ARYLSULFONYLACETONITRILES. II†. CYCLIZATION OF REACTIONS OF ARYLAMIDES OF ARYLSULFONYLCYANOTHIOACETIC ACID

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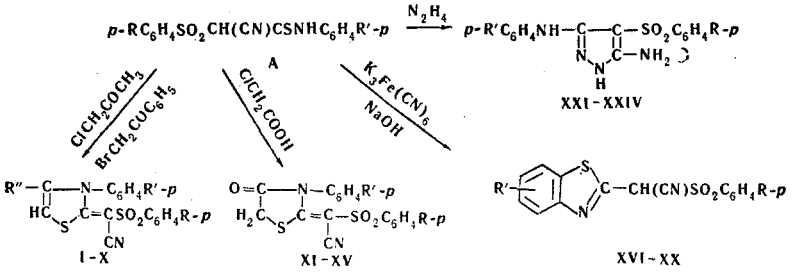
Condensation of the arylamides of arylsulfonylcyanothioacetic acid (A) with α-halocarbonyl and α-halocarboxy-compounds (chloroacetone, ω-bromoacetophenone, and chloroacetic acid) affords 3-aryl-4-methyl(aryl)-2-[(arylsulfonyl)cyanomethylene]-4,5-thiazolines and 3-aryl-[2(arylsulfonyl)cyanomethylene]-5H-4-thiazolidones. Oxidative cyclization of A has given derivatives of 2-[(arylsulfonyl)cyanomethyl]-benzothiazole. Reaction of A with hydrazine hydrate affords 3-aryl-amino-4-arylsulfonyl-5-aminopyrazoles. On the basis of their chemical properties and IR spectra, the pyrazole derivatives are assumed to possess the amine structure.

Arylamides of arylsulfonylcyanothioacetic acid (described by us previously [1]) are convenient and readily-accessible starting materials for the preparation of various heterocyclic systems bearing arylsulfonyl and cyano-substituents on one of the carbon atoms of the side chain. In contrast to the arylamides of arylsulfonylthioacetic acid [2], which do not undergo oxidative cyclization and do not react with chloroacetic acid, and to arylamides of bis(arylsulfonyl)thioacetic acid [3], which do not condense with α-halocarbonyl compounds, arylamides of arylsulfonylcyanothioacetic acid react readily with both.

On boiling A with chloroacetone or ω-bromoacetophenone in alcohol for 3-5 h, 3-aryl-4-methyl(aryl)-2-[(arylfulsonyl)cyanomethylene]-4,5-thiazolines (I-X, Table 1) were obtained. They were colorless or pale yellow crystalline solids, which were insoluble in nonpolar organic solvents and in water. They dissolved readily in acetone, and were moderately soluble in alcohol and acetic acid. They crystallized from alcohol.



The condensation of A with chloroacetic acid proceeded readily. A quantitative yield of 3-aryl-2-[(arylsulfonyl)cyanomethylene]-5H-4-thiazolidones was obtained after boiling with sodium acetate in alcohol for only 10-15 min (XI-XV, Table 2). These compounds are colored, high-melting crystalline compounds, which are insoluble in nonpolar organic solvents and in water. They dissolve readily in acetone and crystallize from alcohol.

† For Part I, see [1].

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TABLE 1. 3-Aryl-4-methyl(aryl)-2-[(arylsulfonyl)cyanomethylene]-4, 5-thiazolines (I-X)

Compound	R	R′	R″	Mp, °C (decomp.)	Molecular formula	S, % Found	S, % Calculated	Yield, %
I	H	CH_3	CH_3	211—212	$C_{19}H_{16}N_2O_2S_2$	17,1	17,4	90
II	H	Cl	CH_3	234—235	$C_{18}H_{13}ClN_2O_2S_2$	16.6	16,5	80
III	H	I	CH_3	243—244	$C_{18}H_{13}IN_2O_2S_2$	13,2	13,3	72
IV	CH_3	H	CH_3	245—246	$C_{19}H_{16}N_2O_2S_2$	17,2	17,4	86
V	CH_3	Cl	CH_3	208—209	$C_{19}H_{15}ClN_2O_2S_2$	15,9	15,9	73
VI	CH_3	Br	CH_3	220	$C_{19}H_{15}BrN_2O_2S_2$	14,4	14,3	97
VII	H	CH_3	C_6H_5	173	$C_{24}H_{18}N_2O_2S_2$	14,9	14,9	93
VIII	H	I	C_6H_5	267—268	$C_{23}H_{15}IN_2O_2S_2$	11,6	11,8	89
IX	CH_3	H	C_6H_5	270	$C_{24}H_{18}N_2O_2S_2$	14,7	14,8	77
X	Cl	Br	C_6H_5	224	$C_{23}H_{14}BrClN_2O_2S_2$	11,9	12,1	82

TABLE 2. 3-Aryl-2-[(arylsulfonyl)cyanomethylene]-5H-3-thiazolidones (XI-XV)

Compound	R	R′	Mp, °C (decomp.)	Molecular formula	S, % Found	S, % Calculated	Yield, %
XI	H	H	255—256	$C_{17}H_{12}N_2O_3S_2$	17,7	18,0	92
XII	H	CH_3	236—237	$C_{18}H_{14}N_2O_3S_2$	17,3	17,3	95
XIII	H	Cl	251—252	$C_{17}H_{11}ClN_2O_3S_2$	16,3	16,4	94
XIV	CH_3	Br	257—258	$C_{18}H_{13}BrN_2O_2S_2$	14,1	14,3	98
XV	CH_3	I	265—266	$C_{18}H_{13}IN_2O_2S_2$	12,9	12,9	96

Compounds A undergo oxidative cyclization with potassium ferricyanide in aqueous alkaline solution to give derivatives of 2-[(arylsulfonyl)-cyanomethylene]benzothiazole (XVI-XX, Table 3). These are colorless, high-melting crystalline solids, soluble with difficulty in organic solvents and insoluble in water. They dissolve in aqueous-alcoholic alkalies, and crystallize from acetic acid.

The compounds A are convenient starting materials for the synthesis of 3-arylamino-4-arylsulfonyl-5-aminopyrazoles, which have not been reported in the literature. Amongst these compounds, physiologically active substances have been found, which have effects on the central nervous system [4], possess marked anticonvulsive activity, and have analgesic and other properties. Since, on mixing the reagents, hydrogen sulfide is liberated and heat is evolved, it seems likely that the reaction of A with hydrazine hydrate proceeds via the formation of the hydrazone $p\text{-}RC_6H_4SO_2CH(CN)NHC(=N\text{–}NH_2)$, which we could not isolate, even when the reaction was carried out with cooling. The postulated hydrazone could not be obtained, either by reaction of cyanothioacetic arylamides with hydrazine hydrate [6]. Despite the fact that the first stage of the reaction proceeds in the cold, in order to obtain the cyclized products (XXI-XXIV), it is necessary to boil the reaction mixture, since cyclization of the intermediate compounds appears to take place slowly. Compounds XXI-XXIV (Table 4) are colorless, crystalline substance which dissolve readily in most organic solvents and in sulfuric and hydrochloric acids, but are insoluble in water. They crystallize well from aqueous alcohol. Bands due to vibration of the nitrile group are absent from the IR spectra of XXI-XXIV, indicating the completeness of the cyclization. The absence of vibrational deformational bands

TABLE 3. 2-[(Arylsulfonyl)cyanomethyl]benzothiazoles (XVI-XX)

Compound	R	R′	Mp, °C (decomp.)	Molecular formula	N, % Found	N, % Calculated	Yield, %
XVI	H	H	209—210	$C_{15}H_{10}N_2O_2S_2$	9,1	8,9	91
XVII	Cl	H	232—233	$C_{15}H_9ClN_2O_2S_2$	8,1	8,0	92
XVIII	H	6-CH_3	226—227	$C_{16}H_{12}N_2O_2S_2$	8,4	8,5	95
XIX	CH_3	6-Br	235—236	$C_{16}H_{11}BrN_2O_2S_2$	7,0	6,9	88
XX	CH_3	6-I	239—240	$C_{16}H_{11}IN_2O_2S_2$	6,2	6,2	92

TABLE 4

Compound	R	R′	Mp, °C	Molecular formula	N, % Found	N, % Calculated	Yield, %
XXI	H	Cl	210	$C_{15}H_{13}ClN_4O_2S$	15,9	16,1	92
XXII	CH_3	Br	198	$C_{16}H_{15}BrN_4O_2S$	13,8	13,8	91
XXIII	CH_3	Br	136	$C_{16}H_{15}BrN_4O_2S \cdot H_2O$	13,3	13,2	—
XXIV	CH_3	I	205	$C_{16}H_{15}IN_4O_2S$	12,2	12,3	51
XXV	Cl	H	146	$C_{15}H_{13}ClN_4O_2S$	S 8,8	S 9,2	85

due to the CH group of the pyrazole ring suggests the amino-structure for these compounds, since it is usually assumed that, in 3,4-pyrazole derivatives, the proton at $C_{(4)}$ participates in tautomeric conversion at $C_{(5)}$ [7].

EXPERIMENTAL

3-(p-Iodophenyl)-4-methyl-2-[(phenylsulfonyl)cyanomethylene]-4,5-thiazoline (III). A mixture of 0.22 g (0.5 mmole) of phenylsulfonylcyanothioacetic acid p-iodoanilide and 0.1 g (1.1 mmole) of chloroacetone in 3 ml of alcohol was boiled for 3 h. The crystals which separated on cooling were filtered off, washed with a small quantity of cold alcohol, and dried. Recrystallization from alcohol gave 0.17 g of coarse crystals.

Compounds I-VI (Table 1) were synthesized similarly.

3-(p-Tolyl)-4-phenyl-2-[(phenylsulfonyl)cyanomethylene]-4,5-thiazoline (VII). 0.16 g (0.5 mmole) of phenylsulfonylcyanothiacetic acid p-toluidide and 0.13 g (0.7 mmole) of ω-bromoacetophenone were dissolved in 3 ml of alcohol, and the mixture was boiled for 4-5 h. The crystals which separated on cooling were filtered off, washed with cold alcohol, and dried to give 0.19 g. Purification was effected by crystallization from alcohol. Colorless needles.

Compounds VIII-X (Table 1) were synthesized similarly.

3-Phenyl-2-[(phenylsulfonyl)cyanomethylene]-5H-4-thiazolidone (XI). A mixture of 0.2 g (0.63 mmole) of phenylsulfonylcyanothioacetic acid anilide, 0.2 g (2.1 mmole) of chloroacetic acid, and 0.5 g of crystalline sodium acetate in 3 ml of alcohol was boiled for 10-15 min. The crystals which separated on cooling were filtered off, washed with 100 ml of water and 15 ml of alcohol, and dried to give 0.22 g. Crystallized from alcohol as colorless needles.

Compounds XI-XV (Table 2) were obtained similarly. IR spectra of XI-XV, cm^{-1}: 2220 (C=N); 1740 (C=O); 1120-1160 and 1340-1360 (SO_2); 1510, 1230, 1210, 1190, and 1080 (vibrations of the heterocyclic ring) [8].

2-[(Phenylsulfonyl)cyanomethyl]-6-methylbenzothiazole (XVIII). A solution of 0.33 g (0.1 mmole) of phenylsulfonylcyanothiacetic acid p-toluidide and 2.2 g (54 mmole) of sodium hydroxide in a mixture of 10 ml of water and 5 ml of alcohol was added with stirring to a solution of 0.8 g (2.4 mmole) of potassium ferricyanide in 20 ml of water containing 30 g of ice. The mixture was stirred for 5-6 h and kept overnight at room temperature. The yellow solution was filtered and acidified with concentrated hydrochloric acid to pH 1-2. The resulting precipitate was filtered off, washed with water, and dried. After two recrystallizations from acetic acid–alcohol (1:4), the yield was 0.3 g of fine, colorless needles.

XVI-XX (Table 3) were obtained similarly. IR spectra, cm^{-1}: 2190 (C=N); 3280 (tert-CH); 1320-1340 and 1120-1160 (SO_2); 1540 (vibration of the thiazole ring) [9, 10].

3-(p-Bromophenylamino)-4-p-tolylsulfonyl)-5-aminopyrazole (XXII, XXIII). One milliliter of 50% hydrazine hydrate was added to a mixture of 0.22 g (0.5 mmole) of p-tolylsulfonylcyanothioacetic acid p-bromoanilide and 0.5 ml of alcohol. On adding the first drops of hydrazine hydrate, hydrogen sulfide was evolved (lead acetate paper), with slight evolution of heat, all the anilide dissolving. The mixture was boiled for 10-12 h, diluted with 10 ml of water, and the resulting precipitate filtered off, washed with water, and dried. Crystallization from 40% alcohol gave 0.18 g of long, colorless needles. Recrystallization from aqueous alcohol gave material containing a molecule of water (XXIII). Anhydrous material (XXII) was obtained by drying XXIII for 5-6 h at 130°.

Compounds XXI-XXV (Table 4) were obtained similarly. IR spectra, cm^{-1} 3370-3480 (NH); 1320-1340 and 1120-1160 (SO_2); 1610, 1560-1555, and 1485-1465 (vibrations of the pyrazole ring).

IR spectra were taken on a UR-10 spectrometer. The compounds were compressed in KBr disks (1.5 mg of compound per 100 mg of KBr). Recording in the range 700-400 cm^{-1} was carried out with KBr prisms, in the 1800-700 cm^{-1} range with NaCl prisms, and in the 4000-1800 cm^{-1} range with LiF prisms.

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