ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 4, pp. 825–828. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © K.V. Turov, T.K. Vinogradova, V.S. Brovarets, B.S. Drach, 2010, published in Zhurnal Obshchei Khimii, 2010, Vol. 80, No. 4, pp. 664–667.

Reactions of 4-Tosyl-2-phenyl-5-chloro-1,3-thiazole with N-, O-, and S-Nucleophiles

K. V. Turov, T. K. Vinogradova, V. S. Brovarets, and B. S. Drach[†]

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev-94, 02660 Ukraine
e-mail: brovarets@bpci.kiev.ua

Received June 25, 2009

Abstract—The accessible two-center electrophilic substrate 4-tosyl-2-phenyl-5-chloro-1,3-thiazole reacts regioselectively with N-, O-, and S- nucleophiles to eliminate a chloride ion. The analog of this substrate, 4-tosyl-2-phenyl-5-*p*-chlorophenylsulphonyl-1,3-thiazole, reacts with "soft" and "hard" nucleophiles differently: with the participation of C^5 or C^4 center, respectively, that seems to be caused by the principle of "symbiosis" in the transition state.

DOI: 10.1134/S1070363210040249

To continue the study of nucleophilic substitution in electron-deficient thiazole substrates [1, 2], we investigated the reactivity of one of key trisustituted thiazoles obtained on heating 3-tosyl-1-phenyl-1,4,4-trichloro-2-aza-1,3-diene (**I**) with thiourea, as it had been described earlier [3]. Resulting 4-tosyl-2-phenyl-5-chloro-1,3-thiazole (**II**) obtained in a high yield reacts in mild conditions with N-, O-, and S-nucleophiles to eliminate the chloride anion and to form the corresponding substituted thiazoles **III–VI** (Scheme 1). The high reactivity of the C^5 center in substrate **II** originates from the electrophilic influence of the tosyl group of the neighboring C^4 center of the thiazole ring, whereas the nature of the nucleophilic agent practically does not affect the substitution regioselectivity.

The analog of substrate **II** containing the *p*-chlorophenylsulfonyl group in position 5 (substrate **VII**) reacts with the "soft" and "hard" nucleophiles differently. "Soft" arylsulfanyl groupes are entered into position 5 of the thiazole ring, and "hard" aryloxy groups replace the tosyl anion at atom C^4.

To introduce alkylsulfanyl groups, first a thiol group was introduced in position 5 of the thiazole ring, and then it was alkylated: **II** → **III** → **IX**. Morpholine and benzylamine act on substrate **VII** similarly to "hard" sodium phenylates (conversions **VII** → **X** or **XI**, see the table).

Different reactions of **VII** with "soft" and "hard" bases can be explained by a transition state stabilization in the case when the number of equal in nature groups at a reactive center increases. In this case the initial structure **A** can give rise to two types of relatively stable transition states **B** and **C**, which are formed upon the attack of "soft" nucleophiles on C^5, and also of "hard" nucleophiles, on C^4. In both cases the number of substituents close in nature increases in the corresponding positions: in the structure **B** two "soft" substituents are at the center C^5, and in the structure **C** three "hard" groups are bound with the center C^4 (Scheme 2).

According to the "symbiosis" principle [4], the formation of the transition states **B** and **C** occurs faster as compared to alternative structures that provides a high regioselectivity of the center C^4 reaction with "hard" bases and of center C^5, with "soft" bases.

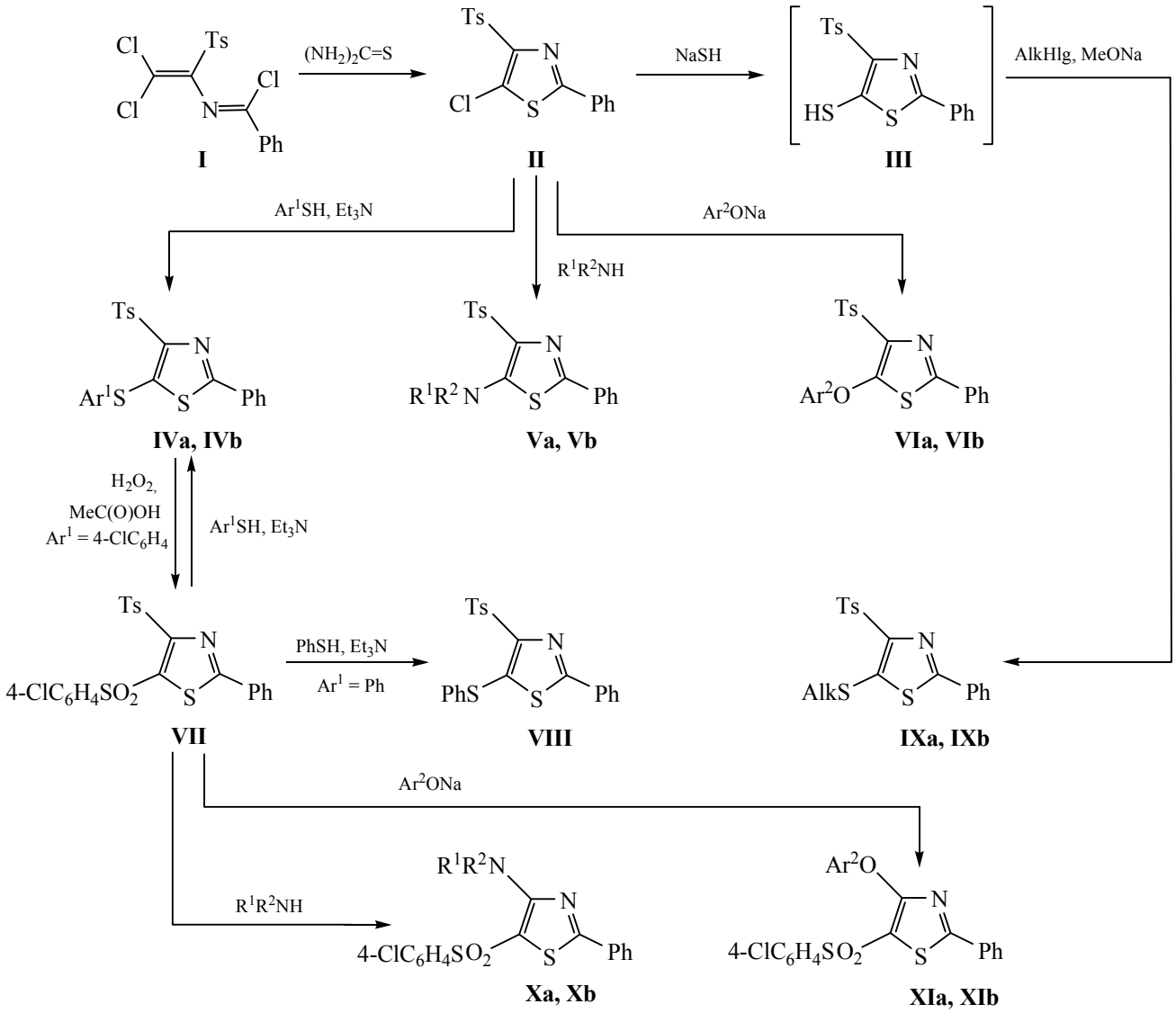
In conclusion we note that the preparative worth of the conversions presented in Scheme 1 will be considered later on.

EXPERIMENTAL

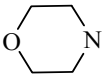
The ^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer in a $CDCl_3$ solution with TMS as the internal reference.

[†] Deceased.

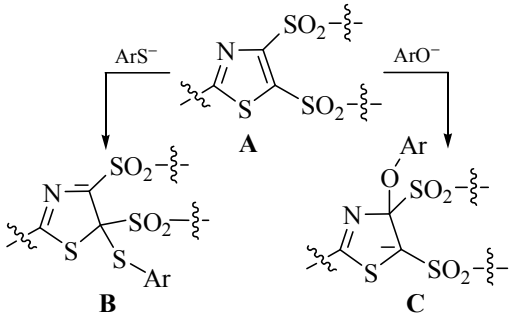
Scheme 1.



Ar^1 = 4-MeC_6H_4 (**IVa**), 4-ClC_6H_4 (**IVb**); Ar^2 = Ph (**VIa, XIa**), 4-MeC_6H_4 (**VIb, XIb**);

R^1R^2N =  (**Va, Xa**), $PhCH_2NH$ (**Vb, Xb**); Alk = Me (**IXa**), 4-$ClC_6H_4CH_2$ (**IXb**).

Scheme 2.



Yields, constants, and elemental analysis data for compounds **II–XI**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			Cl(N)	S		Cl(N)	S
II	74	150–151 (EtOH)	9.76	18.17	$C_{16}H_{12}ClNO_2S_2$	10.13	18.33
IVa	87[a]	151–152 (EtOH)	(3.56)	21.76	$C_{23}H_{19}NO_2S_3$	(3.20)	21.98
IVb	91[a]	144–145 (EtOH)	7.58	20.89	$C_{22}H_{16}ClNO_2S_3$	7.74	21.00
Va	72	195–196 (EtOH)	(6.68)	15.89	$C_{20}H_{20}N_2O_3S_2$	(6.99)	16.01
Vb	74	169–170 (EtOH)	(6.32)	15.09	$C_{23}H_{20}N_2O_2S_2$	(6.67)	15.25
VIa	73	102–103 (EtOH)	(3.79)	15.84	$C_{22}H_{17}NO_3S_2$	(3.44)	15.74
VIb	76	103–104 (EtOH)	(3.58)	15.36	$C_{23}H_{19}NO_3S_2$	(3.32)	15.21
VII	85	168–169 (EtOH–DMF, 1:1)	7.10	19.57	$C_{22}H_{16}ClNO_4S_3$	7.23	19.63
VIII	78	102–103 (EtOH)	(3.54)	22.67	$C_{22}H_{17}NO_2S_3$	(3.31)	22.71
IXa	72	153–154 (EtOH–DMF, 10:1)	(4.12)	26.49	$C_{17}H_{15}NO_2S_3$	(3.87)	26.61
IXb	89	164–165 (EtOH–DMF, 10:1)	7.42	20.45	$C_{23}H_{18}ClNO_2S_3$	7.51	20.38
Xa	73	150–151 (EtOH)	8.15	15.02	$C_{19}H_{17}ClN_2O_3S_2$	8.42	15.23
Xb	77	104–105 (EtOH)	7.87	14.42	$C_{22}H_{17}ClN_2O_2S_2$	8.04	14.54
XIa	74	106–107 (EtOH)	8.42	15.05	$C_{21}H_{14}ClNO_3S_2$	8.28	14.99
XIb	76	124–125 (EtOH)	7.85	14.23	$C_{22}H_{16}ClNO_3S_2$	8.02	14.51

[a] Yield for procedure *a*.

2-Phenyl-5-chloro-1,3-thiazol-4-yl tosylate (II). Thiourea, 30 mmol, was added to a suspension of 10 mmol of compound **I** [3] in 50 ml of acetonitrile, the mixture was boiled for 2 h, the solvent was removed *in vacuo*, water, 100 ml, was added to the residue, and the precipitate was filtered off and purified by recrystallization. ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 7.31–7.43 m (5H$_{arom}$), 7.70–7.72 m (2H$_{arom}$), 8.09–8.11 m (2H$_{arom}$).

5-Sulfanyl-2-phenyl-1,3-thiazol-4-yl tosylate (III). Potassium hydrosulfite, 3 mmol, was added to a solution of 1.5 mmol of compound **II** in 10 ml of THF, the mixture was heated for 3 h at 60°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, the mixture was acidified with concentrated hydrochloric acid to pH 2, and the precipitate was filtered off and used without purification for further conversions. Yield of unpurified compound 56 %.

5-*p*-Tolylsulfanyl(*p*-chlorophenylsulfanyl)-2-phenyl-1,3-thiazol-4-yl tosylates (IVa, IVb). *a*. To a solution of 1.5 mmol of compound **II** in 10 ml of acetonitrile equimolar amounts of the corresponding thiophenol and triethylamine were added, the mixture was boiled for 2 h, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by recrystallization.

b. To a solution of 1.5 mmol of compound **VII** in 10 ml of acetonitrile equimolar amounts of the corresponding thiophenol and triethylamine were added, the mixture was left to stand for 24 h at 20°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by recrystallization. The test of mixing samples obtained by the produres *a* and *b* mode did not show a melting point depression. ^{1}H NMR spectrum, δ, ppm, **IVa**: 2.44 s (3H, CH_3), 2.46 s (3H, CH_3), 7.26–7.28 m (2H$_{arom}$), 7.31–7.43 m (5H$_{arom}$), 7.53–7.55 m (2H$_{arom}$), 7.70–7.72 m (2H$_{arom}$), 8.09–8.11 m (2H$_{arom}$); **IVb**: 2.46 with (3H, CH_3), 7.32–7.46 m (7H$_{arom}$), 7.54–7.56 m (2H$_{arom}$), 7.73–7.75 m (2H$_{arom}$), 8.07–8.09 m (2H$_{arom}$).

5-Morpholine(benzylamino)-2-phenyl-1,3-thiazol-4-yl tosylates (Va, Vb). Morpholine or benzylamine, 2.5 mmol, was added to a solution of 0.85 mmol of compound **II** in 10 ml of dioxane, the mixture was heated for 24 h at 100°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by recrystallization. ^{1}H NMR spectrum, δ, ppm, **Va**, 2.45 s (3H, CH_3), 3.24 m (4H, 2 CH_2), 3.92 m (4H, 2CH_2), 7.30–7.45 m (5H$_{arom}$), 7.75–7.82 m (2H$_{arom}$), 8.00–8.02 m (2H$_{arom}$); **Vb**: 2.44 s (3H, CH_3), 4.86 m (2H, CH_2), 7.29–7.41 m (5H$_{arom}$), 7.38–7.56 m (8H$_{arom}$), 7.78–7.85–7.87 m (2H$_{arom}$).

5-Phenyloxy(*p*-tolyloxy)-2-phenyl-1,3-thiazol-4-yl tosylates (VIa, VIb). To a solution of 1.5 mmol of compound **II** in 10 ml of THF a corresponding sodium phenolate, 1.6 mmol, was added, the mixture was left to stand for 24 h at 20°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by crystallization. ^{1}H NMR spectrum, δ, ppm, **VIa**: 2.45 s (3H, CH_3), 7.18–7.20 m ($2H_{arom}$), 7.28–7.30 m ($1H_{arom}$), 7.33–7.35 m ($2H_{arom}$), 7.38–7.46 m ($5H_{arom}$), 7.79–7.81 m ($2H_{arom}$), 8.01–8.03 m ($2H_{arom}$); **VIb**: 2.46 s (3H, CH_3), 7.34–7.46 m ($7H_{arom}$), 7.54–7.56 m ($2H_{arom}$), 7.73–7.75 m ($2H_{arom}$), 8.07–8.09 m ($2H_{arom}$).

2-Phenyl-5-(*p*-chlorophenylsulfonyl)-1,3-thiazol-4-yl tosylate (VII). To a solution of 3.5 mmol of compound **IVb** in 10 ml of trifluoroacetic acid, 1 ml of 30% aqueous solution of hydrogen peroxide was added, the mixture was boiled for 1.5 h, 1 ml more of 30% aqueous solution of hydrogen peroxide was added, and the mixture was boiled for 1.5 h more, cooled to 20°C, poured out in 50 ml of water, and the precipitate was filtered off and purified by recrystallization. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 7.32–7.46 m ($7H_{arom}$), 7.54–7.56 m ($2H_{arom}$), 7.73–7.75 m ($2H_{arom}$), 8.11–8.13 m ($2H_{arom}$).

2-Phenyl-5-phenylsulfanyl-1,3-thiazol-4-yl tosylate (VIII). To a solution of 1.5 mmol of compound **VII** in 10 ml of acetonitrile equimolar amounts of thiophenol and triethylamine were added, the mixture was left to stand for 24 h at 20°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by crystallization. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 7.30–7.53 m ($8H_{arom}$), 7.62–7.64 m ($2H_{arom}$), 7.71–7.73 m ($2H_{arom}$), 8.09–8.11 m ($2H_{arom}$).

5-Methylsulfanyl(*p*-chlorobenzylsulfanyl)-2-phenyl-1,3-thiazol-4-yl tosylates (IXa, IXb). To a suspension of 0.85 mmol of compound **III** in 5 ml of methanol equimolar amounts of sodium methylate and methyliodide or *p*-chlorobenzyl chloride were added, the mixture was left to stand for 5 h at 20°C, and the precipitate was filtered off and purified by recrystallization. ^{1}H NMR spectrum, δ, ppm, **IXa**: 2.44 s (3H, CH_3), 2.67 s (3H, CH_3), 7.30–7.46 m ($5H_{arom}$), 7.82–7.84 m ($2H_{arom}$), 8.03–8.05 m ($2H_{arom}$); **IXb**: 2.39 s (3H, CH_3), 4.44 s (2H, CH_2), 7.31–7.44 m ($5H_{arom}$), 7.84–7.86 m ($2H_{arom}$), 8.05–8.07 m ($2H_{arom}$).

4-Morpholino(benzylamino)-2-phenyl-1,3-thiazol-5-yl 4-chlorobenzenesulfonates (Xa, Xb). Morpholine or benzylamine, 2.5 mmol, was added to a solution of 0.85 mmol of compound **VII** in 10 ml of dioxane, the mixture was heated for 24 h at 100°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by recrystallization. ^{1}H NMR spectrum, δ, ppm, **Xa**: 3.26 m (4H, $2CH_2$), 3.97 m (4H, $2CH_2$), 7.30–7.45 m ($5H_{arom}$), 7.75–7.82 m ($2H_{arom}$), 8.00–8.02 m ($2H_{arom}$); **Xb**: 4.83 m (2H, CH_2), 7.29–7.41 m ($5H_{arom}$), 7.38–7.56 m ($9H_{arom}$), 7.78–7.80 m ($2H_{arom}$), 7.85–7.87 m ($2H_{arom}$).

2-Phenyl-4-phenyloxy-(*p*-tolyloxy)-1,3-thiazol-5-yl 4-chlorobenzenesulfonates (XIa, XIb). To a solution of 1.5 mmol of compound **VII** in 10 ml of THF a corresponding sodium phenylate, 1.6 mmol, was added, the mixture was left to stand for 24 h at 20°C, the solvent was removed *in vacuo*, water, 10 ml, was added to the residue, and the precipitate was filtered off and purified by crystallization. ^{1}H NMR spectrum, δ, ppm, **XIIa**: 7.09–7.11 m ($2H_{arom}$), 7.18–7.26 m ($1H_{arom}$), 7.31–7.59 m ($7H_{arom}$), 7.79–7.81 m ($2H_{arom}$), 8.06–8.08 m ($2H_{arom}$); **XIIb**: 2.39 s (3H, CH_3), 6.97–6.99 m ($2H_{arom}$), 7.16–7.18 m ($2H_{arom}$), 7.38–7.56 m ($5H_{arom}$), 7.79–7.81 m ($2H_{arom}$), 8.06–8.08 m ($2H_{arom}$).

REFERENCES

1. Turov, K.V. and Drach, B.S., *Zh. Obshch. Khim*., 2008, vol. 78, no. 4, p. 648.
2. Turov, K.V. and Vinogradova, T.K., *Zh. Obshch. Khim*., 2008, vol. 78, no. 11, p. 1897.
3. Kharchenko, A.V., Seferov, S.O., Zyabrev, V.S., Chervonyi, V.A., Vdovenko, S.I., and Drach, B.S., *Ukr. Khim. Zh*., 1993, vol. 59, no. 6, p. 637.
4. Pearson, R.J. and Zongstad, I., *Usp. Khim*., 1969, no. 7, p. 1223.