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SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES, BENZOXAZOLES, AND BENZOTHIAZOLES FROM ARYLSULFONYL(THIO)PROPIONITRILES

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The reaction of nitriles and of methyl imino ester hydrochlorides of arylsulfonyl(thio)propionic acids with o-phenylenediamine, o-aminophenol, and o-aminothiophenol has been studied. A series of new 2-substituted benzazoles has been synthesized containing arylsulfonyl(thio)propionic acid fragments.

Keywords: benzimidazole, benzoxazole, benzothiazole, imino ester hydrochlorides of carboxylic acids, nitriles, condensation.

Derivatives of benzimidazole and their oxygen and sulfur analogs possess a wide spectrum of biological activity [1-3]. However there is no information in the literature on benzazoles containing arylsulfonyl(thio)carboxylic acid fragments. The latter, as is known, are used as intermediates in the synthesis of dyestuffs [4], herbicides [5], plant growth regulators [6], medicinal preparations [7], etc. Previously we synthesized new derivatives of arylsulfonyl(thio)acetic acids, possessing antitumor, neurotropic, antiaggregation, analgesic, and radioprotective activity [8].

Data are given in the present work on the preparation of the 2-substituted benzazoles **1a-o** containing an arylsulfonyl(thio)ethyl grouping. Nitriles of aryl-sulfonyl(thio)propionic acids **2a,b** were used as starting materials. These are readily obtained by the cyanoethylation of the appropriate thiophenols and sulfinic acids.

We have investigated two routes to obtain 2-substituted benzazoles **1a-o**. One was the one-stage condensation of arylsulfonyl(thio)propionitriles with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol in a medium of polyphosphoric acid (PPA) and the other a two-stage synthesis through the intermediate formation of the methyl imino ester hydrochlorides of arylsulfonyl(thio)propionic acids **3a-i**.

Quantum-chemical calculations carried out by us, by the PM-3 method with full optimization of the geometric parameters, show that the charge distribution on the molecules of arylsulfonyl(thio)propionitriles **2** is much closer to that of unsubstituted propionitrile than to trichloroacetonitrile which contains electron-withdrawing substituents.

The size of the total charge on the nitrile group was -0.219 for compounds **2**, -0.223 for propionitrile, and -0.173 sp. u. for trichloroacetonitrile. The influence of the ArSO$_n$ fragment on the nitrile group is smoothed by the two methylene groups.

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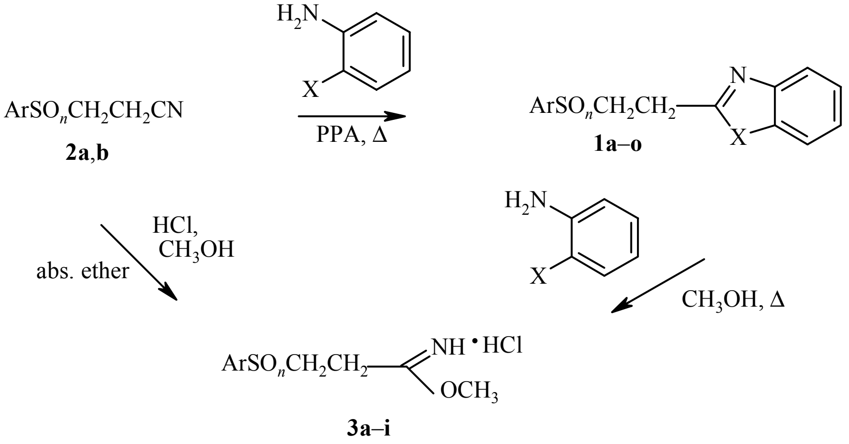

1a-l, 2a, 3a-f *n* = 2; **1m-o, 2b, 3g-i** *n* = 0; **1a-d** X = NH, **a** Ar = 4-ClC_6H_4,
b Ar = 4-MeC_6H_4, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = $C_{10}H_7$; **1e-h** X = O, **e** Ar = 4-MeC_6H_4,
f Ar = 3,4-$Cl_2C_6H_3$, **g** Ar = 4-BrC_6H_4, **h** Ar = 4-$MeOC_6H_4$; **1i-l** X = S, **i** Ar = 4-ClC_6H_4,
j Ar = 4-BrC_6H_4, **k** Ar = 4-$MeOC_6H_4$, **l** Ar = $C_{10}H_7$; **1m,n** X = O, **m** Ar = 4-ClC_6H_4,
n Ar = 4-BrC_6H_4; **o** X = NH, Ar = Ph; **3 a** Ar = 4-ClC_6H_4, **b** Ar = 4-MeC_6H_4,
c Ar = 4-$MeOC_6H_4$, **d** Ar = $C_{10}H_7$, **e** Ar = 3,4-$Cl_2C_6H_3$, **f** Ar = 4-BrC_6H_4; **g** Ar = 4-ClC_6H_4**,**
h Ar = 4-BrC_6H_4, **i** Ar = Ph

The theoretical results are in good agreement with the experimental data on the reactivity of nitriles **2** in the reactions investigated. We were unable to effect their immediate conversion into imino esters **3a-i** under the base catalyzed conditions (CH_3OK in methanol, 10 wt. % in relation to nitrile **2**, temperature 20 and 64°C) recommended for highly electrophilic nitriles in [9]. At the same time under the conditions of the Pinner reaction, when the electrophilicity of the nitrile group is enhanced by the formation of the imino carbocation RC^{+}=NH by the action of hydrogen chloride, nitrile **2** readily adds alcohol and the appropriate imino esters hydrochlorides **3a-i** were obtained in 80-90% yield (Table 1). Room temperature proved to be more preferable for the Pinner reaction than 0-5°C [10], at which the yields of products **3a-i** were 20-25% lower. Absolute ether was used as solvent for arylthiopropionitriles **2a-f**, while for arylsulfonylpropionitriles **2g-i** toluene was used or a 3:1 mixture of it with nitrobenzene (the solubilizing effect of ether proved to be insufficient in these cases). In

TABLE 1. Characteristics of the Obtained Compounds **3a-i**

Compound	Empirical formula	Found Cl, % / Calculated Cl, %	mp, °C	Yield, %
3a	$C_{10}H_{12}ClNO_3S\cdot HCl$	23.56 23.78	181-183	88.4
3b	$C_{11}H_{15}NO_3S\cdot Cl$	12.91 12.76	169-172	90.2
3c	$C_{11}H_{15}NO_4S\cdot HCl$	11.63 12.07	138-140	88.0
3d	$C_{14}H_{15}NO_3S\cdot HCl$	11.32 11.30	173-175	78.0
3e	$C_{10}H_{11}Cl_2NO_3S\cdot HCl$	32.68 31.97	194-195	88.1
3f	$C_{10}H_{12}BrNO_3S\cdot HCl$	9.84 10.35	189-191	84.5
3g	$C_{10}H_{12}ClNOS\cdot HCl$	26.26 26.64	79-80	81.3
3h	$C_{10}H_{12}BrNOS\cdot HCl$	11.92 11.41	53-56	79.8
3i	$C_{10}H_{13}NOS\cdot HCl$	15.61 15.30	Oil	81.6

TABLE 2. Characteristics of the Synthesized Compounds **1a-o**

Com-pound	Empirical formula	Found, % Calculated, %					mp, °C	^{1}H NMR spectrum, δ, ppm	Yield, %
		C	H	N	S	Hal			
1	2	3	4	5	6	7	8	9	10
1a	$C_{15}H_{13}ClN_2O_2S$	54.32 56.16	4.22 4.08	9.05 8.73	9.72 10.00	10.60 11.05	174-175	3.17 (2H, t, $\underline{CH_2}$–Het); 3.83 (2H, t, SO_2CH_2); 7.10-7.93 (8H, m, H_{arom}); 12.00 (1H, br. s, NH)	82.6
1b	$C_{16}H_{16}N_2O_2S$	63.11 63.98	5.45 5.37	9.66 9.33	10.62 10.68	—	178-181	2.42 (3H, t, CH_3); 3.17 (2H, t, $\underline{CH_2}$–Het); 3.75 (2H, t, SO_2CH_2); 7.07-7.80 (8H, m, H_{arom}); 12.00 (1H, br. s, NH)	63.0
1c	$C_{16}H_{16}N_2O_3S$	61.39 60.74	4.91 5.10	8.70 8.85	9.95 10.14	—	169-170	3.17 (2H, t, $\underline{CH_2}$–Het); 3.71 (2H, t, SO_2CH_2); 3.84 (3H, s, CH_3O); 7.08-7.83 (8H, m, H_{arom}); 12.00 (1H, br. s, NH)	83.7
1d	$C_{19}H_{16}N_2O_2S$	67.14 67.84	4.76 4.79	8.10 8.33	9.28 9.53	—	202-203	3.21 (2H, t, $\underline{CH_2}$–Het); 3.85 (2H, t, SO_2CH_2); 7.09-8.60 (11H, m, H_{arom}); 12.00 (1H, br. s, NH)	74.1
1e	$C_{16}H_{15}NO_3S$	60.87 63.77	4.84 5.02	4.60 4.65	10.13 10.65	—	139-141	3.27 (2H, t, $\underline{CH_2}$–Het); 3.79 (2H, t, SO_2CH_2); 7.32-7.80 (8H, m, H_{arom})	69.5
1f	$C_{15}H_{11}Cl_2NO_3S$	53.05 50.58	3.19 3.11	3.92 3.93	9.27 9.00	19.63 19.90	152-154	3.35 (2H, t, $\underline{CH_2}$–Het); 3.98 (2H, t, SO_2CH_2); 7.32-8.08 (7H, m, H_{arom})	72.7
1g	$C_{15}H_{12}BrNO_3S$	52.67 50.40	4.04 3.97	3.57 3.67	8.29 8.41	20.12 20.96	166-167	3.30 (2H, t, $\underline{CH_2}$–Het); 3.87 (2H, t, SO_2CH_2); 7.32-7.85 (8H, m, H_{arom})	63.6

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
1h	$C_{16}H_{15}NO_4S$	$\frac{61.36}{60.55}$	$\frac{4.91}{4.76}$	$\frac{4.36}{4.41}$	$\frac{10.07}{10.10}$	—	140-141	3.27 (2H, t, $\underline{CH_2}$–Het); 3.73 (2H, t, SO_2CH_2); 3.81 (3H, s, CH_3O); 7.05-7.80 (8H, m, H_{arom})	90.9
1i	$C_{15}H_{12}ClNO_2S_2$	$\frac{55.73}{53.33}$	$\frac{3.42}{3.58}$	$\frac{4.23}{4.15}$	$\frac{19.72}{18.98}$	$\frac{10.10}{10.49}$	155-156	3.45 (2H, t, $\underline{CH_2}$–Het); 3.89 (2H, t, SO_2CH_2); 7.35-7.95 (8H, m, H_{arom})	71.5
1j	$C_{15}H_{12}BrNO_2S_2$	$\frac{49.41}{47.13}$	$\frac{3.10}{3.16}$	$\frac{3.75}{3.66}$	$\frac{15.96}{16.78}$	$\frac{21.62}{20.90}$	153-155	3.45 (2H, t, $\underline{CH_2}$–Het); 3.87 (2H, t, SO_2CH_2); 7.37-7.95 (8H, m, H_{arom})	61.2
1k	$C_{16}H_{15}NO_3S_2$	$\frac{55.60}{57.64}$	$\frac{4.37}{4.53}$	$\frac{4.17}{4.20}$	$\frac{18.97}{19.23}$	—	139-142	3.43 (2H, t, $\underline{CH_2}$–Het); 3.83 (2H, t, SO_2CH_2); 3.87 (3H, s, CH_3O); 7.05-7.95 (8H, m, H_{arom})	75.8
1l	$C_{19}H_{15}NO_2S_2$	$\frac{63.15}{64.56}$	$\frac{4.17}{4.28}$	$\frac{4.00}{3.96}$	$\frac{18.06}{18.14}$	—	132-135	3.50 (2H, t, $\underline{CH_2}$–Het); 3.93 (2H, t, SO_2CH_2); 7.33-8.15 (11H, m, H_{arom})	70.3
1m	$C_{15}H_{12}ClNOS$	$\frac{63.08}{62.17}$	$\frac{4.30}{4.17}$	$\frac{5.07}{4.83}$	$\frac{11.23}{11.07}$	$\frac{12.06}{12.23}$	59-61	3.23 (2H, t, $\underline{CH_2}$–Het); 3.47 (2H, t, SO_2CH_2); 7.37-7.95 (8H, m, H_{arom})	81.8
1n	$C_{15}H_{12}BrNOS$	$\frac{51.30}{53.90}$	$\frac{3.74}{3.62}$	$\frac{4.22}{4.19}$	$\frac{9.20}{9.59}$	$\frac{23.89}{23.91}$	73-74	3.25 (2H, t, $\underline{CH_2}$–Het); 3.45 (2H, t, SO_2CH_2); 7.32-7.65 (8H, m, H_{arom})	67.8
1o	$C_{15}H_{14}N_2S$	$\frac{69.90}{70.83}$	$\frac{5.54}{5.55}$	$\frac{11.16}{11.01}$	$\frac{13.08}{12.61}$	—	163-166	3.14 (2H, t, $\underline{CH_2}$–Het); 3.45 (2H, t, SO_2CH_2); 7.10-7.45 (8H, m, H_{arom}); 12.00 (1H, br. s, NH)	74.1

addition to the classic variant of carrying out the Pinner reaction we also tried the method proposed in [11]. Although it was simpler to carry out preparatively (hydrogen chloride is formed directly in the reaction mixture by the interaction of equimolar quantities of thionyl chloride and water) the yields of imino esters hydrochlorides were significantly reduced (40-70%), and the purity of the products was not always satisfactory. This was probably caused by side reactions linked with the introduction of water into the reaction mixture.

The imino esters hydrochlorides **3a-i** synthesized by us proved to be convenient synthons for obtaining the desired benzazoles **1a-o**. The best yields of these products were achieved on boiling equimolar quantities of reactants (see Scheme) in methanol for 4-6 h (Table 2).

Investigations on the one-step process of obtaining benzazoles from arylsulfonyl(thio)propionitriles (see Scheme) in PPA were carried out at 110-170°C and a reaction time of 2-8 h. It was established that satisfactory yields (up to 70%) of compounds **1a-d** may be achieved at 150-170°C after 6 h. Compounds with $n = 2$, X = O, S were formed in yields no greater than 26-32%, and with $n = 0$, X = NH 10-15% and marked resinification of the reaction mixture was observed. The one-step condensation in PPA may therefore be recommended only for the synthesis of 2-(2-arylsulfonylethyl)benzimidazoles **1a-d**. Samples of compounds obtained by the one- and two-step methods were identical in melting point and spectral characteristics.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 instrument for nujol suspensions. The ^{1}H NMR spectra were taken on a Bruker AM-300 instrument with an operating frequency of 300 MHz, internal standard was HMDS. The arylsulfonyl(thio)propionitriles **2** were synthesized by the known procedure of [12]. Products **1a-d**, and **1o** were analyzed by potentiometric titration in acetic acid solution using a 0.1 M solution of $HClO_4$ in CH_3COOH at an equivalent equal to unity [13].

Synthesis of 2-(2-Benzimidazolyl)ethyl Aryl Sulfones (1a-d). A mixture of 4-methylphenylsulfonylpropionitrile (10 mmol), *o*-phenylenediamine (10 mmol), and polyphosphoric acid (15 g) was heated to 150-170°C and maintained at this temperature for 6 h. After cooling to 90°C the reaction mixture was poured into water and aqueous ammonia added until the mixture was alkaline. The precipitated solid product **1** was filtered off, washed with water, dried, and recrystallized from aqueous alcohol.

Synthesis of Methyl Imino Esters Hydrochlorides of Arylsulfonyl(thio)propionic Acids (3a-i). A solution of arylthiopropionitrile **2** (10 mmol) in ether and absolute methanol (10 mmol) or a solution of arylsulfonylpropionitrile (10 mmol) in a mixture (3:1) of toluene and nitrobenzene and absolute methanol (10 ml) was saturated with dry hydrogen chloride at 20-25°C and stirred. The reaction mixture was maintained at the same temperature for 3 days. The precipitate of solid product **3** was filtered off, washed with ether, dried in vacuum, and recrystallized from a mixture of absolute ether and glacial acetic acid.

Synthesis of 2-[2-Arylsulfonyl(thio)ethyl]benzazoles (1a-o). A mixture of imino ester hydrochloride **3a-i** (10 mmol) and *o*-phenylenediamine, *o*-aminophenol, or *o*-aminothiophenol (10 mmol) in absolute methanol was boiled for 4-6 h. The reaction mixture was then cooled, and poured into aqueous sodium bicarbonate solution (10 mmol). The precipitated solid product **1** was filtered off, washed with water, dried, and recrystallized from aqueous alcohol.

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