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A Convenient Synthetic Approach to Derivatives of 5-Phenylsulfonyl-2-Thiouracil and Its Condensed Analogs

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Abstract—3-Amino-2-phenylsulfonylacrylonitrile, an available multicenter reagent, when treated successively with phenyl, ethyl, or allyl isothiocyanate and hydrochloric acid forms N^3-substituted 5-phenylsulfonylthiouracils. Some of them were found to be suitable starting mateials for preparing of thiazoline and thiodiazolidine structures fused with the 4-pyrimidone system.
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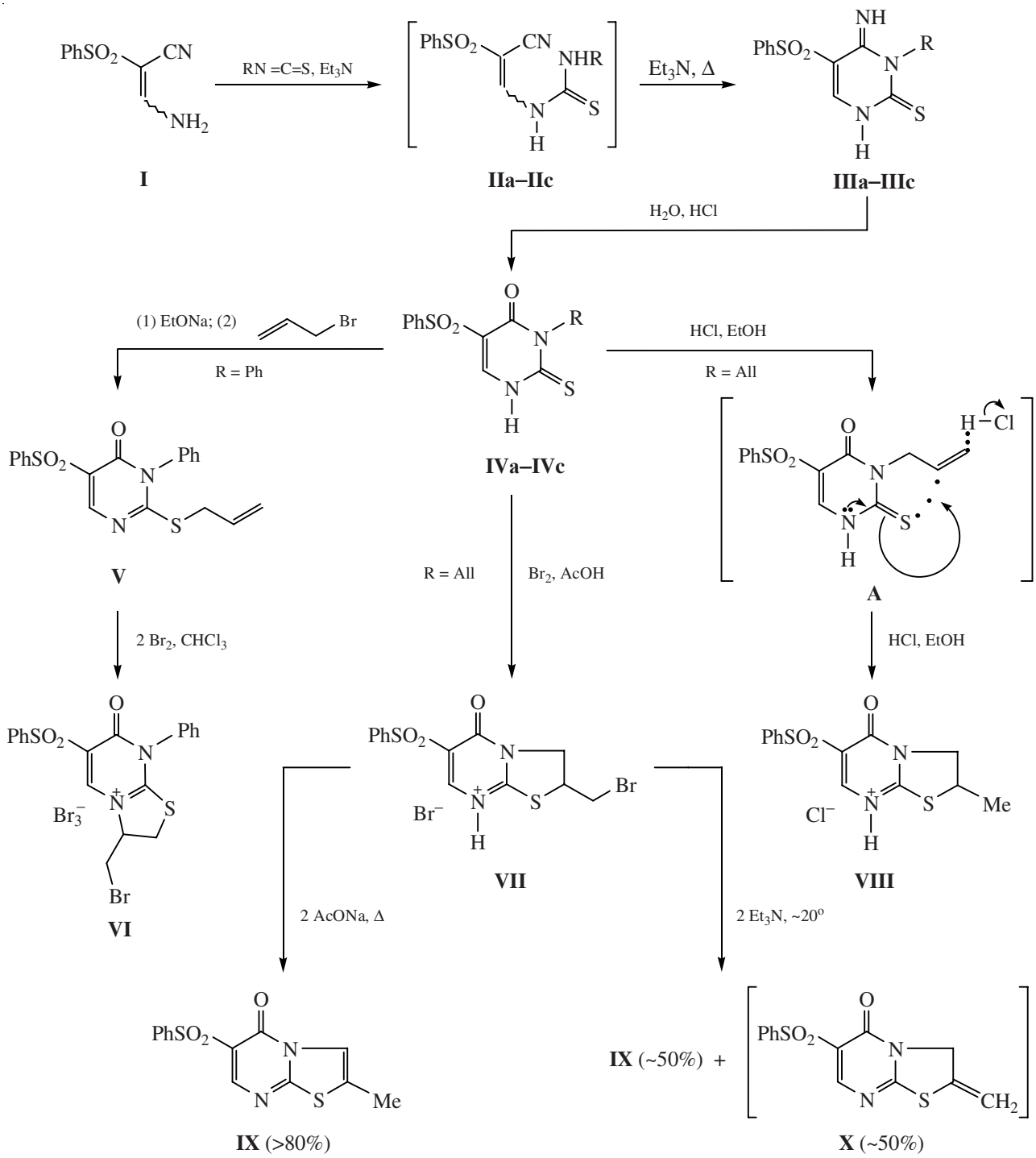
Development of facile synthetic procedures for preparing pyrimidine bases containing strong electron-acceptor groups on the C^5 atom presents significant interest not only for investigations into specific reactivity of such electron-deficient systems, but also for preparing bioregulators of diverse action. In this connection our research into transformations of 5-nitropyrimidines [1] and functionalized 5-pyrimidylphosphonium salts [2] over the past 15 years proved to be important. Quite recently [3] we offered a convenient synthetic approach to 5-arylsulfonyl-substituted uracils and cytosines on the basis of enaminonitriles of the general formula RNHCH=C(CN)·SO_2Ar. In their turn, these compounds are easily formed from the products of condensation of arylsulfonylacetonitriles with triethoxymethane [4]. In the present work we showed that the sequence of transformations **I** → **II** → **III** → **IV** → **V** holds promise as a route to previously unknown 5-phenylsulfonylthiouracil derivatives, which significantly extends the range of methods for preparing such compounds [5–12]. As seen from the scheme, reagent **I** is treated with phenyl, ethyl, or allyl isothiocyanate in the presence of triethylamine, and cyclization products **II** are heated with 10% HCl. Under these conditions, N^3-substituted 5-phenylsulfonylthiouracils **IV** are formed in high yields (Table 1). Despite the fact, that only three representatives of compounds **IV** were prepared, the application field of the suggested approach is undoubtedly wider, since many alkyl and aryl isothiocyanates can evidently react with enaminonitrile **I** according to a [2+4]-cycloaddition scheme characteristic of two model heterocumulenes, ethyl and phenyl isothiocyanates.

Note that the use of allyl isothiocyanate in this reaction allows one to introduce the allyl radical specifically to the N^3 center of the thiouracil system. At the same time, to synthesize an *S*-allyl derivative of 3-phenyl-5-phenylsulfonylthiouracil, we used to success the transformation **IVa** → **V** presented in the scheme. Under the action of bromine or HCl, substituted thiouracils containing *S*- and *N*-allyl groups undergoexpected intramolecular cyclizations to form substituted thiazoline and thiazolidine fragments fused with the 4-pyrimidone system (structures **VI–X**. The regioselectivity of such electrophilic cyclizations was repeatedly discussed previously. Therefore, in considering the structure of compounds **VI–VIII** we took account of publications concerning cyclizations of *S*-allyl [13–15] and *N*-allyl [16] derivatives of pyrimidine bases. Even though the mechanism of such cyclizations is intricate [17, 18], their motive forces are evident, because they are connected with the effect of halogens, halogen chlorides, and some other electrophilic agents on the electron density distribution in the allyl group, which can lead to transition states like A and favor cyclization (see scheme).

It is interesting that treatment of the reaction product of N^3-allyl-5-phenylsulfonylthiouracil with bromine with triethylamine under ordinary conditions gives a mixture of two condensed bases **IX, X** in a 1 : 1



I **IIa–IIc** **IIIa–IIIc**

IVa–IVc

V **A**

VI **VII** **VIII**

IX (>80%) **X** (~50%)

R = Ph (**a**), Et (**b**), CH_2=$CHCH_2$ (**c**).

ratio. This mixture cannot be separated by crystallization, and preparative synthesis of product **IX** is better performed by dehydrobromination of compound **VI** with sodium acetate. Isomeric pairs of condensed bases similar to **IX** and **X** have already been described [15].

Note in conclusion that the structure of all the compounds presented in the scheme not only follows from the procedure of their synthesis, but is also consistent with their IR and ^{1}H NMR spectra (Table 2). The IR spectra of compounds **III–IX** lack absorption bands in the range 2100–2300 cm^{-1}, implying that the

Table 1. Yields, constants, and elemental analyses of compounds **III–IX**

Comp. no.	Yield, %	mp, °C (EtOH)	Found, %		Formula	Calculated, %	
			S (Cl, Br)	N		S (Cl, Br)	N
IIIb	54	>300	20.93	13.58	$C_{13}H_{13}N_3O_2S_2$	20.86	13.67
IIIc	60	>300	21.84	14.17	$C_{12}H_{13}N_3O_2S_2$	21.71	14.23
IVb	78	251-253	20.85	9.14	$C_{13}H_{12}N_2O_3S_2$	20.80	9.08
IVc	79	244–246	21.63	9.56	$C_{12}H_{12}N_2O_3S_2$	21.64	9.45
V	86	213–215	16.78	7.33	$C_{19}H_{16}N_2O_3S_2$	16.68	7.29
VI	71	178–180[a] (decomp.)	9.21 (44.56)	4.26	$C_{19}H_{16}Br_4N_2O_3S_2$	9.11(45.39)	3.98
VII	95	157–159	13.82 (34.44)	6.03	$C_{13}H_{12}Br_2N_2O_3S_2$	13.70(34.13)	5.98
VIII	63	241–243	18.70 (10.30)	8.05	$C_{13}H_{13}ClN_2O_3S_2$	18.60(10.28)	8.12
IX	80	226–228	20.98	9.10	$C_{13}H_{10}N_2O_3S_2$	20.93	9.14

[a] Compound **VI** was not additionally purified.

Table 2. Spectral data for compounds **III–IX**

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (DMSO-d_6)
IIIb	1630 (C=NH), 3100–3300 (NH_{assoc})	5.03–5.25 m (4H, $2CH_2$), 5.78 m (1H, CH), 7.59–7.73 m (3H, C_6H_3), 8.00–8.30 m (4H, NH, C_6H_2, C^6–H)
IIIc	1625 (C=NH), 3050–3350 (NH_{assoc})	1.18 t (3H, CH_3), 4.53 m 7.59–7.73 m (3H, C_6H_3), 8.00–8.10 m (4H, NH, C_6H_2, C^6–H)
IVb	1675 (C=O), 3100–3350 (NH_{assoc})	4.77 m (2H, CH_2), 5.12 m (2H, CH_2), 5.75 m (1H, CH), 7.56–7.91 m (5H, C_6H_5), 8.10 s (1H, C^6–H), 13.43 br.s (1H, NH)
IVc	1670 (C=O), 3050–3350(NH_{assoc})	1.12 t (3H, CH_2), 4.20 m (2H, CH_2), 7.56–8.00 m (5H, C_6H_5), 8.08 s (1H, C^6–H), 13.37 br.s (1H, NH)
V	1700 (C=O), 3100–3600 (bands are absent)	3.81 d (2H, SCH_2), 5.14 d, 5.31 d (2H, CH_2), 5.83 m (1H, CH), 7.30–7.98 m (10H, $2C_6H_5$), 8.63 s (1H, C^6–H)
VI	1730 (C=O, band with a shoulder), 3100–3600 (bands are absent)	3.17 m (2H, CH_2), 4.01 m (2H, CH_2), 4.93 m (1H, CH), 7.14–7.94 m (10H, $2C_6H_5$), 8.57 s (1H, C^5–H)
VII	1705 (C=O), 3080 (NH)	3.91 m (2H, CH_2), 4.38 m (3H, CH_2, CH), 6.87 br.s (1H, NH), 7.57–7.99 m (5H, C_6H_5), 8.47 s (1H, C^7–H)
VIII	1725 (C=O, band with a shoulder), 3200–3400 (NH_{assoc})	0.94 d (3H, CH_3), 3.60 d.d, 3.94 d.d (2H, CH_2), 3.67 m (1H, CH), 7.07–7.49 m (5H, C_6H_5), 8.01 s (1H, C^7–H), 8.36 br.s (1H, NH)
IX	1685 (C=O), 3150–3600 (bands are absent)	2.42 s (3H, CH_3), 7.58–8.01 m (6H, $2C_6H_5$, C^3–H), 8.70 s (1H, C^7–H)
X[a]	–	5.06 s (2H, CH_2), 5.53 d (2H, CH_2), 7.58–8.02 (5H, C_6H_5), 8.56 s (1H, C^7–H)

[a] The ^1H NMR spectrum of compound **X** is extracted from the spectrum of the mixture of compounds **IX** and **X**.

cyano group of reagent **I** is involved in cyclization just on early stages of the process. Furthermore, the carbonyl group of the 4-pyrimidone fragment in all the thiouracil derivatives **IV–IX** is readily identified by IR spectroscopy (ν_{CO} 1670–1730 cm^{-1}). At the same time, evidence for the similar nature of compounds **IV–IX** is provided by the observation the ^1H NMR spectra of a narrow singlet signal at 8.0-8.7 ppm, assignable to the proton at the C^6 center the 4-pyrimidone ring. Finally, the presence of the corresponding substituents in the mononuclear (**IV, V**) and condensed (**VI–X**) heterocyclic structures was also confirmed by means of ^1H NMR spectra (Table 2).

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets. The ^1H NMR spectra

were taken on a Varian VXR-300 spectrometer in DMSO-d_6 against internal TMS. Compounds **IIIa** and **IVa** were prepared by the procedure described in [3].

3-Alkyl-4-imino-5-phenylsulfonyl-3,4-dihydro-1*H*-pyrimidine-2(1*H*)-thiones (IIIb, IIIc). A mixture of 0.0048 mol of 3-amino-2-phenylsulfonylacrylonitrile (**I**) [4], 0.0053 mol of alkyl isothiocyanate, and 0.0053 mol of triethylamine was heated from 25°C to 95°C over the course of 10–15 min, kept at that temperature for 15–20 min, and then diluted with 25 ml of ethanol. The precipitate that formed was filtered off, washed with 25 ml of acetone, and compounds **IIIb** and **IIIc** were purified by crystallization.

3-Alkyl-2-thioxo-5-phenylsulfonyl-3,4-dihydro-3*H*-pyrimidin-4-ones (IVb, IVc) were prepared by acid hydrolysis of the corresponding imino compounds by the procedure described in [3].

2-Allylsulfanyl-1-phenyl-5-phenylsulfonylpyrimidin-3*H*-4-one (V). To a solution of 0.003 mol of sodium ethylate in 15 ml of absolute ethanol, 0.003 mol of compound **IVa** was added, and the suspension formed was stirred until the solid phase dissolved completely. Allyl bromide, 0.004 mol, was added to the solution, and the mixture was refluxed for 30 min and then cooled. The precipitate formed was filtered off, washed in succession with ethanol and water, and compound **V** was purified by crystallization.

3-Bromomethyl-7-oxo-8-phenyl-6-phenylsulfonyl-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidinium tribromide (VI). To a solution of 0.0013 mol of compound **V** in 25 ml of anhydrous chloroform a solution of 0.0027 mol of bromine in 15 ml of anhydrous chloroform was added under stirring and cooling with ice. The reaction mixture was stirred at 0°C for 20 min, the precipitate was filtered off, washed with chloroform, and dried in an oil-pump vacuum at 30–40°C to obtain compound **VI**. The product was analyzed without additional purification.

2-Bromomethyl-5-oxo-6-phenylsulfonyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,3-*a*]pyrimidinium bromide (VII). To a suspension of 0.0016 mol of compound **IVb** in 30 ml of acetic acid, a solution of 0.0019 mol of bromine in 5 ml of acetic acid was added with stirring over the course of 15–20 min. The mixture was stirred for 3 h, the precipitate that formed was filtered off, washed in succession with acetic acid and absolute diethyl ether, and compound **VII** was purified by crystallization.

2-Methyl-5-oxo-6-phenylsulfonyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidinium chloride (VIII). Compound **IVb**, 0.002 mol, was suspended in 40 ml of absolute ethanol, and anhydrous hydrogen chloride was passed through the suspension over the course of 2 h with stirring under reflux. After cooling, the precipitate that formed was filtered off, and compound **VIII** was purified by crystallization.

2-Methyl-6-phenylsulfonyl-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidin-5-one (IX). A mixture of 0.0013 mol of compound **VII** and 0.0026 mol of anhydrous sodium acetate was refluxed with stirring for 8 h. The precipitate that formed was filtered off, washed with water, and compound **IX** was purified by crystallization.

2-Methylene-6-phenylsulfonyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (X). A solution of 0.0013 mol of compound **VII** and 0.0026 mol of triethylamine in 30 ml of acetonitrile was stirred at 20–25°C for 10–12 h. The precipitate that formed was filtered off, washed with water, dried, and crystallized from ethanol to obtain a mixture of compounds **IX** and **X** in a ~1 : 1 ratio (by ^{1}H NMR). Attempted separation of this mixture by crystallization failed.

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