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N-Nitrosation of (*E*)-2-(benzylidene-amino)ethanols

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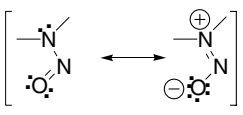
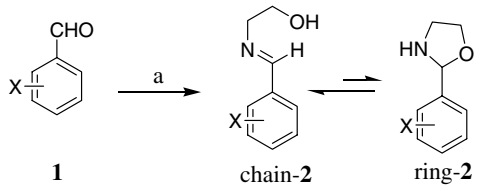
Abstract—Reaction of (*E*)-2-(benzylidene-amino)ethanol **2** with nitric oxide afforded an (*E*)-rotamer dominant mixture of (*E*)- and (*Z*)-*N*-nitroso-2-aryl-1,3-oxazolidine **3** at room temperature in good overall yields.

N-Nitroso compounds, in general, possess intriguing properties with an impact on medicine and biochemistry.[1] For example, they have been implicated in mutagenesis and carcinogenesis, but have also been successfully employed in enzyme inhibition and active site mapping.[2] The partial double bond character of N–NO bond (Scheme 1) leads to the rotation around N–NO bond to be restricted. As a result, an (*E*) and (*Z*) conformational isomerization occurs.[3]

N-Nitrosamines have been prepared by various approaches such as the nitrosation of amines by $NaNO_2$ and an acid,[4] the nucleophilic substitution of nitric oxide (NO) or another nitroso compounds by a nitrogen anion under a strong basic condition,[5] or the acid-catalyzed addition of HO–NO.[3b] Among them, the production of *N*-nitroso-2-aryl-1,3-oxazolidines with a five-membered ring containing nitrogen and oxygen is particularly of importance.[4b] *N*-nitroso-1,3-oxazolidine was prepared from aminoethanol in the presence of excess sodium nitrite in aqueous acidic solution, but in very low yield.[4b] Indeed, 2-aryl-1,3-oxazolidines **2** can be easily accessible from benzaldehyde **1** (Scheme 2).[6] Compound **2** exists as a ring–chain tautomer of an imine,



Scheme 1. Resonance in *N*-nitrosamines.



Scheme 2. Ring–chain tautomerism of **2**. (a) 2-Aminoethanol, THF, $MgSO_4$, 1 h.

(*E*)-2-(benzylidene-amino)ethanol, with a chain structure (chain-**2**) and a 2-aryl-1,3-oxazolidine with a five-membered ring structure (ring-**2**) containing nitrogen and oxygen atoms. Yet, ring-**2** desired for the further chemical manipulation is the minor species at equilibrium[6a] and both tautomers are unstable and decompose in the presence of water. Therefore, the conversion of chain-**2** into stable monocyclic **3** (Scheme 3) is certainly of significance.

As part of our ongoing research program on the chemistry of NO,[7–11] we studied the reaction of NO with compound **2**. However, we had to address two issues and these were (a) that NO led to the cleavage of C=N bonds in Schiff bases,[12] and (b) that the reaction of NO with secondary amines afforded diazenium-1,2-diolates.[13] Hence, the nitrosation of amines was carried out smoothly using NO in the absence of strong bases such as KH.[5]

In the present work, we will report our results on the reaction of NO with tautomeric mixture **2**. It gave five-membered N,O-containing ring compounds, *N*-nitroso-2-aryl-1,3-oxazolidines **3**, as an (*E*)-structure

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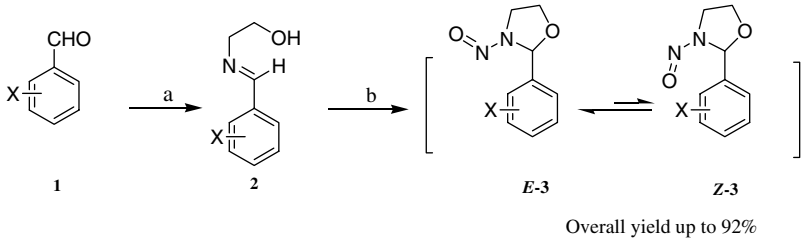


Scheme 3. Reagents and conditions: (a) 2-Aminoethanol, THF, $MgSO_4$, 1 h; (b) NO (trace O_2), THF, 2 h.

dominant mixture of (*E*)- and (*Z*)-conformer (Scheme 3). In a representative experiment,[14] treatment of *o*-chlorobenzaldehyde (**1b**) with 2-aminoethanol and $MgSO_4$ in anhydrous tetrahydrofuran (THF) for 1 h gave rise to a mixture of chain- and ring-**2b** (Scheme 3). Purified NO was then directly bubbled through the above stirred solution at room temperature for ca. 2 h. 2-*o*-Chlorophenyl-*N*-nitroso-1,3-oxazolidine **3b** was obtained as a colorless crystal in 90% isolated yield (Table 1). Its structure was characterized by ^1H and ^{13}C NMR, gHMQC, MS, HRMS, and X-ray crystallography diffraction. Figure 1 shows **3b** existing as a single *E*-conformation in solid.[15,3a] Furthermore, X-ray diffraction data indicate that O(1), N(1), N(2), C(7), C(9), and C(8) lie almost on a plane except for O(2). The bond length of N(1)–N(2) is given at 1.329 Å, being shorter than a normal N–N single bond length of 1.449 Å.[16] These observations imply partial double bond character of the N–N(O) bond in **3b**, in a manner similar to the N–C(O) bond in amides,[4c] caused by the delocalization of π-electrons on N=O bond onto the N–NO bond through the conjugation interaction. It will largely hinder the rotation of N–NO bond. Otherwise, the phenyl moiety linked at C(7) is found to be perpendicular with respect to the C(7)–N(2)–C(9)–C(8) plane. In addition, two sets of ^1H NMR peaks display **3b** existing in solution as a mixture of two conformers, (*E*)-**3b** and (*Z*)-**3b**.[17]

Table 1. Reaction of (*E*)-2-(benzylidene-amino)ethanol **2** with NO in THF

Benzaldehyde	X	Yield of **2** (%)	Chain-**2**/ ring-**2**[a]	Yield of **3** (%)	(*E*)-**3**/ (*Z*)-**3**[b]
1a	H	98	98:2	88	84:16
1b	*o*-Cl	96	95:5	90	86:14
1c	*p*-Cl	98	94:6	90	82:18
1d	*p*-NO_2	94	82:18	92	76:24
1e	*p*-OCH_3	90	88:12	83	84:16
1f	*o*-OCH_3	92	90:10	85	86:14
1g	*p*-CH_3	98	96:4	88	85:15
1h	*m*-NO_2	96	85:15	90	77:23
1i	*o*-NO_2	95	88:12	91	78:22
1j	*o*-CH_3	97	95:5	90	84:16
1k	*m*-Cl	97	96:4	89	82:18

[a] The ratio of chain-**2** to ring-**2** was evaluated using the characteristic ^1H NMR peaks at 8.69–8.14 (N=CH) and 5.69–5.30 ppm (N–CH–O).

[b] The ratio of (*E*)-**3** to (*Z*)-**3** was evaluated using the characteristic ^1H NMR peaks at 6.516–6.917 ((*E*)-**3**, N–CH–O) and 6.293–6.541 ppm ((*Z*)-**3**, N–CH–O).

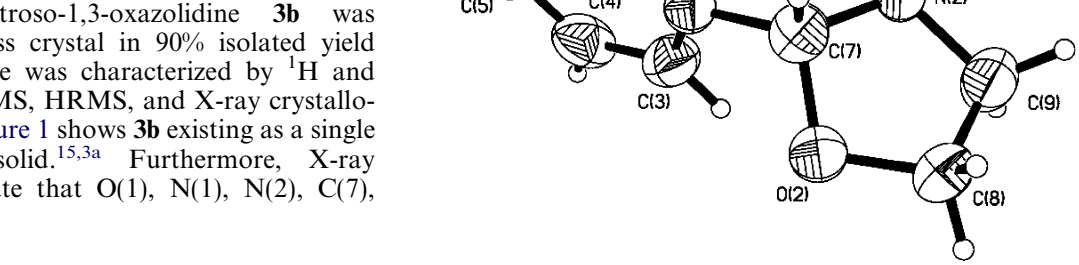
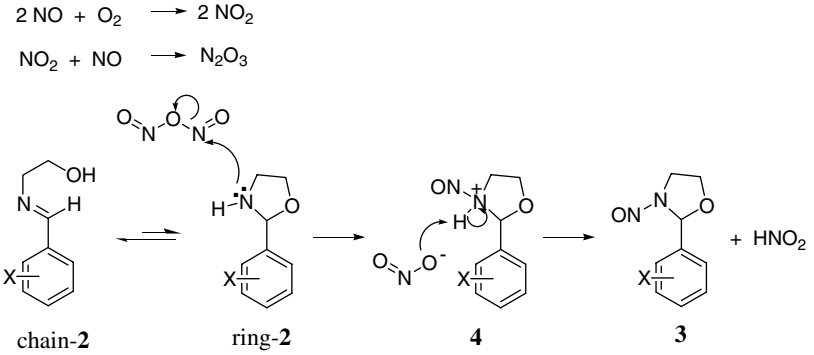
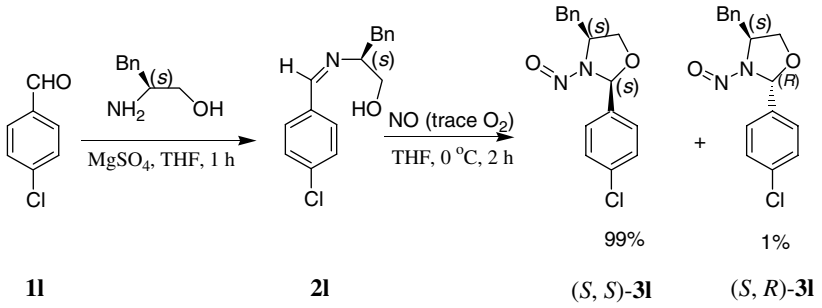


Figure 1. Molecular structure of **3b**.

A proposed mechanism for the N-nitrosation of **2** is depicted in Scheme 4. It appears that a trace of O_2



Scheme 4.



Scheme 5.

retained in reaction system plays a key role in the initiation of reactions under consideration. NO is readily oxidized to NO_2 and then converted into N_2O_3. Displacement of the good leaving group nitrite ($^{-}$ONO) from N_2O_3 by the Lewis basic nitrogen of ring-**2** leads to form **4**, which then undergoes a deprotonation to give end product **3**. Thus the process has the tendency to roll the tautomerisation of **2** from chain-**2** to ring-**2**.

Further study was carried out to extend the substrate scope for chiral oxazolidines. As an example, *N*-nitroso-2-(2*S*)-(4′-chlorophenyl)-4-(4*S*)-4-benzyl-1,3-oxazolidine **3l** was prepared using a chiral 2-aminoethanol, 2-(2*S*)-amino-2-(4′-chlorophenyl)ethanol, in a yield of 92% and a high diastereoselectivity (Scheme 5) with the ratio of (*S*,*S*)-**3l** and (*S*,*R*)-**3l** up to 95/5 at room temperature and up to 99/1 at 0 °C.[18] Representatively, the structure of (*S*,*S*)-**3l** (CCDC-630583) was established by X-ray crystallography diffraction (Fig. 2).

In conclusion, an efficient approach to prepare (*E*)- and (*Z*)-*N*-nitroso-2-aryl-1,3-oxazolidines has been developed herein. It offered advantages for a high diastereoselectivity in the preparation of *N*-nitroso-2-aryl-1,3-oxazolidines.

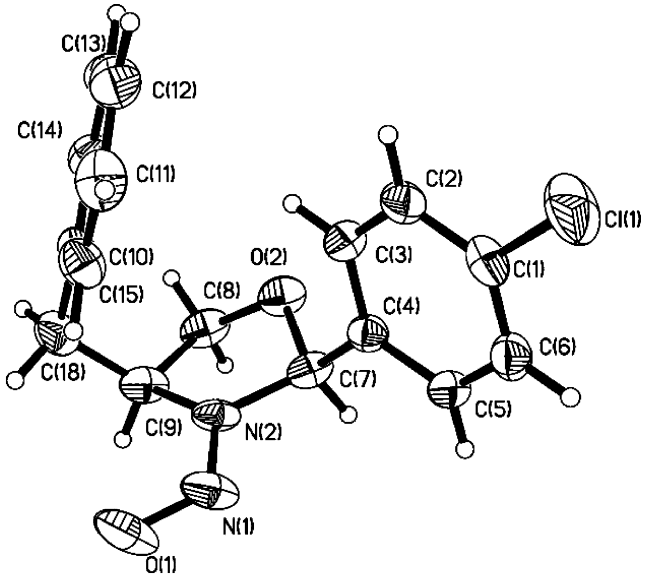


Figure 2. Molecular structure of (*S*,*S*)-**3l**.

Acknowledgment

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References and notes

1. (a) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, D.; Chen, S. *J. Org. Chem.* **1996**, *61*, 7986; (b) Darbeau, R. W.; Gibble, R. E.; Pease, R. S.; Siso, L. M.; Heurtin, D. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1084.
2. Ron, W. D.; Rebecca, S. P.; Edson, V. P. *J. Org. Chem.* **2002**, *67*, 2942.
3. (a) Karaghiosoff, K.; Klapötke, T. M.; Mayer, P.; Piotrowski, H.; Polborn, K.; Willer, R. L.; Weigand, J. J. *J. Org. Chem.* **2006**, *71*, 1295; (b) Wu, H.; Loeppky, R. N.; Glaser, R. *J. Org. Chem.* **2005**, *70*, 6790–6801.
4. (a) Butler, R. N.; Scott, F. L. *J. Org. Chem.* **1966**, 3182; (b) Saavedra, J. E. *J. Org. Chem.* **1981**, *46*, 2610; (c) Ohwada, T.; Miura, M.; Tamaka, H.; Sakamoto, S.; Yamaguclin, K.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *133*, 10164.
5. Zhu, X. Q.; Xian, M.; Wang, K.; Cheng, J. P. *J. Org. Chem.* **1999**, *64*, 4187.
6. (a) Fulop, F.; Mattinen, J. *Tetrahedron* **1990**, *46*, 6545; (b) Lerestif, J. M.; Perrocheau, J. *Tetrahedron* **1995**, *51*, 6757. As expected, these products were confirmed to be formed as an equilibrium mixture of 2-aryl-1,3-oxazolidine and imine which were identified by ^{1}H NMR spectra. The ratios of the former to latter ranged from 18:82 to 2:98 evaluated using ^{1}H NMR peaks at 5.69–5.30 (N–CH–O) and 8.69–8.14 ppm (N=CH). Ring–chain tautomers of 2-aryl-1,3-oxazolidines were prepared by the reaction of the corresponding aromatic aldehydes with an appropriate amino alcohol in refluxing dry THF in the presence of anhydrous $MgSO_4$ for 1 h.
7. (a) Liu, Z. Q.; Li, R.; Yang, D. S.; Wu, L. M. *Tetrahedron Lett.* **2004**, *45*, 1565; (b) Wu, W. T.; Liu, Q.; Shen, Y. L.; Li, R.; Wu, L. M. *Tetrahedron Lett.* **2007**, *48*, 1653.
8. Liu, Z. Q.; Fan, Y.; Li, R.; Zhou, B.; Wu, L. M. *Tetrahedron Lett.* **2005**, *46*, 1023.
9. Liu, Z. Q.; Zhou, B.; Liu, Z. L.; Wu, L. M. *Tetrahedron Lett.* **2005**, *46*, 1096.
10. Yang, D. S.; Lei, L. D.; Liu, Z. Q.; Wu, L. M. *Tetrahedron Lett.* **2003**, *44*, 7245.
11. Li, R.; Liu, Z. Q.; Zhou, Y. L.; Wu, L. M. *Synlett* **2006**, 1367.
12. Hrabie, J. A.; Srinivasan, A.; George, C.; Keefer, L. K. *Tetrahedron Lett.* **1998**, *39*, 5933.
13. Hrabie, J. A.; Klose, J. R. *J. Org. Chem.* **1993**, *58*, 1472.

14. A representative procedure: treatment of 140 mg of *o*-chlorobenzaldehyde **1b** with 61 mg of 2-aminoethanol **1** and 360 mg of $MgSO_4$ in 30 mL of anhydrous THF for 1 h gave rise to a mixture of chain- and ring-**2b**. NO was produced by the reaction of a 1 M H_2SO_4 solution with saturated aqueous solution of $NaNO_2$ under an argon atmosphere. H_2SO_4 was added dropwise. NO was carried by argon and purified by passing it through a series of scrubbing flasks containing 4 M NaOH, distilled water, and $CaCl_2$ in this order. Purified NO was then bubbled through the stock solution, stirred at room temperature for ca. 2 h. The stock solution was kept at a pressure of up to +10 mm H_2O column over local atmospheric pressure at 20 °C. After completion of the reaction, as indicated by TLC, the mixture was concentrated under vaccum, purified by column chromatography on silica gel (200–300 mesh, ethyl acetate–petroleum ether), and recrystallized from ethyl acetate, yielding colorless crystal **3b** (190 mg, 90% yield). Compound **3b** was characterized by ^1H and ^{13}C NMR, HMQC, MS, HRMS, and X-ray crystallography diffraction. Data for 2-(2-chlorophenyl)-3-nitrosooxazolidine ((*E*)-**3b**, (*Z*)-**3b**): colorless crystal, mp 44.2 °C; IR (KBr) ν_{max} 3435.4 (vs), 3065.0 (vs), 2901.6 (s), 1410.3 (s), 1268.9 (s, ν_{sym} NO) cm^{-1}; MS (EI, 70 eV) *m*/*z* 212 (M^+, 28), 168 (100), 139 (38), 125 (63), 111 (28), 89 (66), 75 (52); HMRS-ESI *m*/*z* calcd for $C_9H_9N_2O_2Cl$+Na 235.0244, found 235.0245, error −0.6 ppm. (*E*)-**3b**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.05–7.47 (m, 4H, –Ph-*o*-Cl), 6.92 (s, 1H, –N–CH–O), 4.38–4.42 (m, 1H, –O–CH_e), 4.17–4.21 (m, 1H, –O–CH_a), 3.96–4.00 (m, 1H, –N–CH_e), 3.74–3.79 (m, 1H, –N–CH_a); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.25 (–Ph-*o*-Cl), 132.98 (–Ph-*o*-Cl), 131.13 (–Ph-*o*-Cl), 130.20 (–Ph-*o*-Cl), 128.68 (–Ph-*o*-Cl), 127.06 (–Ph-*o*-Cl), 88.66 (–N–CH–O), 64.84 (–O–CH_2), 43.69 (–N–CH_2). (*Z*)-**3b**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.05–7.47 (m, 4H, –Ph-*o*-Cl), 6.54 (s, 1H, –N–CH–O), 4.85–4.89 (m, 1H, –N–CH_a), 4.51–4.55 (m, 1H, –N–CH_e), 4.31–4.34 (m, 1H, –O–CH_e), 4.15–4.21 (m, 1H, –O–CH_a); ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.38 (–Ph-*o*-Cl), 131.97 (–Ph-*o*-Cl), 130.60 (–Ph-*o*-Cl), 130.29 (–Ph-*o*-Cl), 127.67 (–Ph-*o*-Cl), 126.87 (–Ph-*o*-Cl), 87.74 (–N–CH–O), 65.38 (–O–CH_2), 48.12 (–N–CH_2). Crystal data for **3b**: $C_9H_9N_2O_2Cl$, Mr = 212.63, orthorhombic, space group *P*2(1)2(1)2(1) with cell parameters: $a = 6.6705(2)$ Å, $b = 10.9436(3)$ Å, $c = 13.3939(4)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, $V = 977.75(5)$ $Å^3$, $\rho_{calcd} = 1.444$ mg/m^3, $Z = 4$, $T = 273(2)$ K, $\mu = 0.365$ cm^{-1}, $F_{000} = 440$, $-8 \leqslant h \leqslant 8$, $-13 \leqslant k \leqslant 11$, $-16 \leqslant l \leqslant 16$, $4.80° \leqslant 2\theta \leqslant 51.96°$, 1921 data collected, 1537 unique data ($R_{int} = 0.0335$), 128 refined parameters. GOF(F^2) = 1.044, $R_1 = 0.0434$, $wR_2 = 0.1196$. The X-ray crystallographic structure of **3b** is shown in Figure 1. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-608039.
15. Looney, C. E.; Phillips, W. D.; Reilly, E. L. *J. Am. Chem. Soc.* **1957**, *79*, 6136.
16. Ren, X. Y.; Liu, Z. Y. *Struct. Chem.* **2005**, *6*, 567.
17. The peaks at 6.917 and 3.964–4.004 as well as 3.742–3.792 ppm are assigned to C(7)–H and C(9)–H of (*E*)-**3b**, respectively, and those at 6.540 and 4.890–4.855 as well as 4.550–4.506 ppm, characterized by gHMQC, to C(7)–H and C(9)–H of (*Z*)-**3b**, respectively. Compared with (*Z*)-**3b**, C(7)–H of (*E*)-**3b** shows a downfield chemical shift, whereas C(9)–H shows an upfield chemical shift.[4b] The ratio of (*E*)-**3b** to (*Z*)-**3b** is estimated from the integral of the peak at 6.917 and 6.540 ppm and indicates that (*E*)-**3b** is the preferable conformation of **3b**.
18. The dienantiomers were purified and isolated by column chromatography on silica gel (200–300 mesh, ethyl acetate–petroleum ether) and recrystallization from ethyl acetate, yielding (*S*,*S*)-**3l** and (*S*,*R*)-**3l** as colorless crystals in a yield of 91% and 1%, respectively. It was estimated that (*E*)-(*S*,*S*)-**3l**:(*Z*)-(*S*,*S*)-**3l** = 59:41 and (*E*)-(*S*,*R*)-**3l**:(*Z*)-(*S*,*R*)-**3l** = 51:49.