SYNTHESIS OF PYRAZOLE, ISOXAZOLE, AND PYRIMIDINE DERIVATIVES FROM 2-ARYLSULFONYL-2-CYANOVINYL ETHYL ETHERS

V. M. Neplyuev, T. A. Sinenko, and P. S. Pel'kis

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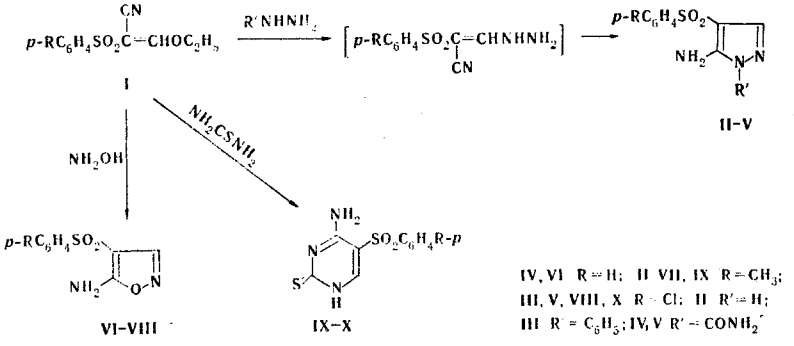
1-Substituted 4-arylsulfonyl-5-aminopyrazoles were obtained by condensation of 2-arylsulfonyl-2-cyanovinyl ethyl ethers with hydrazine or its derivatives (phenylhydrazine and semicarbazide); condensation with hydroxylamine gave 4-arylsulfonyl-5-aminoisoxazoles, and condensation with thiourea gave 2-thioxo-4-amino-5-arylsulfonyl-1,2-dihydropyrimidines.

In order to obtain compounds with possible physiological activity containing an arylsulfonly substituent in the heteroring we investigated the reaction of 2-arylsulfonyl-2-cyanovinyl ethyl ethers (I) with hydrazine and its derivatives, hydroxylamine, and thiourea.

1-Substituted 4-arylsulfonyl-5-aminopyrazoles (II-V, Table 1) were synthesized by condensation with hydrazine or substituted hydrazines (phenylhydrazine and semicarbazide).

The IR spectra of II-V contain bands at 1570 and 1495 cm^{-1} (vibrations of the pyrazole ring [1, 2]) and bands at 1320 and 1440 cm^{-1} (SO_2); characteristic absorption bands at 2220 (C≡N) and 1280 and 1080 cm^{-1}, which are characteristic for the C–O bond of an ether, are absent. In addition to the absorption bands of a pyrazole ring, absorption bands at 1630 (C=O) and 3380 cm^{-1} (NH) [3], which correspond to a primary amide group, appear in the IR spectra of III and IV.

The reaction of esters I with hydrazine and substituted hydrazines begins with nucleophilic substitution of the ether group to give N-(2-arylsulfonyl-2-cyanovinyl)-N'-substituted hydrazines. The isolation of pure noncyclic N-[2-(p-tolylsulfonyl)-2-cyanovinyl]hydrazine as an intermediate (see the experimental section), the IR spectrum of which contains characteristic



absorption bands at 2215 (C≡N), 1620 (C=C), and 1675 cm^{-1} (δ NH), serves as a confirmation of this. The same bands are observed in the IR spectrum of the similarly constructed unsubstituted enamine 2-(p-tolylsulfonyl)-2-cyanovinylamine; this confirms the structure of the isolated enehydrazine. During its cyclization to 4-(p-tolysulfonyl)-5-aminopyrazole (II), the intensity of the C≡N band decreases until it vanishes completely.

Ethers I react readily with hydroxylamine to give 4-arylsulfonyl-5-aminoisoxazoles (VI-VIII). We were unable to isolate intermediate noncyclic products in this reaction. The IR spectra of VI-VIII confirm their structures as cyclic products [3430, 3330 (NH_2); 1310, 1165, 1130 (SO_2); 1640, 1495, 1450, 670, 610 cm^{-1} (vibrations of an isoxazole ring [4, 5]); absorption at 2220 cm^{-1} is absent].

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TABLE 1. 1,4,5-Substituted Pyrazoles (II-V), 4-Arylsulfonyl-5-aminoisoxazoles (VI-VIII), and 2-Thioxo-4-amino-5-arylsulfonyl-1,2-dihydropyrimidines (IX, X)

Compound	mp, °C	Found, %	Empirical formula	Calc., %	R_f	Yield, %
II	154	C 50,5 H 4,7 N 17,5	$C_{10}H_{11}N_3O_2S$	50,6 4,7 17,8	0,82	55
III	167	N 12,9 Cl 10,2	$C_{15}H_{12}ClN_3O_2S$	12,6 10,6	0,83	82
IV	200	C 45,2 H 3,5 N 20,6	$C_{10}H_{10}N_4O_3S$	45,1 3,8 21,0	0,80	43
V	188	N 18,6 Cl 11,3	$C_{10}H_9ClN_4O_3S$	18,5 11,7	0,75	65
VI	128	C 48,4 H 3,8 N 12,4	$C_9H_8N_3O_3S$	48,2 3,6 12,5	0,80	63
VII	113	N 11,5 S 13,4	$C_{10}H_9N_2O_3S$	11,8 13,5	0,79	68
VIII	130	C 42,1 H 2,5 N 10,8	$C_9H_7ClN_2O_3S$	41,6 2,7 10,8	0,88	60
IX	270	N 14,3 S 22,3	$C_{11}H_{11}N_3O_2S_2$	14,5 22,8	0,86	57
X	290	C 39,7 H 3,0 N 13,5	$C_{10}H_8ClN_3O_2S_2$	39,8 2,7 13,9	0,85	56

2-Thioxo-4-amino-5-arylsulfonyl-1,2-dihydropyrimidines (IX-X) were synthesized by heating ethers I with thiourea and subsequent cyclization in the presence of alkali. The thione form of IX-X in the crystalline state is confirmed by the IR spectra, which do not contain bands of thiol groups at 2250-2600 cm^{-1}. It must be noted that the lactam form was also observed in the crystalline state for 5-amino-6-thioxo- and 4(6)-hydroxypyrimidines [6, 7]. The IR spectra of IX-X contain absorption bands at 1320 and 1150 (SO_2), 3440 (NH), and at 1585, 1550, 1480, and 1440 cm^{-1} (vibrations of the pyridine ring [8]).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The purity of the products was monitored by thin-layer chromatography (TLC) on silica gel under standard conditions on Silufol UV-254 plates at room temperature in an n-butanol–acetic acid–water system (5:3:2). The R_f values of the synthesized compounds are presented in Table 1.

4-(p-Tolylsulfonyl)-5-aminopyrazole (II). A 0.03-g (0.6 mmole) sample of hydrazine hydrate was added at room temperature to a solution of 0.13 g (0.5 mmole) of 2-(p-tolylsulfonyl)-2-cyanovinyl ethyl ether in 10 ml of alcohol, and the mixture was stirred for 5 h. The precipitate was removed by filtration, washed with alcohol, and crystallized from alcohol to give 0.07 g of II. Compounds III-V were similarly synthesized (Table 1).

2-(p-Tolylsulfonyl)-2-cyanovinylhydrazine. A 0.06-g (1.2 mmole) sample of hydrazine hydrate was added to a suspension of 0.25 g (1 mmole) of 2-(p-tolylsulfonyl)-2-cyanovinyl ethyl ether in 25 ml of water, and the mixture was stirred at room temperature for 2 h. The precipitate was removed by filtration, washed with water, and crystallized from water to give 0.15 g (65%) of a product with mp 141°C. Found: N 17.4%. $C_{10}H_{11}N_3O_2S$. Calculated: N 17.7%. The product was cyclized to 4-(p-tolylsulfonyl)-5-aminopyrazole (II) by stirring in alcohol (5 h) at room temperature.

4-Phenylsulfonyl-5-aminoisoxazole (VI). A 0.07-g (1 mmole) sample of hydroxylamine hydrochloride was added to a suspension of 0.25 g (1 mmole) of 2-phenylsulfonyl-2-cyanovinyl ethyl ether in 10 ml of water, and the mixture was made alkaline to pH 8 with 1% NaOH solution. It was then stirred at room temperature for 5 h, and the resulting precipitate was removed by filtration, washed with water, dried, and crystallized from 40% aqueous alcohol to give 0.14 g of product.

Compounds VII and VIII were similarly obtained (Table 1).

2-Thioxo-4-amino-5-(p-chlorophenylsulfonyl)-1,2-dihydropyrimidine (X). A mixture of 0.14 g (0.5 mmole) of 2-(p-chlorophenylsulfonyl)-2-cyanovinyl ethyl ether, 0.04 g (0.5 mmole) of thiourea, and 5 ml of toluene was refluxed for 6 h, after which the solvent was removed by evaporation, and the residue was refluxed in 10 ml of alcohol. The mixture was filtered, the alcohol-insoluble portion was treated with 10 ml of

5% NaOH in alcohol, and the mixture was allowed to stand at room temperature for 1 h. It was then acidified to pH 1 with concentrated HCl, and the precipitate was removed by filtration, washed with water, and dried to give 0.1 g of product.

Compound IX was similarly synthesized (Table 1).

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1,2,6-PHOSPHADIAZINE-1,3-DIONE DERIVATIVES

I. S. Levi, L. D. Garaeva, É. M. Osipova, and M. N. Preobrazhenskaya

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A number of new 1-aryloxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones were obtained from arylphosphoric acid dichlorides through the corresponding diamidophosphoric acid esters. Conversion of the 1-phenoxy and 1-ethoxy derivatives to 6-methyl-4-hydroxypyrimidine under Vilsmeier formylation conditions was observed. These compounds were thionated to give the corresponding 1,3-dithiones; the 1-phenoxy derivative was subsequently methylated in the 6 position and animated to give the phosphorus-containing analog of 6-methyl-2-thiocytosine. The bromination of the 1-ethoxy compound and replacement of the bromine by a secondary amine residue were studied.

1-Alkoxy(aryloxy)-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones are structural analogs of 6-methyluracil. The introduction of hydrophobic or hydrophilic substituents in the uracil molecule affects the ability of the compounds to react with enzymes. We have previously synthesized phosphoric analogs of 6-methyluracil containing various alkoxy groups in the 1 position [1]. In the present paper we describe the preparation of a number of 1-aryloxyphosphadiazinediones (IIa-e) from the corresponding diamidophosphoric acid esters (Ia-e, Table 1) by the method proposed by Zavialov and co-workers [2] for the synthesis of 1-phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIf). The reactivities of compounds of this class were studied in the case of phosphauracil IIf and 1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIg) in order to create from them analogs of the components of nucleic acids or coenzymes (analogs of uridine, cytidine, and folic acid).*

Bromination of 1-ethoxy compound IIg in carbon tetrachloride–dimethylformamide (DMF) leads to 4-bromo-1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (III), in the UV spectrum of which, as in the spectra of 5-halouracils, a bathochromic shift to 276 nm (Table 3) as compared with the spectrum of the starting compound (λ_{max} 258 nm) is observed. The PMR spectrum does not contain a signal of the 4-H proton, and, as in the spectrum of starting IIg, the signals of the protons of the ethoxy group are doubled because of coupling with the phosphorus atom ($J_{\alpha\text{-HP}} = 9$ Hz, $J_{\beta\text{-HP}} = 1$ Hz).

* See the display at top of next page after Table 1.

Oncological Science Center, Academy of Medical Sciences of the USSR, Moscow 115478.

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