Tetrahedron Letters 50 (2009) 6779–6782

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselectivity in 2-X-pyrazine aminations by *O*-mesitylenesulfonylhydroxylamine

Gennady I. Borodkin [a,b,*], Aleksey Yu. Vorob'ev [a,b], Makhmut M. Shakirov [a], Vyacheslav G. Shubin [a]

[a] *Vorozhtsov Novosibirsk Institute of Organic Chemistry, Acad. Lavrentiev Ave. 9, Novosibirsk 630090, Russia*
[b] *Novosibirsk State University, Pirogov st. 2, Novosibirsk 630090, Russia*

ARTICLE INFO

Article history:
Received 27 May 2009
Revised 7 September 2009
Accepted 18 September 2009
Available online 24 September 2009

Keywords:
Amination
Selectivity
N-Amine salts
Azines
Mechanism
Linear free energy relationship
DFT calculations

ABSTRACT

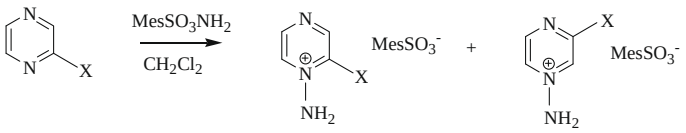
The regioselectivity of 2-X-pyrazine aminations by *O*-mesitylenesulfonylhydroxylamine was studied experimentally and the results are discussed from the viewpoint of electronic and steric factors. DFT calculations are consistent with the reaction proceeding according to an S_N2 mechanism.

N-Amine salts of N-heteroaromatic compounds are used widely as reagents in aminations of aromatic compounds,[1] and as intermediates in syntheses of *N*-imines and various heterocyclic compounds.[2–12] Nitrogen-rich salts of *N*-amines manifest themselves as high energy materials.[13–15] Azaarenes, in which two or several nitrogens are in different environments, exhibit marked alteration in reactivity patterns.[3,5] The factors determining the regioselectivity of amination of such compounds are not clear as yet. The electronic influence of substituents in 3-Br, 4-Me, and 5-NO_2-1,10-phenanthrolines on reactions with *O*-mesitylenesulfonylhydroxylamine was studied earlier.[16] It was found that the ratio of isomeric amino-cations formed was determined by their relative stability.

In continuation of our studies on the regioselectivity of azine amination, we chose to examine substituted pyrazines as model compounds. This choice was determined by their wide use in the synthesis of *N*-amine salts.[5] Besides, unlike 1,10-phenanthroline, in a pyrazine molecule both nitrogen atoms are situated in the same ring and the proximity of a substituent to the reaction center can result in certain differences in the amination process. When a substituent is located at a point remote from the reaction center, only electronic effects need usually be considered. When the structural modification is close to this center, our understanding is less advanced.

Reaction of 2-X-pyrazines **1a–i** with *O*-mesitylenesulfonylhydroxylamine in CH_2Cl_2 leads to salts **2** and **3**. The nitrile group prevents amination of **1j**, whereas the *tert*-butyl substituent in **1f** directs the amination to position 4, exclusively.

Interestingly, the amination of 2-(*N*-acetylamino)pyrazine **1i** results in the formation of 2-methyl[1,2,4]triazolo[1,5-*a*]pyrazine



1 a-j **2a-e,g-i** **3a-i**

X = H (**a**), Me (**b**), Et (**c**), Pr (**d**), *i*-Pr (**e**), *t*-Bu (**f**), CH(OH)Me (**g**), NH_2 (**h**), NHAc (**i**), CN (**j**)

* Corresponding author. Tel.: +7 383 330 7651; fax: +7 383 330 9752.
E-mail address: gibor@nioch.nsc.ru (G.I. Borodkin).

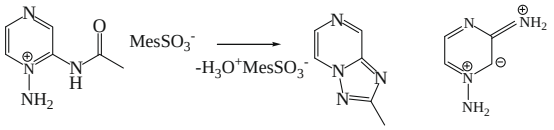
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.103

Table 1
^{1}H chemical shifts (δ, ppm) and spin–spin coupling constants (Hz) of cations **2** and **3**[a]

X	Cation	X	H-2	H-3	H-5	H-6	NH_2[b]
H	**2a**	—	8.74 (1H, ddd, 4.0, 1.6, 1.0)	9.14 (1H, dd, 4.0, 1.0)	9.14 (1H, dd, 4.0, 1.0)	8.74 (1H, ddd, 4.0, 1.6, 1.0)	9.60 (2H)
Me	**2b**	2.67 (3H, ddd, 0.8, 0.8, 0.4)	—	9.13 (1H, qd, 0.8, 0.7)	8.97 (1H, dq, 4.0, 0.8)	8.80 (1H, ddq, 4.0, 0.7, 0.4)	9.08 (2H)
	3b	2.60 (3H, ddd, 0.7, 0.7, 0.7)	8.71 (1H, dqd, 1.5, 0.7, 0.7)	—	9.01 (1H, dqd, 3.9, 0.7, 0.7)	8.62 (1H, ddq, 3.9, 1.5, 0.7)	9.51 (2H)
Et	**2c**	1.30 (3H, t, 7.4) 3.05 (2H, qddd, 7.4, 0.8, 0.7, 0.4)	—	9.08 (1H, td, 0.8, 0.8)	8.98 (1H, dt, 4.0, 0.7)	8.84 (1H, ddt, 4.0, 0.8, 0.4)	9.6 (2H)
	3c	1.24 (3H, t, 7.6) 2.87 (2H, qdd, 7.6, 0.6, 0.5)	8.78 (1H, ddt, 1.6, 0.9, 0.5)	—	9.03 (1H, dd, 3.9, 0.9)	8.66 (1H, ddt, 3.9, 1.6, 0.6)	9.6 (2H)
Pr	**2d**	0.95 (3H, t, 7.4) 1.71 (2H, tq, 7.8, 7.4) 3.01 (2H, t, 7.8)	—	9.08 (1H, d, 0.8)	8.98 (1H, d, 4.0)	8.85 (1H, dd, 4.0, 0.8)	9.6 (2H)
	3d	0.88 (3H, t, 7.4) 1.66 (2H, tq, 7.6, 7.4) 2.80 (2H, t, 7.6)	8.80 (1H, dd, 1.6, 0.9)	—	9.04 (1H, dd, 3.9, 0.9)	8.68 (1H, dd, 3.9, 1.6)	9.1 (2H)
i-Pr	**2e**	1.32 (6H, d, 6.8) 3.64 (1H, sept, 6.8)	—	9.19 (1H)[c]	8.99 (1H, d, 4.0)[c]	8.81 (1H, d, 4.0)[c]	9.5 (2H)
	3e	1.23 (6H, d, 6.9) 3.16 (1H, sept, 6.9)	8.83 (1H, dd, 1.5, 0.9)	—	9.05 (1H, dd, 3.9, 0.9)	8.67 (1H, dd, 3.9, 1.5)	9.5 (2H)
t-Bu	**3f**	1.35 (9H, s)	8.82 (1H, dd, 1.5, 0.9)	—	9.10 (1H, dd, 3.8, 0.9)	8.63 (1H, dd, 3.8, 1.5)	9.5 (2H)
CH(OH)Me	**2g**	1.55 (3H, d, 6.6) 5.34 (1H, qdd, 6.6, 0.6, 0.6) 5.2 (1H, br s)	—	9.22 (1H, dd, 0.8, 0.6)	9.05 (1H, dd, 4.0, 0.6)	8.81 (1H, dd, 4.0, 0.8)	9.1 (2H)
	3g	1.44 (3H, d, 6.6) 4.91 (1H, qdd, 6.6, 0.8, 0.8) 5.2 (1H, br s)	8.80 (1H, ddd, 1.7, 0.9, 0.8)	—	9.04 (1H, dd, 3.9, 0.9)	8.66 (1H, ddd, 3.9, 1.7, 0.8)	9.6 (2H)
NH_2	**2h**	8.84 (2H, br s)	—	8.61 (1H, d, 1.0)	7.90 (1H, d, 4.4)	8.07 (1H, dd, 4.4, 1.0)	7.14 (2H)
	3h	7.68 (2H, br s)	7.84 (1H, dd, 1.5, 0.9)	—	7.80 (1H, dd, 3.8, 1.5)	8.37 (1H, dd, 3.8, 0.9)	9.0 (2H)
NHAc	**3i**	2.20 (3H, s) 11.6 (1H, br s)	9.42 (1H, dd, 1.5, 0.9)	—	8.83 (1H, dd, 3.9, 0.9)	8.43 (1H, dd, 3.9, 1.5)	9.6 (2H)

[a] Spectra in DMSO-d_6. Chemical shifts are referenced to TMS with DMSO as a secondary internal standard (δ 2.50 ppm).
[b] Broad singlet.
[c] Some constants are not determined because of low signal intensity.

4.[17] The corresponding 1-amino-2-(*N*-acetylamino)pyrazinium **2i** undergoes rapid ring closure, such that cation **2i** cannot be observed.



2i **4** **5**

For the cations that were observed, the structures were established by means of ^{1}H NMR spectroscopy (Table 1). In addition, the structures of cations **2a**,**h** and **3i** were determined by X-ray diffraction.[18] Assignment of the proton signals was accomplished using various 2D-NMR techniques. Application of NOESY techniques was based on detection of the Overhauser effect between the protons of the NH_2 group and H-2(6) located in proximity to each other. The ^nJ(H,H) values of the cations were determined by analysis of the spin systems (i.e., simulation and iteration) in the ^{1}H NMR spectra. The resonance due to H-2 in cation **3h** occurs at a relatively high frequency. This is readily explained in terms of a contribution from the resonance structure **5**.

The isomeric ratio (**2:3**) was determined by ^{1}H NMR spectroscopy (Table 2). The ratio is kinetically controlled and highly responsive to substituent effects. The kinetic control was confirmed by the invariance of the ^{1}H NMR spectra of ions **2h** and **3i** after aging solutions of the respective salts in DMSO-d_6 at 100 °C for four hours. Consequently, intramolecular and/or intermolecular transfer of the NH_2^+ cation from one nitrogen atom to another in the pyrazinium ring does not occur.

Taking into account the proximity of the reaction center to the X-substituent in 2-X-pyrazines, it can be assumed that the ratio of isomeric cations is determined not only by electronic effects, but also by steric effects. The difference in the inductive influence of the alkyl substituents at positions 2 and 3 is probably insignificant. It has been proven that in the case of X = alkyl, only steric effects are essential (Table 2, Fig. 1)[†]:

$$\lg(\mathbf{2}:\mathbf{3}) = (-0.19 \pm 0.07) + (0.84 \pm 0.15)E_s^o \quad r = 0.958, \quad s = 0.13, \quad n = 5 \tag{1}$$

$$\lg(\mathbf{2}:\mathbf{3}) = (-0.18 \pm 0.04) - (0.41 \pm 0.03)F \quad r = 0.990, \quad s = 0.06, \quad n = 5 \tag{2}$$

In the case of other substituents, the electronic effect is significant: a correlation of lg (**2:3**) with Eq. (3) using the σ_I, σ_R^o, and E_s^o constants gives the following result (Table 2):

$$\lg(\mathbf{2}:\mathbf{3}) = (-0.24 \pm 0.08) + (0.87 \pm 0.98)\sigma_I - (1.03 \pm 0.60)\sigma_R^o + (0.94 \pm 0.11)E_s^o \quad r = 0.977, \; s = 0.12, \; n = 8 \tag{3}$$

In order to gain an insight into the reactivity and regioselectivity of the amination of X-pyrazines **1** (X = H, Me, Et, Pr, *i*-Pr, $CH(OH)CH_3$, NH_2) in terms of their prediction, the energy barriers were calculated using the DFT/PBE/3z method[23–25] (cf. Ref. 18). For pyrazines **1b–e**,**g**,**h**, the asymmetry of the transition state structures was taken into account based on their dependence on the nature of the X-substituent on the ring. Table 2 gives the lowest barriers from these variants for each substituent X. All the transition states have a single negative normal mode and the oscillatory vector corresponds to the movement of the NH_2 group from the oxygen atom of the OSO_2Mes group to the nitrogen atom of the pyrazine (Fig. 2). The intrinsic reaction coordinates (IRCs) go from the transition states directly to the products or to the reactants.

[†] As carefully checked, the correlations are statistically reliable. Two-parametric correlations between lg(**2**:**3**) and the $E_S^o(F)$-, σ_I-constant result in no statistically significant changes.

Table 2
Ratio of isomeric cations **2** and **3**, σ_I, E_s, E_s^o and σ_R^o-constants of substituents and differences in calculated energy barriers

X	lg (**2**:**3**)	σ_I[19]	σ_R^o[20,21]	E_s[20]	E_s^o[b]	F[22]	$E_{calcd}^{\neq}$[c] (kJ/mol)	$\Delta E_{calcd}^{\neq}$ (kJ/mol)
H	0.0	0	0.00	1.24	0.25	−0.28	62.8	0.00
Me	−0.173 ± 0.003[a]	−0.01	−0.10	0.00	0.00	0.00	57.3 (57.7)	−0.38
Et	−0.498 ± 0.017[a]	−0.01	−0.10	−0.07	−0.27	0.73	59.3 (58.5)	0.84
Pr	−0.478 ± 0.012[a]	−0.01	−0.11	−0.36	−0.56	0.52	63.3 (58.4)	1.17
i-Pr	−1.020 ± 0.055[a]	0.01	−0.12	−0.47	−0.87	2.12	72.0 (58.6)	13.43
CH(OH)Me	−0.479 ± 0.003[a]	0.04	−0.08	0.09	−0.44	0.64	73.3 (64.2)	9.08
NH_2	0.406 ± 0.015[a]	0.17	−0.47	0.00[d]	0.00	—	36.3 (54.1)	−17.87
NHAc	−0.473 ± 0.019[a]	0.28	−0.41	−0.75[d]	−0.95	—	[e]	[e]

[a] This value is given as the standard deviation of 5–8 measurements in the NMR spectra.
[b] The E_s^o constant was corrected for the hyperconjugation effect of the α-hydrogen and α-carbon atoms, which is related to the Taft E_s constant by the following equation: $E_s^o = E_s - 0.33(3 - n_H) - 0.13n_C$.[22]
[c] Activation barrier for the amination of the 3-X isomer is given in parentheses.
[d] The values are calculated in accordance with the isosteric principle.[22]
[e] The transition state was not found.

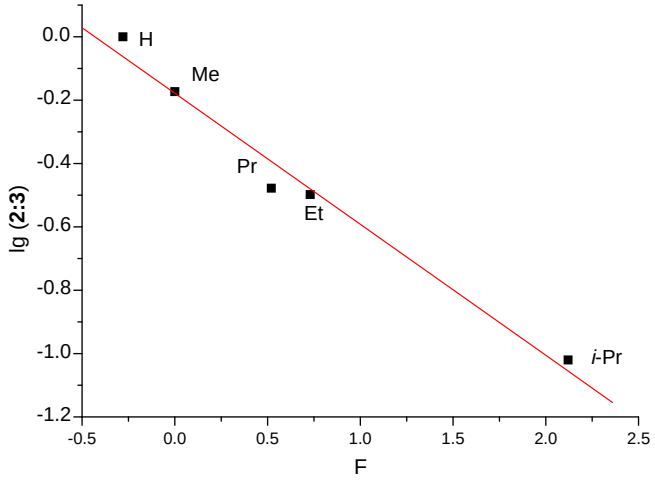


Figure 1. Plot of lg(**2**:**3**) versus F.

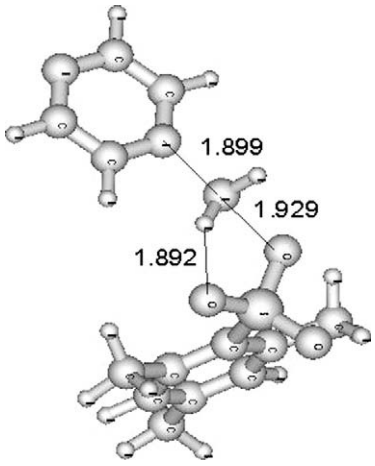


Figure 2. Calculated transition state for the amination of pyrazine **1a** with *O*-mesitylensulfonylhydroxylamine. Distances between atoms are in Å.

The N-1, N (NH_2), and O (SO_3Mes) atoms in all the transition states are almost linear (angles N–N–O = 173–176°). These geometries are identical to those typically observed for transition states of S_N2 reactions.[26,27] Comparison of the values of lg(**2**:**3**) with the differences in activation energy for the formation of cations **2** and **3**, ($\Delta E_{calcd}^{\neq}$) gives the following relationship:

$$\lg(\mathbf{2}:\mathbf{3}) = (-0.28 \pm 0.08) - (0.042 \pm 0.009)\Delta E_{calcd}^{\neq}$$
$$r = 0.91,\ s = 0.21,\ n = 7 \quad (4)$$

The calculated activation barriers for amination in the case of 2-CN-pyrazine ($E_{calcd}^{\neq} = 77.0$ and 79.5 kJ/mol for positions 1 and 4, respectively) are higher than those for the other pyrazines (Table 2). This is in agreement with the data mentioned above regarding the inertness of compound **1j**.

Thus, the results obtained with the use of the linear free energy relationship testify that the regioselectivity of the amination of 2-X-pyrazines is determined by both the electronic and steric effects of substituents X. To the best of our knowledge, the linear free energy relationship has never been used with respect to the regioselectivity of azine amination. DFT calculations corroborate the experimental results and are consistent with the reaction proceeding according to an S_N2 mechanism. Data on the difference in activation barriers for the formation of cations **2** and **3** obtained using the DFT method are in accordance with the experimental data on the regioselectivity of the amination reaction.

Acknowledgments

This study was performed with financial support by the Russian Foundation for Basic Research (Project No. 09-03-00116-a) and the Russian Academy of Sciences (Program No. 5.1.4). We thank Dr. Z. Todres for critical reading of this work and helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.103.

References and notes

1. Borodkin, G. I.; Shubin, V. G. *Russ. J. Org. Chem.* **2005**, *41*, 473–504.
2. Sadykov, A. S.; Kurbatov, Yu. V.; Zalyalieva, S. V. *N-Imines of Pyridine Bases*; FAN: Tashkent, 1982. in Russian.
3. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1–17.
4. Tamura, Y.; Ikeda, M.. In *Adv. Heterocycl. Chem.*; Academic Press: London, 1981; Vol. 29, pp 71–139.
5. Ivanov, A. Yu.; Lobanov, P. S. *Modern Problems of Organic Chemistry*; St.-Petersburg Univ. Publ: St.-Petersburg, 1998. 79–97; in Russian.
6. Katritzky, A. R.; Ballesteros, P.; Tomas, A. T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1495–1500.
7. Andreev, R. V.; Borodkin, G.I. *Materials of Conference 'Organic Synthesis in New Century'*; Saint Petersburg, 2002, p 64; in Russian.
8. Abe, N.; Odagiri, K.; Otani, M.; Fujinaga, E.; Fujii, H.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1339–1346.
9. Billert, T.; Beckert, R.; Döring, M.; Wuckelt, J.; Fehling, P.; Görls, H. *J. Heterocycl. Chem.* **2001**, *38*, 205–211.

10. Martínez, V.; Burgos, C.; Alvarez-Builla, J.; Fernández, G.; Domingo, A.; García-Nieto, R.; Gago, F.; Manzanares, I.; Cuevas, C.; Vaquero, J. J. *J. Med. Chem.* **2004**, *47*, 1136–1148.
11. Dowling, J. E.; Vessels, J. T.; Haque, S.; Chang, H. X.; van Vloten, K.; Kumaravel, G.; Engber, T.; Jin, X.; Phadke, D.; Wang, J.; Ayyub, E.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4809–4813.
12. Filák, L.; Riedl, Z.; Egyed, O.; Czugler, M.; Hoang, C. N.; Schantl, J. G.; Hajós, G. *Tetrahedron* **2008**, *64*, 1101–1113.
13. Olah, G. A.; Sassaman, M. B.; Zuanic, M.; Rao, C. B.; Prakash, G. K. S.; Gilardi, R.; Flippen-Anderson, J.; George, C. *J. Org. Chem.* **1992**, *57*, 1585–1588.
14. Xue, H.; Gao, Y.; Twamley, B.; Shreeve, J. M. *Chem. Mater.* **2005**, *17*, 191–198.
15. Wang, R.; Gao, H.; Ye, C.; Twamley, B.; Shreeve, J. M. *Inorg. Chem.* **2007**, *46*, 932–938.
16. Andreev, R. V.; Borodkin, G. I.; Shakirov, M. M.; Shubin, V. G. *Russ. J. Org. Chem.* **2004**, *40*, 1379–1381.
17. *2-Methyl[1,2,4]triazolo[1,5-a]pyrazine* (**4**). Yellow solid, mp 130–132 °C (lit. 132–132.5 °C, Tamura, Y.; Kim, J.-H.; Ikeda, M. *J. Heterocycl. Chem.* **1975**, *12*, 107–110); δ_H (200 MHz, $CDCl_3$): 2.62 (3H), 9.14 (1H, d, J = 2 Hz), 8.42 (1H, dd, J = 4.4, 2 Hz), 8.08 (1H, d, J = 4.4 Hz) (*cf.* Okamoto, T.; Torigoe, Y.; Sato, M.; Isogai Y. *Chem. Pharm. Bull.* **1968**, *16*, 1154).
18. Andreev, R. V.; Borodkin, G. I.; Vorob'ev, A. Yu.; Gatilov, Yu. V.; Shubin, V. G. *Russ. J. Org. Chem.* **2008**, *44*, 292–301.
19. Charton, M. In *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; J. Wiley and Sons: New York, 1981; pp 119–251.
20. Exner, O. In *Correlation Analysis in Chemistry. Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; pp 439–540.
21. Grindley, T. B.; Johnson, K. F.; Katritzky, A. R.; Keogh, H. J.; Thirkettle, C.; Brownlee, R. T. C.; Munday, J. A.; Topsom, R. D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 276–282.
22. Palm, V. A. *Foundations of Quantitative Theory of Organic Reactions*; Leningrad: Khimia, 1977. 226–232 and 319–321; in Russian.
23. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.
24. Laikov, D. N. *Chem. Phys. Lett.* **1997**, *281*, 151–156.
25. Laikov, D. N.; Ustynyuk, Y. A. *Russ. Chem. Bull.* **2005**, *54*, 820–826.
26. Vayner, G.; Houk, K. N.; Jorgensen, W. L.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 9054–9058.
27. Martínez, A. G.; Vilar, E. T.; Barcina, J. O.; Cerero, S. M. *J. Org. Chem.* **2005**, *70*, 10238–10246.