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Synthesis of 4-Tosyl-5-chloro-1,3-thiazole-2-carbonitrile and Its Transformations

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Abstract—Reaction of the available 1-tosyl-2,2-dichloroethenyl isothiocyanate with sodium cyanide yields new clearly electrophilic substrate of thiazole nature containing the nitrile group, the tosyl residue, and the chlorine atom at C^2, C^4, and C^5 respectively. The direction of the reaction of this substrate with nucleophile depends significantly on the nature of the latter. It was used in regioselective syntheses of a series of the unknown previously trifunctional thiazoles.

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Systematic studies of nucleophilic substitution at C^4 and C^5 carbon atoms of 1,3-thiazole ring which were begun recently, were significantly complicated by the fact that only small number of suitable objects was known. Therefore syntheses of new highly reactive electrophilic substrates of thiazole nature present obvious interest. In this work we delveloped one of such procedures carried out by means of cyclocondensation of the available 1-tosyl-2,2-dichloroethenyl isothiocyanate **I** with sodium cyanide. As it is shown in the scheme, the first step is evidently the addition of cyanide anion to the isothiocyanate group of the reagent **I**. Then the intermediate compound **II** or the product of its cyclization **III** eliminates sodium chloride and forms trisubstituted thiazole **IV** containing the nitrile group and the tosyl residue in the positions 2 and 4, and the reactive chlorine atom at the C^5 carbon atom.

Electrophilic substrate **IV** is a yellowish crystalline substance which is formed in high yield. It is quite stable at storage and is suitable for the preparative syntheses of a large number of new functionalized thiazole derivatives. Some of them **V–XIII** are presented in the scheme and in Table 1.

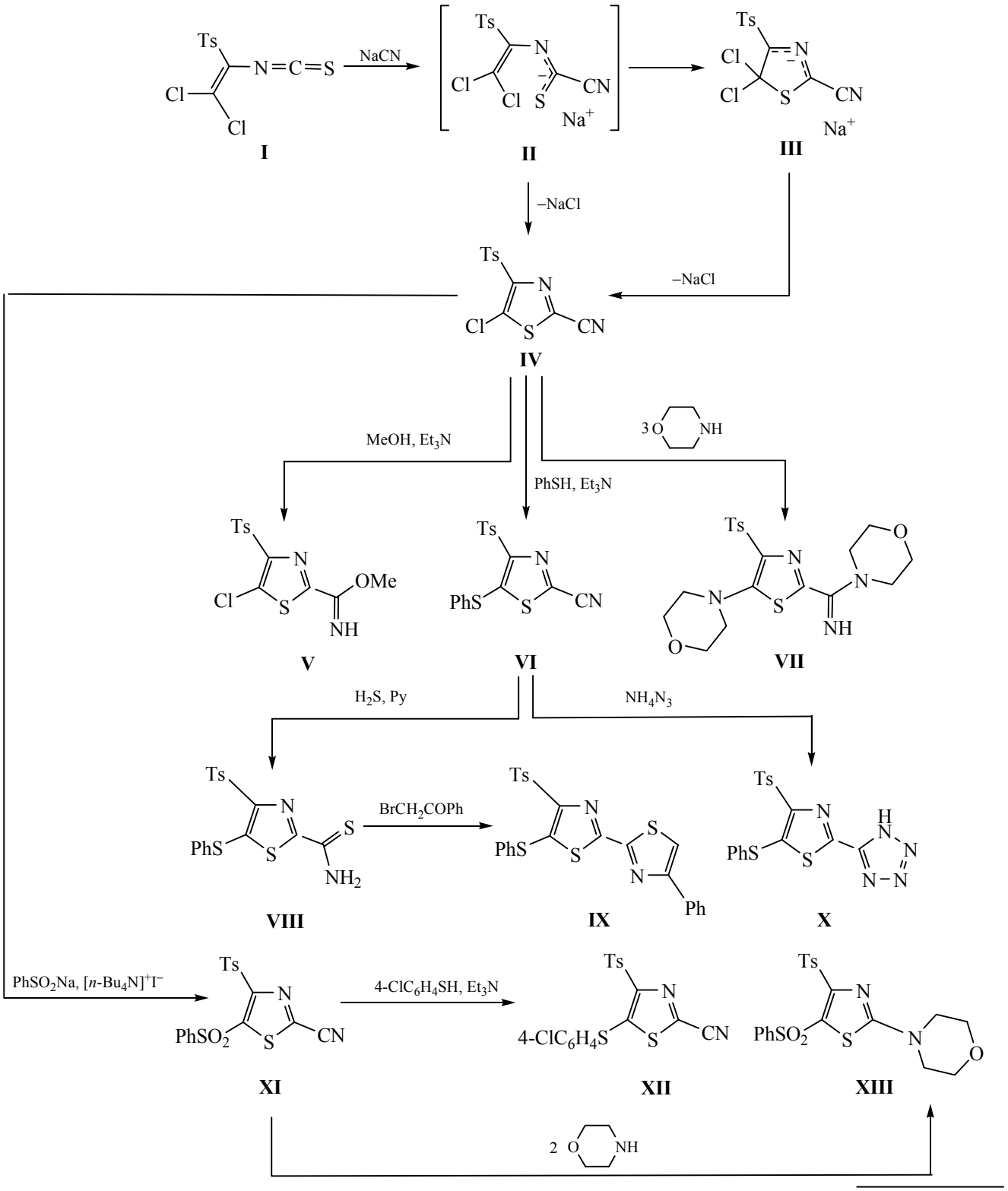
It is interesting that substrate **IV** reacts in different manner with methanol and thiophenol in the presence of triethylamine. In the first case the "hard" nucleophile adds at the C≡N bond, while in the second event the "soft" nucleophile attacks the position 5 of the thiazole ring (see the transformations **IV** → **V** and **IV** → **VI**). At the same time the morpholine even at 20°C reacts with both electrophilic centers giving the corresponding trifunctional thiazole **VII**.

Note that the product of condensation of the substrate **IV** with thiophenol remains a quite pronounced electrophile as seen from the transformations **VI** → **VIII** and **VI** → **X** proceeding under mild conditions.

Consider finally the reaction of compound **IV** with sodium benzenesulfinate leading to the electrophilic substrate **XI** which is the most reactive compared to the other thiazoles presented in the scheme. Similarly to substrate **IV** its analog **XI** reacts with soft and hard nucleophiles by different pathways. The reaction of "soft" *p*-chlorothiophenol in the presence of triethylamine proceeds as the nucleophilic substitution of phenylsulfonyl group at C^5 center of compound **XI**. At the same time a "harder" morpholine attacks C^2 carbon atom resulting in the transformation **XI** → **XIII** accompanied by elimination of the cyanide anion.

The introduction of the electron-donor morpholino group in the position 2 of the thiazole ring decreases the electrophilicity of the C^5 center, and therefore compound **XIII** does not take part in further reaction with morpholine.

[†] Deceased.



Structures of new substrate **IV** and the products of its transformations **V**–**XIII** agree with the IR and NMR data presented in Table 2. For example, the comparison of the IR spectra of compounds **I**, **IV** shows that the disappearance of the broad band of asymmetric vibrations of isothiocyanate group at 2040 cm^{-1} is accompanied by the appearance of a narrow band of the C≡N bond at 2250 cm^{-1}. These

Table 1. Yields, constants, and elemental analysis data for compounds **IV–XIII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Claculated, %	
			S	N(Cl)		S	N(Cl)
IV	87	167–168 (EtOH–CH_3CN, 1:1)	12.31	9.12(11.32)	$C_{11}H_7ClN_2O_2S_2$	12.46	9.38(11.87)
V	73	124–125 (MeOH)	19.24	8.17(9.96)	$C_{12}H_{11}ClN_2O_3S_2$	19.38	8.47(10.72)
VI	88	210–211	25.64	7.31	$C_{17}H_{12}N_2O_2S_3$	25.82	7.52
VII	76	145–146 (EtOH)	14.54	12.27	$C_{19}H_{24}N_4O_4S_2$	14.69	12.83
VIII	72	247–248 (EtOH–DMF, 5:1)	30.92	5.94	$C_{17}H_{14}N_2O_2S_4$	31.55	6.89
IX	84	163–164 (EtOH–DMF, 5:1)	25.14	5.21	$C_{25}H_{20}N_2O_2S_4$	25.21	5.51
X	68	195–196 (EtOH–H_2O, 10:1)	23.02	16.17	$C_{17}H_{13}N_5O_2S_3$	23.15	16.85
XI	76	159–160 (EtOH)	23.49	6.37	$C_{17}H_{12}N_2O_4S_3$	23.78	6.93
XII	72	209–210 (EtOH)	23.11	6.21(8.34)	$C_{17}H_{11}ClN_2O_2S_3$	23.64	6.88(8.71)
XIII	81	195–196 (EtOH)	20.48	5.63	$C_{20}H_{20}N_2O_5S_3$	20.70	6.03

Table 2. Spectral data of compounds synthesized **IV–XIII**

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
IV[a]	2.46 s (3H, CH_3), 7.36–7.38 m (2H$_{arom}$), 7.94–7.96 m (2H$_{arom}$)
V	2.45 s (3H, CH_3), 3.95 s (3H, OCH_3), 7.36–7.38 m (2H$_{arom}$), 7.96–7.98 m (2H$_{arom}$), 8.76 s (1H NH)
VI[b]	2.34 s (3H, CH_3), 7.38–7.40 m (2H$_{arom}$), 7.56–7.78 m (5H$_{arom}$), 8.08–8.10 m (2H$_{arom}$)
VII[c]	2.43 s (3H, CH_3), 3.46 m (8H$_{morph}$), 3.70 m (8H$_{morph}$), 7.34–7.36 m (2H$_{arom}$), 7.94–7.96 m (2H$_{arom}$), NH$_{ex}$
VIII[d]	2.31 s (3H, CH_3), 7.34–7.36 m (2H$_{arom}$), 7.51–7.72 m (5H$_{arom}$), 7.98–8.00 m (2H$_{arom}$), 8.62 s (2H, NH_2)
IX	2.45 s (3H, CH_3), 7.26–7.40 m (5H$_{arom}$), 7.46–7.54 m (4H$_{arom}$), 7.64–7.66 m (2H$_{arom}$), 7.80–7.82 m (2H$_{arom}$), 8.07–8.09 (2H$_{arom}$)
X[e]	2.44 s (3H, CH_3), 7.37–7.39 m (2H$_{arom}$), 7.47–7.57 m (3H$_{arom}$), 7.62–7.64 m (2H$_{arom}$), 8.01–8.03 m (2H$_{arom}$), NH$_{ex}$
XI	2.37 s (3H, CH_3), 7.41–7.43 m (2H$_{arom}$), 7.56–7.58 m (2H$_{arom}$), 7.74 m (2H$_{arom}$), 7.88 m (1H$_{arom}$), 8.08–8.10 m (2H$_{arom}$)
XII	2.49 s (3H, CH_3), 7.44–7.46 m (2H$_{arom}$), 7.56–7.58 m (2H$_{arom}$), 7.74–7.76 m (2H$_{arom}$), 7.89–7.91 m (2H$_{arom}$)
XIII	2.43 s (3H, CH_3), 3.44 m (4H$_{morph}$), 3.68 m (4H$_{morph}$), 7.32–7.34 m (2H$_{arom}$), 7.59–7.75 m (5H$_{arom}$), 8.02–8.04 m (2H$_{arom}$)

[a] IR spectrum, ν, cm^{-1}: 1150, 1350 (SO_2); 2250 (C≡N). [b] IR spectrum, ν, cm^{-1}: 1150, 1375 (SO_2); 2225 (C≡N). [c] IR spectrum, ν, cm^{-1}: 1150, 1350 (SO_2); 1610 (C≡N); 3310 (NH). [d] IR spectrum, ν, cm^{-1}: 1125, 1370 (SO_2); 3310, 3410 (NH_2). [e] 1125, 1325 (SO_2); 3450 (NH).

data confirm the formation of a cyclic structure. On the other hand, the addition of methanol, morpholine, and hydrazoic acid to the C≡N bond of substrates **IV**, **VI** leads to the disappearance of the narrow band in the range 2250–2260 cm^{-1} belonging to the nitrile group. At the same time the presence of the tosyl residue in compound **IV** and its derivatives **V–XIII** agrees with the fact that in ^{1}H NMR spectra of all these compounds a singlet of methyl group bound with the phenylene fragment is observed in the range 2.43–2.49 ppm. Besides this signal in the spectrum of compound **V** two singlets at 3.95 and 8.76 ppm were observed. They

belong to the methoxy group and the imine fragment confirming reliably that the addition of methanol to the C≡N bond of substrate **IV** takes place.

EXPERIMENTAL

IR spectra were recorded on an UR-20 spectrometer in KBr pellets. ^{1}H NMR spectra were taken on a Varian Mercury-400 spectrometer in DMSO-d_6 against internal TMS.

1-Tosyl-2,2-dichloroethenyl isothiocyanate (I) was prepared as described in [1].

4-Tosyl-5-chloro-1,3-thiazole-2-carbonitrile (IV). To a solution of 45 mmol of compound **I** in 50 ml of acetone 45 mmol of sodium cyanide were added, and the mixture obtained was stirred for 24 h at 20°C. The solvent was removed in a vacuum, the residue was treated with 15 ml of ethanol, the precipitate formed was filtered off and crystallized from 1:1 ethanol–acetonitrile mixture.

Methyl 4-tosyl-5-chloro-1,3-thiazol-2-imidocarboxylate (V). To a suspension of 3 mmol of compound **IV** in 10 ml of methanol 6 mmol of triethylamine were added, the mixture obtained was heated for 5 h at 65°C and cooled to 20°C. The precipitate formed was filtered off and crystallized from methanol.

4-Tosyl-5-phenylthio-1,3-thiazole-2-carbonitrile (VI). To a solution of 1.7 mmol of compound **IV** in 10 ml of benzene equimolar amounts of thiophenol and triethylamine were added, the mixture obtained was stirred for 20 h at 20°C. The precipitate formed was filtered off and washed with water and ethanol.

5-Morpholino-4-tosyl-1,3-thiazol-2-imidocarboxamorpholide (VII). To a solution of 1.7 mmol of compound **IV** in 10 ml of acetonitrile 5.5 mmol of morpholine was added, and the mixture obtained was stirred for 20 h at 20°C. After thet solvent was removed in a vacuum, the residue was treated with 5 ml of ethanol, the precipitate formed was filtered off and crystallized from ethanol.

4-Tosyl-5-phenylthio-1,3-thiazole-2-carbothioamide (VIII). A suspension of 5 mmol of compound **VI** in 10 ml of pyridine was saturated with hydrogen sulfide, the mixture obtained was stirred for 2 h at 20°C, and poured in water. The precipitate obtained was filtered off and crystallized from 5:1 ethanol–DMF.

4-Tosyl-2-(4-phenyl-1,3-thiazol-2-yl)-5-phenylthio-1,3-thiazole (IX). To a solution of 3 mmol of compound **VIII** in 5 ml of DMF 10 ml of ethanol and 3 mmol of bromoacetophenone were added. The mixture obtained was stirred for 5 h at 70°C, the solvent was removed in a vacuum, and the residue was treated with 20 ml of a saturated sodium hydrocar-bonate solution. The precipitate formed was filtered off and purified by crystallization from 5:1 ethanol–DMF.

5-[(4-Tosyl-5-phenylthio)-1,3-thiazol-2-yl]-1*H*-tetrazole (X). To a solution of 1.3 mmol of compound **VI** in 10 ml of THF 1.6 mmol of sodium azide and 1.6 mmol of ammonium chloride were added, and the mixture obtained was heated for 6 h at 70°C. The solvent was removed in a vacuum, and the residue was treated with 10 ml of water and 0.5 ml of hydrochloric acid. The crystals formed were filtered off and crystallized from 5:1 ethanol-water mixture.

4-Tosyl-5-phenylsulfonyl-1,3-thiazole-2-carbonitrile (XI). To a solution of 6 mmol of compound **IV** in 20 ml of acetone 7.5 mmol of sodium sulfinate and 0.6 mmol of tetrabutylammonium iodide were added, and the resulting mixture was heated for 10 h at 60°C. The solvent was removed in a vacuum, and the residue was treated with 15 ml of water. The precipitate formed was filtered off and crystallized from ethanol.

4-Tosyl-5-*p*-chlorophenylthio-1,3-thiazole-2-carbonitrile (XII). To a solution of 0.6 mmol of compound **XI** in 10 ml of acetonitrile 0.18 mmol of morpholine was added, and the resulting mixture was stirred for 20 h at 20°C. The solvent was removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate formed was filtered off and crystallized from ethanol.

4-(4-Tosyl-5-phenylsulfonyl-1,3-thiazol-2-yl)morpholine (XIII). To a solution of 0.6 mmol of compound **XI** in 10 ml of acetonitrile 0.8 mmol of 4-chlorothiophenol were added, and the resulting mixture was stirred for 20 h at 20°C. The solvent was removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate formed was filtered off and purified by crystallization from ethanol.

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