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Reaction of 2-(Benzenesulfonyl)-5-(*p*-chlorobenzenesulfonyl)-4-tosyl-1,3-thiazole with O-, N-, S-, and C-Nucleophiles

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Abstract—2-(Benzenesulfonyl)-4-tosyl-1,3-thiazole was synthesized starting from the available 2,2-dichloro-1-tosylethenyl isothiocyanate. The product is a pronounced electrophilic substrate feasible for investigation of the order of nucleophilic substitution at the C^2, C^4, and C^5 centers of the thiazole ring. Different nucleophilic agent first attack the C^2 atom. After that *S*-nucleophiles react with C^5, while *O*- and *N*-nucleophiles, with C^4.

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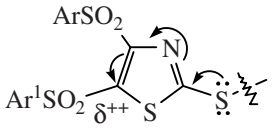
It was recently shown that 2,2-dichloro-1-tosylethenyl isothiocyanate (**I**) can be converted, via simple reactions, to 2,4,5-tritosyl-1,3-thiazole which easily reacts with various nucleophiles [2]. However, the regioselectivity of substitution of one or, especially, two tosyl groups can hardly be established, because this substrate have the same substituents in the 2, 4, and 5 positions of the thiazole ring. We prepared a new substrate of the thiazole series by means of the transformation sequence **II→III→III→IV**, presented in the scheme below. The resulting thiazole has different arenesulfonyl groups at the C^2, C^4, and C^5 atoms.

As the nucleofugicities of the benzenesulfonyl, tosyl, and *p*-chlorobenzenesulfonyl groups differ only slightly, we can correlate, at least qualitatively, the regioselectivity of substitution of arenesulfonyl groups and the nature of the nucleophilic reagent.

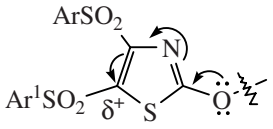
As seen from the scheme and Table 1, by treatment various O-, N-, S-, and C-nucleophiles substrate **IV** can be converted to substituted thiazoles **V–XII**. There-with, the reaction at an equimolar reagent ratio or under extremely mild conditions involves exclusively nucleophilic substitution of the benzenesulfonyl group at C^2 to form compounds **V, VI, XI**, and **XII**) in high isolatable yields.

This agrees with the known high reactivity of thiazoles having an easily leaving group in the *meso* position [3]. At the same time, the reaction of substrate **IV** with ArS^- and ArO^- nucleophiles in at a 1:2 molar ratio gives the corresponding 2,5- and 2,4-disubstituted products, that is compounds **VIII** and **X**, respectively. This result may well be explained by the different degree of conjugation of the sulfur and oxygen lone pairs with the π system of the thiazole ring. Therefore, the electron density on the C^5 carbon atom in structure **A** is evidently lower than in structure **B**.



A

$\delta^{++} > \delta^{+}$ due to weak conjugation

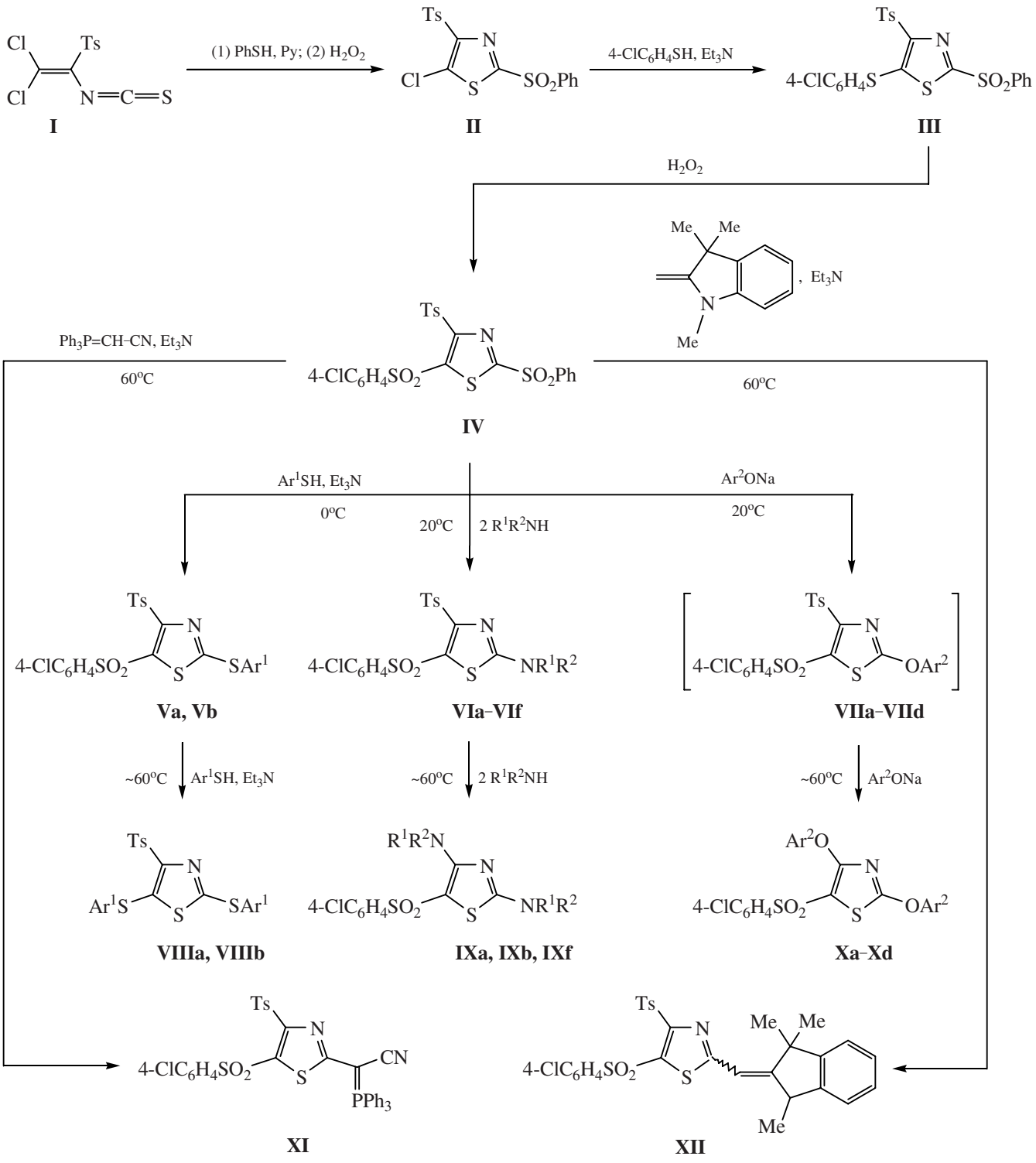


B

$\delta^{+} < \delta^{++}$ due to strong conjugation

Hence, substituted 2-hydroxy and 2-aminothiazoles feature a strong *n*,π conjugation, which decreases the electrophility of C^5 and favors the competing reactions **VII→IX** and **VIII→X**. Contrary to that, the electron density on C^5 in 2-sulfanylthiazole is only slightly affected due to a weak *n*,π conjugation, and, therefore, the nucleophilic substitution **VI→VIII** is prevailing.

Note in conclusion that in the scheme we presented, for the sake of simplicity and illustrativeness, only main reaction pathways and omitted side processes. As the yields of the main products after crystallization are higher than 60% (Table 1), it is clear that substrate **IV** and its analogs present interest not only for exploring the reactivity of the three electrophilic centers in the thiazole ring, but also for preparative synthesis of trifunctionalized thiazoles hardly available by other



Ts = 4-$MeC_6H_4SO_2$; Ar^1 = Ph (**VIIIa**), 4-MeC_6H_4 (**Va, VIIIb**), 4-ClC_6H_4 (**Vb**); Ar^2 = Ph (**VIIa, Xa**), 4-MeC_6H_4 (**VIIb, Xb**), 4-ClC_6H_4 (**VIIc, Xc**), 4-$MeOC_6H_4$ (**VIId, Xd**). R^1R^2N = Me_2N (**VIa, IXa**), (**VIb, IXb**), (**VIc**), H_2N (**VId**), MeNH (**VIe**), $PhCH_2NH$ **VIf, IXf**).

Table 1. Yields, constants, and elemental analyses of compounds **II–XII**

Comp. no.	Yield. %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			Cl	S		Cl	S
II	85	137–138 (EtOH)	8.59	23.30	$C_{16}H_{12}ClNO_4S_3$	8.56	23.24
III	61	205–206 (EtOH)	6.59	24.71	$C_{22}H_{16}ClNO_4S_4$	6.79	24.57
IV	80	208–209 (EtOH–CH_3CN, 5:1)	6.47	23.08	$C_{22}H_{16}ClNO_6S_4$	6.40	23.15
Va	74	162–163 (EtOH)	6.42	23.66	$C_{23}H_{18}ClNO_4S_4$	6.61	23.92
Vb	70	160–161 (EtOH)	12.61	23.15	$C_{22}H_{15}Cl_2NO_4S_4$	12.74	23.05
VIa	85	179–180 (EtOH)	7.72	21.10	$C_{18}H_{17}ClN_2O_4S_3$	7.76	21.05
VIb	90	164–165 (EtOH)	6.89	18.95	$C_{21}H_{21}ClN_2O_4S_3$	7.13	19.35
VIc	92	204–205 (EtOH)	7.15	19.63	$C_{20}H_{19}ClN_2O_5S_3$	7.10	19.28
VId	78	243–245 (EtOH–CH_3CN, 10:1)	8.34	22.43	$C_{16}H_{13}ClN_2O_4S_3$	8.28	22.43
VIe	81	195–196 (EtOH)	8.07	21.56	$C_{17}H_{15}ClN_2O_4S_3$	8.03	21.70
VIf	67	118–119 (EtOH)	6.86	18.43	$C_{23}H_{19}ClN_2O_4S_3$	6.83	18.53
VIIIa	78	119–120 (EtOH)	–	28.08	$C_{22}H_{17}NO_2S_4$	–	28.15
VIIIb	86	142–143 (EtOH)	–	26.01	$C_{24}H_{21}NO_2S_4$	–	26.52
IXa	72	124–125 (EtOH)	10.00	18.46	$C_{13}H_{16}ClN_3O_2S_2$	10.25	18.54
IXb	81	157–158 (EtOH)	8.00	14.91	$C_{19}H_{24}ClN_3O_2S_2$	8.32	15.05
IXf	76	143–145 (EtOH)	7.20	13.54	$C_{23}H_{20}ClN_3O_2S_2$	7.54	13.64
Xa	75	169–170 (EtOH)	7.98	14.43	$C_{21}H_{14}ClNO_4S_2$	7.99	14.45
Xb	90	127–129 (EtOH)	7.71	13.26	$C_{23}H_{18}ClNO_4S_2$	7.51	13.59
Xc	78	167–169 (EtOH)	20.58	12.51	$C_{21}H_{12}Cl_3NO_4S_2$	20.74	12.50
Xd	79	108–109 (EtOH)	7.01	12.56	$C_{23}H_{18}ClNO_6S_2$	7.03	12.72
XI	71	154–155 (EtOH–CH_3CN, 5:1)	4.90	13.64	$C_{36}H_{26}ClN_2O_4PS_3$	4.97	13.49
XII	76	220–221 (EtOH)	6.21	16.17	$C_{28}H_{25}ClN_2O_4S_3$	6.06	16.44

Table 2. Spectral data of compounds **II–XII**

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
II	2.44 s (3H, CH_3), 7.41–7.43 м (2H$_{apom}$), 7.67–7.71 m (2H$_{arom}$), 7.81–7.83 m (3H$_{arom}$), 7.99–8.01 m (2H$_{arom}$)
III	2.45 s (3H, SH_3), 7.41–7.44 m (2H$_{arom}$), 7.59–7.66 m (4H$_{arom}$), 7.73–7.75 m (3H$_{arom}$), 7.85–7.93 m (4H$_{arom}$)
IV	2.24 s (3H, CH_3), 7.36–7.38 d (2H$_{arom}$), 7.67–7.71 m (6H$_{arom}$), 7.81 m (1H$_{arom}$), 8.01–8.03 m (2H$_{arom}$), 8.15–8.17 m (2H$_{arom}$)
Va	2.45 s (3H, SH_3), 2.46 s (3H, SH_3), 7.41–7.44 m (4H$_{arom}$), 7.61–7.63 m (2H$_{arom}$), 7.68–7.72 m (4H$_{arom}$), 8.01–8.03 m (2H$_{arom}$)
Vb	2.45 s (3H, SH_3), 7.39–7.41 m (4H$_{arom}$), 7.61–7.75 m (8H$_{arom}$), 8.03–8.06 m (2H$_{arom}$)
VIa	2.43 s (3H, CH_3), 3.10 s [6H, N(CH_3)$_2$], 7.35–7.37 m (2H$_{arom}$), 7.65–7.70 m (4H$_{arom}$), 7.99–8.02 m (2H$_{arom}$)
VIb	1.64 s (6H$_{piperid}$), 2.44 s (3H, CH_3), 3.45 m (4H$_{piperid}$), 7.36–7.38 m (2H$_{arom}$), 7.66–7.72 m (4H$_{arom}$), 8.01–8.03 m (2H$_{arom}$)
VIc	2.44 s (3H, CH_3), 3.44–3.46 m (4H$_{morph}$), 3.68–3.70 m (4H$_{morph}$), 7.37–7.39 m (2H$_{arom}$), 7.67–7.72 m (4H$_{arom}$), 8.02–8.04 m (2H$_{arom}$)
VId	2.44 s (3H, SH_3), 7.37–7.39 d (2H$_{arom}$), 7.65–7.71 m (4H$_{arom}$), 8.01–8.03 m (2H$_{arom}$), 8.23 br.s (2H, NH_2)
VIe	2.43 s (3H, CH_3), 2.80–2.81 d (3H, NH–C<u>H</u>$_3$) 7.35–7.37 m (2H$_{arom}$), 7.64–7.69 m (4H$_{arom}$), 7.99–8.01 m (2H$_{arom}$), 8.85 br.s (1H, NH)
VIf	2.44 s (3H, CH_3), 4.36 s (2H, SH_2), 7.24–7.37 m (7H$_{arom}$), 7.65–7.68 m (4H$_{arom}$), 8.00–8.02 m (2H$_{arom}$), 9.35 br.s (1H, NH)

Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
VIIIb	2.34 s (6H, $2CH_3$), 2.46 s (3H, CH_3), 7.17–7.22 m ($4H_{arom}$), 7.33–7.43 m ($6H_{arom}$), 7.84–7.86 m ($2H_{arom}$)
IXa	3.07 s [12H, $2N(CH_3)_2$], 7.40–7.42 m ($2H_{arom}$), 7.79–7.81 m ($2H_{arom}$)
IXb	1.57 s ($6H_{piperid}$), 1.64 c ($6H_{piperid}$), 3.44–3.47 м ($8H_{piperid}$), 7.39–7.41 м ($2H_{arom}$), 7.79–7.81 m ($4H_{arom}$)
IXf	4.39 m (2H, CH_2), 4.54–5.55 m (2H, CH_2), 7.04 m (1H, NH), 7.20–7.27 m ($10H_{arom}$), 7.46–7.48 m ($2H_{arom}$), 7.74–7.76 m ($2H_{arom}$), 8.95 br.s (1H, NH)
Xa	7.03–7.05 m ($2H_{arom}$), 7.19–7.23 m ($1H_{arom}$), 7.33–7.41 m ($5H_{arom}$), 7.49–7.53 m ($2H_{arom}$), 7.63–7.65 m ($2H_{arom}$), 7.95–7.97 m ($2H_{arom}$)
Xb	2.34 s (3H, CH_3), 2.38 s (3H, CH_3), 6.89–6.91 m ($2H_{arom}$), 7.13–7.21 m ($4H_{arom}$), 7.27–7.29 m ($2H_{arom}$), 7.61–7.63 m ($2H_{arom}$), 7.92–7.94 m ($2H_{arom}$)
Xc	7.06–7.08 m ($2H_{arom}$), 7.34–7.39 m ($4H_{arom}$), 7.47–7.49 m ($2H_{arom}$), 7.63–7.65 m ($2H_{arom}$), 7.94–7.96 m ($2H_{arom}$)
Xd	3.77 s (3H, OCH_3), 3.81 s (3H, OCH_3), 6.86–7.01 m ($6H_{arom}$), 7.24–7.26 m ($2H_{arom}$), 7.62–7.65 m ($2H_{arom}$), 7.93–7.95 m ($2H_{arom}$)
XI	2.32 s (3H, CH_3), 6.95–7.10 m ($4H_{arom}$), 7.45–7.60 m ($14H_{arom}$), 7.70–7.85 m ($3H_{arom}$), 8.00–8.15 m ($2H_{arom}$)
XII	1.48 c (6H, $2CH_3$), 2.45 s (3H, CH_3), 3.22 s (3H, NCH_3), 5.78 c (1H, CH), 6.75–6.81 m ($2H_{arom}$), 7.13–7.15 m ($2H_{arom}$), 7.41–7.43 m ($2H_{arom}$), 7.68–7.78 m ($4H_{arom}$), 8.08–8.10 m ($2H_{arom}$)

methods. Synthetic value of substrates **II, IV** will be considered in future.

EXPERIMENTAL

Spectral parameters of compounds **II–XII** are listed in Table 2. The ^{1}H NMR spectra were taken on a Varian Mercury-400 spectrometer in DMSO-d_6 against internal TMS.

2-(Benzenesulfonyl)-5-chloro-4-tosyl-1,3-thiazole (II). To a solution of 0.08 mol of compound **I** [1] in 150 ml of benzene cooled to 0°C, 0.08 mol of thiophenol was added and then 0.08 mol of pyridine was added with stirring for 1 h. The reaction mixture was stirred for 8 h at 15°C, the solvent was removed in a vacuum. The residue was washed with water and ethanol and then dissolved in 200 ml of boiling acetic acid. After that 15 ml of 30% aqueous hydrogen peroxide was added, the mixture was refluxed for 1 h, and then again was treated with the same amount of hydrogen peroxide and refluxed for 2.5 h. After cooling 10°C, a precipitate formed and was filtered off and crystallized from ethanol.

2-(Benzenesulfonyl)-5-(*p*-chlorophenylsulfanyl)-4-tosyl-1,3-thiazole (III). To a solution of 0.06 mol of compound **II** in 120 ml of THF, cooled to 0°C, a solution 0.06 mol of *p*-chlorothiophenol was added, and then a solution of 0.06 mol of triethylamine in 15 ml of THF was added with stirring over the course of 1 h. The mixture was allowed to stand for 30 h at 5°C. The precipitate that formed was filtered off and washed with ethanol.

2-(Benzenesulfonyl)-5-(*p*-chlorobenzenesulfonyl)-4-tosyl-1,3-thiazole (IV). To a solution of 0.02 mol of compound **III** in 50 ml of boiling trifluoroacetic acid, 5 ml of 30% aqueous hydrogen peroxide was added. The mixture was refluxed for 1 h, treated with the same amount of hydrogen peroxide, refluxed for 2.5 h, and poured into 100 ml of water. The precipitate that formed was filtered off and crystallized from ethanol–acetonitrile, 5:1.

2-(Arylsulfanyl)-5-(*p*-chlorobenzenesulfonyl)-4-tosyl-1,3-thiazoles (Va, Vb). A solution of 0.5 mmol of compound **IV** in 10 ml of THF was cooled to 0°C, and a solution of 0.5 mmol of the corresponding thiol and 0.5 mmol of pyridine in 10 ml of THF was added dropwise with stirring. The mixture was stirred for 3 h at 0°C, the solvent was removed in a vacuum, and the residue was treated with 3 ml of etanol. The precipitate that formed was filtered off and crystallized from ethanol.

2-Amino(benzylamino, dimethylamino, methylamino, morpholino, piperidino)-5-(*p*-chlorobenzenesulfonyl)-4-tosyl-1,3-thiazoles VIa–VIf. To a solution of 0.5 mmol of compound **IV** in 10 ml of

THF, 1 mmol of the corresponding amine was added, and the mixture was allowed to stand for a day at 20° C. The solvent was then removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate that formed was filtered off and crystallized from ethanol.

2,5-Bis(arylsulfanyl)-4-tosyl-1,3-thiazoles VIIIa, VIIIb. To a solution of 0.5 mmol of compound **V** in 10 ml of THF, 1 mmol of the corresponding thiol and 1 mmol of triethylamine were added. The reaction mixture was heated for 3 h at 60°C, the solvent was removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate that formed was filtered off and crystallized from ethanol.

2,4-Bis(benzylamino, dimethylamino, piperidino)-4-tosyl-1,3-thiazoles IXa, IXb, IXf. To a solution of 0.5 mmol of compound **VI** in 10 ml of THF, 2.5 mmol of the corresponding amine was added. The reaction mixture was kept at 60°C for 48 h, the solvent was removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate that formed was filtered off and crystallized from ethanol.

2,4-Diaroxy-4-tosyl-1,3-thiazoles Xa–Xd. A solution of 0.5 mmol of compound **IV** in 10 ml of THF was treated with 2 mmol of the corresponding sodium phenolate. The reaction mixture was allowed to stand for 24 h at 20°C. The solvent was removed in a vacuum, and the residue was treated with 3 ml of ethanol. The precipitate that formed was filtered off and crystallized from ethanol.

[5-(*p*-Chlorobenzenesulfonyl)-4-tosyl-1,3-thiazol-2-yl](triphenylphosphoranylidene)acetonitrile (XI). To a solution of 0.5 mmol of compound **IV** in 10 ml of THF, 1 mmol of (triphenylphosphoranylidene)acetonitrile and 1 mmol of triethylamine were added. The mixture was heated for 10 h at 60°C. The solvent was then removed in a vacuum, the residue was treated with 5 ml of ethanol, and the precipitate that formed was filtered off and crystallized from ethanol-acetonitrile, 5:1.

3[5-(*p*-Chlorobenzenesulfonyl)-4-tosyl-1,3-thiazol-2-yl]methylidene-1,3,3-trimethyl-2,3-dihydro-1*H*-indole (XII). To a solution of 0.5 mmol of compound **IV** in 10 ml of THF, 1 mmol of the Fischer base and 1 mmol of triethylamine were added. The mixture was heated for 8 h at 60°C under argon, the solvent was removed in a vacuum, and the residue was treated with 5 ml of ethanol. The precipitate that formed was filtered off and crystallized from ethanol.

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