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Regioselectivity in the Amination of Methylsulfanyl-Substituted Azines with *O*-Mesitylenesulfonylhydroxylamine*

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Abstract—Reactions of *O*-mesitylenesulfonylhydroxylamine with 2-(methylsulfanyl)pyrazine, 2-(methylsulfanyl)pyrimidine, and 3,5-dimethyl-2-(methylsulfanyl)pyrimidines involve both sulfur and nitrogen atoms. The amination products at the sulfur atom prevail in the resulting mixture of isomeric cations, and the ratio of the $S–NH_2$ and $N–NH_2$ derivatives depends on the substrate nature. The experimental data were interpreted in terms of DFT quantum-chemical calculations.

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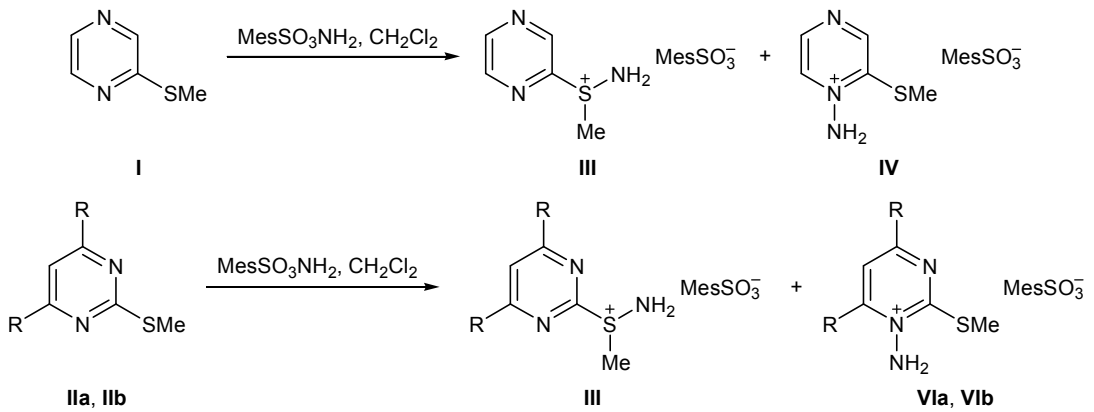
Direct amination of nitrogen-containing heteroaromatic compounds with H_2NX reagents generally occurs at the nitrogen atom [1–6]. If several nonequivalent nitrogen atoms are present, the site of addition of amino group depends on the nature of substituents [1, 4–6]. *O*-Mesitylenesulfonylhydroxylamine $MesSO_3NH_2$ is one of the most widely used reagents for the amination of nitrogen-containing heterocycles [1–6]. Its reactions with alkylsulfanyl-substituted pyridines give the corresponding aminosulfonium salts, i.e., the amination involves sulfur rather than nitrogen atom in the substrate [7, 8].

The goal of the present work was to examine the regioselectivity in the amination of methylsulfanyl-substituted azines with *O*-mesitylenesulfonylhydroxylamine. As substrates we used 2-(methylsulfanyl)pyrazine (**I**), 2-(methylsulfanyl)pyrimidine (**IIa**), and 4,6-dimethyl-2-(methylsulfanyl)pyrimidine (**IIb**). Unlike 2-methylsulfanylpyridine, the amination of azines **I**, **IIa**, and **IIb** with *O*-mesitylenesulfonylhydroxylamine occurred at both sulfur and nitrogen atoms (Scheme 1).

The structure of the products was determined by ^1H and ^{13}C NMR spectroscopy (Tables 1, 2). The

Scheme 1.



R = H (**a**), Me (**b**).

* For preliminary communication, see [1].

Table 1. [1]H NMR spectra of mesitylenesulfonates **III–VI** and their precursors **I**, **IIa**, and **IIb** in DMSO-d_6[a]

Compound no.	MeS	NH_2[b]	2-H	3-H	4-H	5-H	6-H
I[c]	2.54 s	–	–	8.59 d (1.6)	–	8.31 d (2.6)	8.48 d.d (2.6, 1.6)
IIa	2.50 s	–	–	–	8.63 d (5.1)	7.20 t (5.1)	8.63 d (5.1)
IIb	2.46 s, 2.33 s[d]	–	–	–	–	6.91 s	–
III	3.40 s	6.83	–	9.28 d (1.6)	–	8.98 d (2.5)[e]	8.89 d.d (2.5, 1.6)[e]
IV	2.64 s	9.45	8.78 d.d (1.5, 1.0)	–	–	8.91 d.d (3.9, 1.0)[e]	8.43 d.d (3.9, 1.5)[e]
Va	3.39 s	7.01	–	–	9.08 d (4.8)	7.82 t (4.8)	9.08 d (4.8)
VIa	2.63 s	7.91	–	–	9.09 d.d (4.7, 1.8)	7.77 d.d (6.4, 4.7)	9.13 d.d (6.4, 1.8)
Vb	3.34 s, 2.54 s[d]	6.93	–	–	–	7. 56 s	–
VIb	2.73 s, 2.59 s,[d] 2.52 s[d]	7.06	–	–	–	7.61 s	–

[a] The chemical shifts (δ, ppm) are given relative to tetramethylsilane (recalculated from DMSO, δ 2.50 ppm); coupling constants (*J*, Hz) are given in parentheses.
[b] Broadened singlet.
[c] Cf. [9].
[d] 4(6)-Me.
[e] Alternative assignment is possible.

Table 2. [13]C NMR spectra of mesitylenesulfonates **III–VI** and their precursors **I**, **IIa**, and **IIb** in DMSO-d_6[a]

Compound no.	Me	C^2	C^3	C^4	C^5	C^6
I	12.2	157.0	142.9[b]	–	139.5	144.0[b]
IIa	13.5	171.5	–	157.7	117.0	157.7
IIb	13.2, 23.3[c]	170.3	–	166.7	115.6	166.7
III	30.9	150.9	147.8[b]	–	144.9[b]	144.4[b]
IV	12.9	124.8[b]	163.0	–	148.4	123.1[b]
Va	30.9	164.4	–	159.8	123.9	159.8
VIa	14.5	173.2	–	160.6	117.5	152.1
Vb	23.3[c], 30.7	163.4	–	169.6	122.5	169.6
VIb	14.9, 18.7,[c] 24.5[c]	171.8	–	170.5[b]	118.0	166.3[b]

[a] The chemical shifts (δ_C, ppm) are given relative to tetramethylsilane (recalculated from DMSO, δ_C 39.52 ppm).
[b] Alternative assignment is possible.
[c] 4(6)-Me.

chemical shifts of the NH_2 and CH_3 protons in cations **III**, **Va**, and **Vb** are similar to those found for 2-pyridylaminosulfonium mesitylenesulfonate (**VII**) [7, 8]. Signals from protons in the aromatic rings were assigned on the basis of their intensity and multiplicity with account taken of coupling constants (cf. [9]). Signals in the [1]H NMR spectra of cations **IV**, **VIa**, and **VIb** were assigned using NOESY technique [10]. Nuclear Overhauser effects were observed for closely located protons in the NH_2 group and 2-H (6-H) in cations **IV** and **VIa**, CMe protons in **VIb**, and SMe protons in **Vb**. To assign signals in the [13]C NMR spectra of cations **Va** and **VIa** we used two-dimensional proton–carbon spin correlation technique (HXCO). In the [1]H NMR spectra of **III**, **IV**, **Va**, **Vb**, **VIa**, and **VIb**, signals from protons in the aromatic ring and CH_3 group were displaced downfield relative to the corresponding signals of the initial azines, obviously due to the presence of positive charge. In the [13]C NMR spectra of **Va**, **Vb**, **VIa**, and **VIb**, carbon atoms in the α-position with respect to the nitrogen resonated in a weaker field than those located in the β-position, which is typical of pyrimidine derivatives [11]. The MeS carbon signal in the spectra of **III**, **Va**, and **Vb** is

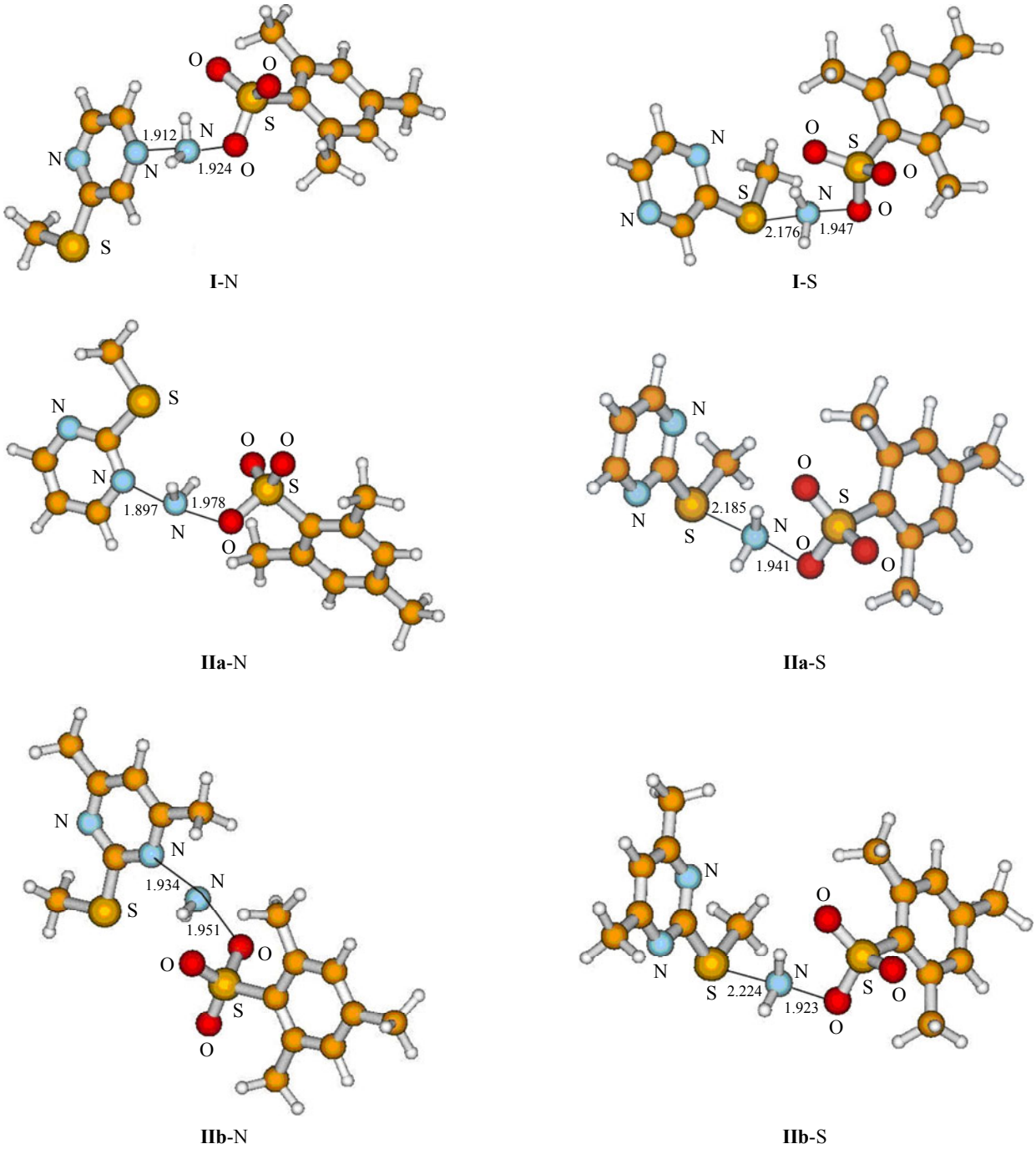


Fig. 1. Calculated (DFT/PBE/3Z) structures of transition states in the amination of azines **I**, **IIa**, **IIb**; N···N, N···S, and N···O distances are given (Å).

displaced downfield by 17–19 ppm relative to the corresponding signals of their precursors **I** and **II** due to the presence of positive charge on the sulfur atom. Likewise, replacement of SMe group by $^{+}SMeNH_2$ resulted in downfield shift (by 5–7 ppm) of signal from the carbon atom in the *para* position with respect to that group.

Obviously, the formation of cations **III**–**VI** is a kinetically controlled process. This follows from the fact that the ^{1}H NMR spectra of mesitylenesulfonates **III** and **Va** in DMSO-d_6 did not change on heating for 60°C over a period of 12 h. Analogous pattern was observed previously for 1-amino-1,10-phenanthrolinium mesitylenesulfonate which underwent neither intra-

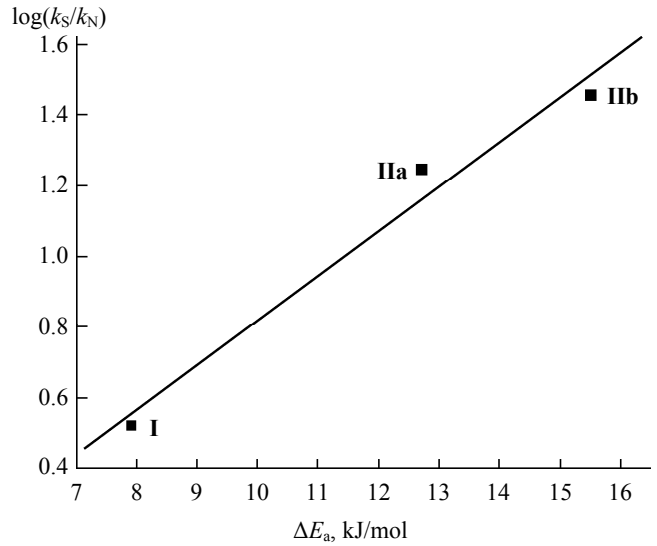


Fig. 2. Correlation of the logarithms of the rate constants for the amination of azines **I**, **IIa**, and **IIb** with the calculated (DFT/PBE/3Z) differences in the energy barriers.

nor intermolecular transfer of the amino group even under fairly severe conditions [5]. Therefore, intra- or intermolecular transfer of the amino group cannot be regarded as complicating factor while studying regioselectivity in the amination of azines.

The ratio of isomeric cations obtained from pyrimidine derivatives (**Va**/**VIa**, **Vb**/**VIb**) is somewhat higher than the ratio of carions **III** and **IV** obtained from 2-methylsulfanylpyrazine (Table 3). In all cases, the sulfur atom in methylsulfanyl-substituted azines is more nucleophilic than the endocyclic nitrogen atom. The lower fraction of cation **VIb** as compared to **VIa** is likely to be determined by stronger steric shielding of the nitrogen center by the neighboring methyl group.

With a view to interpret the obtained experimental data we performed DFT quantum-chemical calculations of the corresponding potential energy surfaces [12–14]. Taking into account that the regioselectivity in the amination at the nitrogen or sulfur atom is determined by the energy difference between the corresponding transition states, the latter were localized on the potential energy surfaces by analysis of Hessian eigenvalues [15]. Hesse matrix for a transition state includes one imaginary frequency, and the oscillator vector shows the direction of motion of the NH_2 group toward the oxygen atoms in the OSO_2Mes group or nitrogen or sulfur atoms in the azine fragment (Fig. 1). The N^1, N (NH_2), and O (SO_3Mes) atoms, as well as S (MeS), N (NH_2), and O (SO_3Mes), are arranged almost linearly (the NNO angle is 173–175°, and the SNO angle is 177–179°), which is typical of S_N2 reactions [16, 17]. In all transition states the N–N bond is somewhat shorter than the N–S bond (Fig. 1). Table 3 contains energy barriers to amination of azines **I**, **IIa**, and **IIb** at the nitrogen and sulfur atoms. Comparison of the logarithms of the partial rate constants for amination at the sulfur and nitrogen atoms (k_S and k_N) with the difference in the corresponding activation energies showed a good agreement between the calculated (DFT) and experimental values (Fig. 2). Estimation of the rate constants for the formation of S- and N-amino derivatives in the amination of 2-methylsulfanylpyridine by linear extrapolation indicated a very small fraction of *N*-aminopyridinium ion (<1%), which is consistent with the experimental data [7, 8]. It should also be noted that the calculated (DFT/PBE/3Z) energy barrier to intramolecular rearrangement of cation **VIa** into **Va** is very high (279 kJ/mol), which corresponds to kinetic control over the amination process.

Table 3. Calculated (DFT/3Z) total energies of transition states (E_{tot}, a.u.), energy barriers (E_a, kJ/mol), and rate constant ratios for the amination of azines **I**, **IIa**, and **IIb** and 2-methylsulfanylpyridine at the sulfur and nitrogen atoms

Compound no.	E_{tot}, a.u.		E_a, kJ/mol		ΔE_a, kJ/mol	k_S/k_N[a]	$\log(k_S/k_N)$
	S	N	S	N			
I	–1729.744643	–1729.742069	53.6	61.5	7.9	3.35	0.525
IIa	–1729.752664	–1729.747835	51.0	63.7	12.7	17.8	1.250
IIb	–1808.261912	–1808.256034	43.4	58.9	15.5	28.9	1.461
2-$MeSC_5H_4N$	–1713.700999	–1713.693350	47.2	67.3	20.1	125[b]	2.097[b]

[a] The ratios of partial rates of formation of the *S*- and *N*-amino derivatives are given with account taken of statistical factor. The rate constants were obtained by averaging of the data from 2–4 parallel runs.

[b] The value was obtained by linear extrapolation.

Thus the regioselectivity in the amination of methylsulfanyl-substituted six-membered nitrogen-containing heteroaromatic compounds (at the nitrogen or sulfur atom) with *O*-mesitylenesulfonylhydroxylamine depends on the number of nitrogen atoms and their position in the ring. In addition, the presence of a methyl group near the reaction center considerably hinders attack by the aminating agent on the nitrogen atom.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-300 and AV-600 spectrometers using the solvent signals as reference ($CHCl_3$, δ 7.24 ppm; DMSO-d_5, δ 2.50 ppm; DMSO-d_6, δ_C 39.52 ppm). Quantum-chemical calculations in terms of the density functional theory (DFT) were performed using PBE functional [12] with the aid of PRIRODA software [13, 14] {triple zeta basis set, (11*s*6*p*2*d*)/[6*s*3*p*2*d*] for C, N, S, O; (5*s*1*p*)/[3*s*1*p*] for H}. Critical points on the potential energy surfaces were identified by calculating Hesse matrices [15].

2-Methylsulfanylpyrazine (99%, from Lancaster), 1,1,3,3-tetraethoxypropane (>98%, from Fluka), acetylacetone of chemically pure grade, thiourea of pure grade, and dimethyl sulfate (distilled prior to use) were commercial products. *O*-Mesitylenesulfonylhydroxylamine ($MesSO_3NH_2$) [2], 2-sulfanylpyrimidine hydrochloride [18], and 4,6-dimethyl-2-sulfanylpyrimidine hydrochloride [19] were synthesized according to known methods. Methylene chloride was purified by washing with a saturated solution of sodium carbonate, followed by heating under reflux over activated charcoal, drying, and distillation over anhydrous calcium chloride [20].

2-Methylsulfanylpyrimidine (cf. [21]**).** Dimethyl sulfate, 0.68 g (7.2 mmol), and water, 5 ml, were added in succession under vigorous stirring to a mixture of 0.73 g (4.9 mmol) of pyrimidine-2-thiol hydrochloride and 1.1 g (8.0 mmol) of potassium carbonate in 5 ml of acetone. The mixture was vigorously stirred for about 20 h and extracted with methylene chloride (3 × 10 ml), and the extracts were combined, dried over Na_2SO_4, filtered through a layer of aluminum oxide, and evaporated. Yield 0.55 g (90%), yellow liquid. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): 2.52 s (3H), 6.92 t (1H, 4.8 Hz), 8.47 d (2H, 4.8 Hz) (cf. [22]).

4,6-Dimethyl 2-methylsulfanylpyrimidine was synthesized in a similar way. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): 2.46 s (3H), 2.33 s (6H), 6.91 s (1H) (cf. [23]).

General procedure for amination of azines. A solution of ~0.75 mmol of *O*-mesitylenesulfonylhydroxylamine in 1.5 ml of methylene chloride (preliminarily dried over Na_2SO_4) was added dropwise under stirring to a solution of ~0.5 mmol of azine **I**, **IIa**, or **IIb** in 1 ml of methylene chloride, cooled to 0°C, the mixture was stirred for 1 h at 0°C, 10 ml of diethyl ether was added, and the mixture was left to stand overnight at –20°C. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 85–95%.

Mesitylenesulfonates **III** and **Va** were isolated by recrystallization of mixtures **III**/**IV** and **Va**/**VIa**, respectively, from propan-2-ol.

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