated *trans* orientation of these substituents.

As follows from the ^{1}H and ^{13}C NMR spectra, thiazole **IV** is formed as a single isomer. Using HMBC $^{1}H–^{13}C$ correlation technique we succeeded in assigning signals from carbon atoms in the thiazole ring. The carbon atom linked to the phenyl group resonated in a weaker field as compared to that connected to the *p*-methoxyphenyl group (δ_C 144.07 and 119.08 ppm, respectively). As a rule, thiazole systems are characterized by downfield signal of C^4 due to stronger deshielding effect of the ring nitrogen atom [15, 16].

The structure of thiazole **IV** was additionally confirmed by nonempirical quantum-chemical calculations of shielding constants for both possible isomers, 5-(4-methoxyphenyl)-4-phenyl-1,3-thiazol-2-amine (**IV**) and 4-(4-methoxyphenyl)-5-phenyl-1,3-thiazol-2-amine (**V**). The geometric parameters of isomers **IV** and **V** were optimized at the B3LYP/6-311G** level of theory, and the shielding constants were calculated in terms of the GIAO/B3LYP approach using three basis sets: Kutzelnigg IGLO-III and Pople–Dunning 6-311++G** and aug-cc-pVTZ basis sets extended by diffuse functions. In addition, the shielding constants were calculated in terms of the polarizable continuum model (PCM), taking into account that the corresponding experimental chemical shifts were measured from solutions in DMSO-d_6. The solvent effect was taken into consideration both at the stage of geometry optimization and at the stage of calculation of shielding constants. The calculated chemical shifts of C^4 and C^5 in the thiazole ring of isomers **IV** and **V** are given in table together with the experimental values. It is seen that the C^4 signal of both isomers **IV** and **V** should appear in a weaker field relative to the C^5 signal. Thus the results of calculations confirm the HMBC data, i.e., formation of isomer **IV**. In our calculations, consideration of the solvent effect, as well as extension of basis sets via inclusion of diffuse functions, did not affect the accuracy of calculation of chemical shifts to an appreciable extent (see table), which is quite consistent with our previous data [17].

To conclude, we have demonstrated that transformations of *N*-(1-aryl-2,2-dichloro-2-phenylethyl)-arenesulfonamides are strongly determined by the

Chemical shifts of C^4 and C^5 (δ_C, ppm) in the thiazole ring of isomers **IV** and **V**, calculated by the GIAO/B3LYP method, and the corresponding experimental values

Comp. no.	Atom	Gas phase			DMSO			δ_C (exptl.)[a]
		IGLO-III	6-311++G**	aug-cc-pVTZ	IGLO-III	6-311++G**	aug-cc-pVTZ	
IV	C^4	145.78	146.45	145.01	144.06	144.57	143.27	144.07
	C^5	126.48	125.17	125.12	126.67	124.30	125.27	119.02
V	C^4	146.24	146.91	145.82	144.40	145.16	144.13	–
	C^5	124.35	123.54	123.99	124.95	123.86	124.44	–

[a] Relative to tetramethylsilane (DMSO-d_6).

nature of aromatic substituent in the *N*-ethyl fragment. The reaction of 4-chloro-*N*-[2,2-dichloro-1-(4-methoxyphenyl)-2-phenylethyl)benzenesulfonamide with thiourea in DMF in the presence of Na_2CO_3 gave previously unknown 5-(4-methoxyphenyl)-4-phenyl-1,3-thiazol-2-amine.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.61 and 100.13 MHz, respectively, using tetramethylsilane as internal reference. The IR spectra were obtained in KBr on a Bruker IFS-25 instrument. Quantum-chemical calculations were performed with the aid of GAUSSIAN03 software package [18]. Initial sulfonamides **Ia** and **Ib** were synthesized according to the procedures described in [3, 19].

Transformations of 4-chloro-*N*-[2,2-dichloro-1-(4-methylphenyl)-2-phenylethyl]benzenesulfonamide (Ia). *a*. A mixture of 2.27 g (0.005 mol) of compound **Ia**, 2.12 g (0.02 mol) of Na_2CO_3, 0.38 g (0.005 mol) of thiourea, and 10 ml of DMF was stirred for 24 h at room temperature. The mixture was diluted with 70 ml of water, and the precipitate was filtered off, dried, and recrystallized from hexane. Yield of chloroaziridine **II** 0.48 g (25%), mp 121–123°C; published data [9]: mp 121–123°C. The spectral parameters of the product coincided with those given in [9].

b. A mixture of 2.27 g (0.005 mol) of compound **Ia**, 2.12 g (0.02 mol) of Na_2CO_3, 0.38 g (0.005 mol) of thiourea, and 10 ml of DMF was stirred for 20 min at 70°C. After dilution with water, a tarry material separated. It was insoluble in water, and we failed to isolate individual substances therefrom.

4-Chloro-*N*-[2-chloro-2-(4-methoxyphenyl)-1-phenylethenyl]benzenesulfonamide (III). A mixture of 2.35 g (0.005 mol) of compound **Ib**, 2.12 g (0.02 mol) of Na_2CO_3, and 10 ml of DMF was stirred for 1 h at 30°C. The mixture was then diluted with 10 ml of water and neutralized with 5% hydrochloric acid, and the precipitate was filtered off, washed with water, dried, and recrystallized from chloroform–acetone (10:1). Yield 1.17 g (54%), mp 131–133°C. IR spectrum, ν, cm^{-1}: 3090–3030 (C–H_{arom}); 2960–2920 (C–H_{aliph}); 1600 (C=C); 1570 (C=C_{arom}); 1330, 1155 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.67 s (3H, Me), 6.74 and 6.97 (4H, *AA′BB′* system, 4-MeOC_6**H**$_4$), 6.98 m and 7.57 m (4H, *o*-H, *m*-H in Ph), 7.13 m (1H, *p*-H), 7.08 and 7.56 (4H, *AA′BB′*, 4-ClC_6H_4), 9.18 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 55.15 (Me); 113.67, 129.12, 131.03, 159.03 (OC_6H_4); 126.67 (=CCl); 127.99, 129.04, 130.13, 131.80 (Ph); 127.76, 128.36, 135.41, 137.40 (ClC_6H_4); 139.94 (=CNH). Found, %: C 57.95; H 4.00; Cl 16.48; N 3.34; S 7.51. $C_{21}H_{17}Cl_2NO_3S$. Calculated, %: C 58.07; H 3.95; Cl 16.33; N 3.22; S 7.38.

5-(4-Methoxyphenyl)-4-phenyl-1,3-thiazol-2-amine (IV). A mixture of 0.94 g (0.002 mol) of compound **Ib**, 0.76 g (0.01 mol) of thiourea, and 0.85 g (0.008 mol) of Na_2CO_3 in 15 ml of anhydrous DMF was stirred for 5 h at 100°C. The mixture was poured into 30–40 ml of water, and the precipitate was filtered off, dried, and washed with 50 ml of 10% aqueous ammonia. Acidification of the filtrate gave 0.36 g (95%) of 4-chlorobenzenesulfonamide. Yield of aminothiazole **IV** (insoluble in aqueous ammonia) 0.50 g (89%), mp 161–162°C. IR spectrum, ν, cm^{-1}: 3366–3273 (NH); 1676 (C=N); 1537, 1503 (C=C_{arom}). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.74 s (3H, Me), 6.86 and 7.13 (4H, *AA′BB′* system, 4-MeOC_6**H**$_4$), 7.06 s (2H, NH_2), 7.24 m and 7.49 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.09 (MeO); 114.19, 119.08, 130.37, 158.38 (C_6H_4); 119.08 (C^5); 127.05, 127.99, 128.31, 135.50 (Ph); 144.07 (C^4); 165.62 (C^2). Found, %: C 67.99; H 5.01; N 9.95; S 11.38. $C_{16}H_{14}N_2OS$. Calculated, %: C 68.06; H 5.00; N 9.92; S 11.35.

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