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REACTION OF N-(1-ARYL-2,2,2-TRICHLOROETHYL)ARENESULFONAMIDES WITH THIOAMIDES. A ROUTE TO 5-ARENESULFONAMIDO-4-ARYLTHIAZOLES

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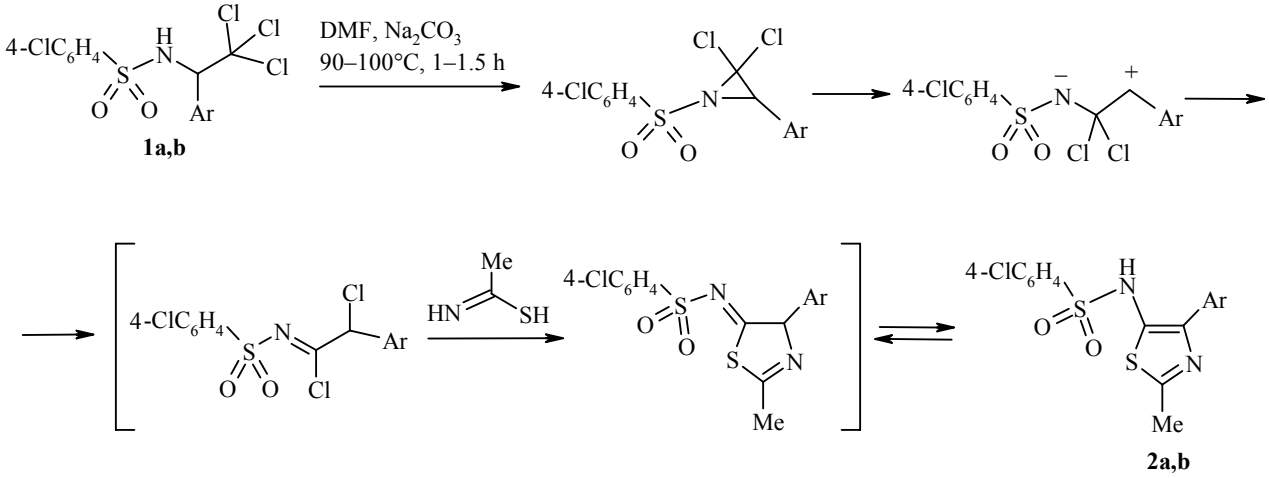
We have developed convenient methods for introducing amidopolyhaloethyl fragments into the structure of aromatic and heteroaromatic compounds [1-3]. This has resolved the problem of the availability of a wide range of polyhaloethylamides of type **1**, the presence of an NH group and of polyhalomethyl fragments leading us to consider them as promising in the synthesis of N-containing heterocyclic systems.



a Ar = Ph, **b** Ar = 4-MeC_6H_4

By systematic study of the reactivity of compound **1** we have found an unexpected reaction in the case of the arenesulfonamides **1a,b** which occurs in aprotic, bipolar media in the presence of inorganic bases and thioacetamide to give the 2-alkyl-5-arenesulfonamido-4-arylthiazoles **2a,b** in 31-34% yield.

* Dedicated to Academician of the Russian Academy of Sciences B. A. Trofimov on his 70th jubilee.

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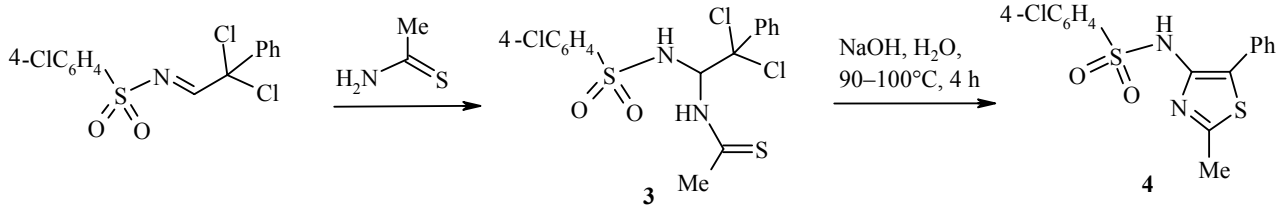
The proposed route for formation of thiazoles **2a,b** includes a cyclization stage of amides **1a,b** to dichloroaziridines which undergo recyclization under the reaction conditions to imidoylchloride intermediates *via* a 1,2-chlorotropic shift and then undergo heterocyclization upon treatment with thioamides followed by prototropic reactions as shown in the scheme.

The formation of substituted chloro- and dichloroaziridine derivatives as a result of the reaction of arenesulfonic acid polychloroethylamides has been reported by us before [4, 5]. The recyclization of dichloroaziridine systems to imidoylchlorides is also known [6]. However, the reactions of trichloroethylamides leading to the synthesis of thiazole series heterocycles in a single stage reaction with thioamides has not been reported in the literature.

We have also brought about an intramolecular cyclization of the N-(2,2-dichloroethyl-2-phenyl-1-thioacetamido)-4-chlorobenzenesulfonamide (**3**) which only leads to the 4-arenesulfonamido-2-methyl-5-phenylthiazole **4**. As is shown by comparison of the physicochemical data for thiazoles **2a** and **4** these compounds are isomers which demonstrates the regiodirection of the chemical reactions of the trichloroethylamides **1** to give the 5-amino-4-arylthiazoles **2a,b**.



3 **4**

The structure of compounds **2a,b** and **4** was confirmed by spectroscopic methods and by elemental analysis. The assignment of signals in the ^{1}H and ^{13}C NMR spectra was carried out by 2D-NOESY, HSQC, HMBC and 2D-INADEDQUATE two dimensional homo- and heteronuclear correlation methods.

The optimization of methods for obtaining thiazoles based on trichloroethylamides of type **1** is currently in progress together with the establishment of the limits and the generality of this novel method to thiazole derivatives.

^{1}H and ^{13}C NMR spectra were obtained using $CDCl_3$ on a Bruker DPX-400 spectrometer (400 and 100 MHz respectively) at 5-10% concentration and with the addition of HMDS as internal standard. Compounds **1a,b** were prepared by method [1] and compound **3** by method [7].

4-Aryl-5-(4-chlorobenzenesulfonamido)-2-methylthiazoles (2a,b) (General Method). 4-Chlorobenzenesulfonic acid N-(1-aryl-2,2,2-trichloroethyl)amide **1a,b** (5 mmol), thioacetamide (1.5 g, 20 mmol), and Na_2CO_3 (2.12 g, 20 mmol) was heated at 90-100ºC in DMF (10 ml) for 90 min. The reaction mixture was cooled, poured into water (50 ml), filtered, and the filtrate was acidified with 10% HCl solution to pH 5-6. The precipitated thiazole **2a,b** was separated, dried, and recrystallized from $CHCl_3$.

5-(4-Chlorobenzenesulfonamido)-2-methyl-4-phenylthiazole (2a) was prepared from amide **1a** (2.0 g, 5 mmol). Yield 0.57 g (31%); mp 172ºC. ^{1}H NMR spectrum, δ, ppm: 2.60 (3H, d, 2-CH_3); 6.88 (1H, br. s, NH); 7.38 and 7.72 (4H, AA'BB', 4-ClC_6H_4); 7.32, 7.39 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 19.17 (CH_3); 126.42, 128.16, 128.32, 128.55, 128.73, 128.96, 138.35, 139.09 (C_6H_4 and C_6H_5); 129.30 (C-4); 138.07 (C-5); 162.76 (C-2). Found, %: C 52.78; H 3.63; Cl 9.65; N 7.75; S 17.70. $C_{16}H_{13}ClN_2O_2S_2$. Calculated, %: C 52.67; H 3.59; Cl 9.72; N 7.68; S 17.57.

5-(4-Chlorobenzenesulfonamido)-2-methyl-4-(4-methylphenyl)thiazole (2b) was prepared from amide **1b** (2.07 g, 5 mmol). Yield 0.64 g (34%), mp 185ºC. ^{1}H NMR spectrum, δ, ppm: 2.38 (3H, s, 2-CH_3); 2.63 (3H, s, 4-C$\underline{H}_3C_6H_4$); 7.15 and 7.30 (4H, AA'BB', 4-$CH_3C_6\underline{H}_4$); 7.31 and 7.65 (4H, AA'BB', 4-ClC_6H_4); 7.35 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 19.54 (2-CH_3); 21.33 ($\underline{C}H_3C_6H_4$); 126.71, 128.55, 128.85, 129.16, 129.69, 138.48, 138.68, 139.30 ($2C_6H_5$); 129.17 (C-4); 138.23 (C-5), 162.90 (C-2). Found, %: C 53.77; H 3.96; Cl 9.49; N 7.47; S 16.98. $C_{17}H_{15}ClN_2O_2S_2$. Calculated, %: C 53.89; H 3.99; Cl 9.36; N 7.39; S 16.92.

4-(4-Chlorobenzene)-2-methyl-5-phenylsulfonamidothiazole (4) 4-Chlorobenzenesulfonic acid N-(2,2-dichloroethyl-2-phenyl-1-thioacetamido)amide (**3**) (0.44 g, 1 mmol) and NaOH (0.20 g, 5 mmol) were refluxed with stirring in water (20 ml) for 4 h. The mixture was then cooled and 10% HCl solution was added until the formation of the precipitated thiazole **4** was complete. The product was separated, dried, and recrystallized from ethanol. Yield 0.30 g (77%); mp 147-148ºC. ^{1}H NMR spectrum, δ, ppm: 2.69 (3H, s, 2-CH_3); 7.01 (1H, s, NH); 7.28, 7.30 (5H, m, C_6H_5); 7.29 and 7.54 (4H, AA'BB', 4-ClC_6H_4). ^{13}C NMR spectrum, δ, ppm: 19.92 (2-CH_3); 128.05, 128.48, 128.58, 128.91, 129.31, 132.58, 136.43, 140.14 (C_6H_4 and C_6H_5); 125.73 (C-4); 149.53 (C-5); 163.81 (C-2). Found, %: C 52.81; H 3.67; Cl 9.85; N 7.79; S 17.83. $C_{16}H_{13}ClN_2O_2S_2$. Calculated, %: C 52.67; H 3.59; Cl 9.72; N 7.68; S 17.57.

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