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Ring opening of 2,3-epoxy phenyl ketones upon reaction with nitric oxide

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Abstract—Epoxide rings of 2,3-epoxy phenyl ketones were cleaved by nitric oxide, affording regioselectively the C-3 ring-opened products, *erythro*-α-hydroxyl nitrates (**2**), in a highly *syn*-selective manner (isolated yield of the *erythro* products up to 91%). Products were identified by NMR, MS, and X-ray crystallography. The reaction is assumed to be initiated by NO_2, unlike a nucleophilic attack.

The biological actions of nitric oxide (NO)[1] have led to large quantities of review papers on its important roles in biology.[2] Yet, its chemistry researches began just recently. It has been known that NO is able to react with various organic compounds such as olefins,[3] imines,[4] amines,[5] amides,[6] oximes,[7] arylhydrazines,[8] etc. However, to the best of our knowledge, no papers have been reported for the reaction of NO with epoxides.

Epoxides (oxiranes), due to their ease of formation and ready reactivity toward nucleophiles, are important starting materials and intermediates in organic synthesis.[9] Among the reports of epoxides, many of those are involved in the ring opening reactions.[10] Most of the nucleophilic ring opening reactions proceed via an S_N2-like mechanism and afford the corresponding *trans*-α-Nu alcohols. The reactivity of the three-membered ring lets us believe that the epoxide cleavage may take place by attack of a reagent such as NO other than powerful nucleophiles such as water, hydroxide, HX, etc. Our great interest in NO stimulated us to the investigation of epoxide ring openings upon reaction with it.

We led NO gas to react directly with 2,3-epoxy phenyl ketones (**1**) at ambient temperature in CH_2Cl_2. In a typical procedure, **1a** (1 mmol, 276 mg) was dissolved in 15 ML of dry CH_2Cl_2. 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. The purified NO was then bubbled through the stock solution, stirred at room temperature for ca. 15 h. After completion of the reaction, as observed by TLC, the mixture was concentrated in vacuo and purified by column chromatography on silica gel (200–300 mesh, ethyl acetate–petroleum ether), recrystallized from ethyl acetate, yielding the colorless crystal **2a** (306 mg, 91%). It was identified by ^1H and ^{13}C NMR, MS, HRMS, IR, and X-ray crystallography diffraction.[11] Its X-ray crystallographic structure is shown in Figure 1 (the deposition number: CCDC-220320). It is clearly shown that **2a** is a C-3 ring-opened product and an *erythro*-α-hydroxyl nitrate (Scheme 1). The specific rotation of **2a** was detected to be zero, which indicated that **2a** was a 1:1

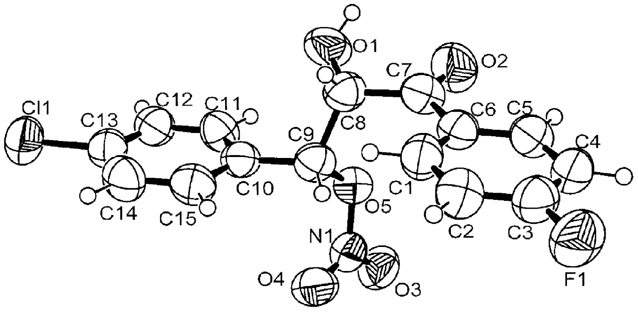

Figure 1. Molecular structure of **2a**.

Keywords: Epoxides; Nitric oxide; Ring open.

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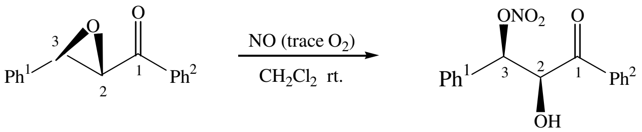


1 **2**

Ph^1, Ph^2 = aryl

isolated yield: up to 91%

Scheme 1.

Table 1. Ring opening of 2,3-epoxy phenyl ketones by NO in CH_2Cl_2

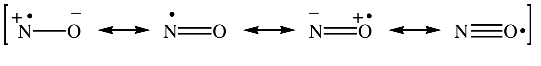
Entry	R^1	R^2	T^a (h)	Yield^b (%)
1a	*p*-Cl–Ph	*p*-F–Ph	15	91
1b	Ph	Ph	14	85
1c	*p*-Cl–Ph	Ph	13	86
1d	Ph	*p*-F–Ph	14	84
1e	*p*-Me–Ph	Ph	13	88
1f	Ph	*p*-MeO–Ph	12	84
1g	*m*-NO_2–Ph	Ph	19	68

[a] The reaction time.

[b] Isolated yields of the *erythro* products after column chromatography.

racemic mixture of two enantiomers: (2*S*,3*R*)- and (2*R*,3*S*)-**2a**. We would like to claim that we did not isolate the *threo* products because of their rare yield. All other *erythro*-α-hydroxyl nitrates (**2**) were also obtained in good yield (Table 1). Two important issues on the regiochemistry could be approached from product structures: (1) the two newly produced functions (OH and ONO_2) lie in the *cis* rather than the normal *trans*; (2) there was a high selectivity for C-3 opening.

No reaction occurred when the system was absolutely protected from air. As known, traces of oxygen oxidizes NO to nitrogen dioxide (NO_2).[12,13] It leads us to assume that the ring opening reactions under consideration are initiated most likely by NO_2, unlike the common nucleophilc ring openings, because NO is not an effective nucleophile from its canonical forms:



Now we try our best to research the mechanism of this novel reaction. To explore the reaction nature, we are presently studying the NO assisted openings of the 2,3-epoxy phenyl ketones in which the substituents on the 2,3-epoxy phenyl ketone moiety are various alkyl groups.

Acknowledgements

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References and notes

1. (a) Williams, D. L. H. *Org. Biomol. Chem.* **2003**, *1*, 441; (b) Batler, A. R.; Williams, D. L. H. *Chem. Soc.* **1993**, *22*, 233; (c) Stamler, J. S.; Singed, D. J.; Loscalzo, J. *Science* **1992**, *258*, 1898; (d) Pfeiffer, S.; Mayer, B.; Hemmens, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1714; (e) Murad, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1857; (f) Furchgott, R. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1871; (g) Ignarro, L. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1883.
2. (a) Wang, P. G.; Xian, M.; Tang, X. P.; Wu, X. J.; Wen, Z.; Cai, T. W.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091; (b) Hrabie, J. A.; Keefer, L. K. *Chem. Rev.* **2002**, *102*, 1135; (c) Gerald, M. R.; Pei, T.; Sovity, P. *Chem. Rev.* **2002**, *102*, 1191; (d) Lan, M. W.; d'Vries, S.; Loccoz, P. M.; Schröder, L.; Karlin, K. D. *Chem. Rev.* **2002**, *102*, 1201.
3. d'Ischia, M. *Tetrahedron Lett.* **1996**, *36*, 8881.
4. (a) Nagano, T.; Takizawa, H.; Hirobe, M. *Tetrahedron Lett.* **1995**, *36*, 8239; (b) Hrabie, J. A.; Srinivasan, A.; George, C.; Keefer, L. K. *Tetrahedron Lett.* **1998**, *39*, 5933.
5. Drago, R. S.; Paulk, F. E. *J. Am. Chem. Soc.* **1960**, *82*, 96.
6. Itoh, T.; Nagata, K.; Matsuga, Y.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **1997**, *38*, 5017.
7. Mao, Y. Z.; Liu, Z. L.; Wu, L. M. *Chin. J. Chem.* **2000**, *18*, 789.
8. Itoh, T.; Nagata, K.; Matsuga, Y.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **1997**, *38*, 4117.
9. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
10. (a) Delgado, A.; Leclerc, G.; Cinta Lobato, M.; Mauleon, D. *Tetrahedron Lett.* **1988**, *29*, 3671; (b) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82; (c) Mitani, M.; Matsumoto, H.; Gouda, N.; Koyama, K. *J. Am. Chem. Soc.* **1990**, *112*, 1286; (d) Myers, A. G.; Widdowson, K. L. *Tetrahedron Lett.* **1988**, *29*, 6389; (e) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2531; (f) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044; (g) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (h) Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 667.
11. Data for **2a**: Mp 107.6 °C; dec 146.8 °C; IR (KBr): 3463, 2902, 1684, 1640, 1595, 1506, 1277, 1232, 1122, 820, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (1H, d, $J = 7.2$ Hz), 5.32 (1H, dd, $J = 7.2$ Hz, $J = 3.6$ Hz), 6.03 (1H, d, $J = 3.6$ Hz), 7.20 (2H, t, $J = 8.0$ Hz), 7.32 (4H, m), 7.93 (2H, dd, $J = 8.0$ Hz, $J = 5.6$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 73.9, 83.4, 116.6, 128.8, 129.0, 130.1, 131.4, 132.2, 135.6, 166.5, 195.5; HRESIMS m/z calcd for $C_{15}H_{11}NO_5ClF$ (MNH_4^+): 357.0648, found: 357.0648; Crystal data for **2a**: $C_{15}H_{11}ClFNO_5$, $M_r = 339.70$, orthorhombic, space group $Pca2(1)$, $a = 16.956(3)$ Å, $b = 10.200(2)$ Å, $c = 8.538(2)$ Å, $\beta = 90.00(1)°$, $V = 1476.7(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.528$ g cm^{-3}, $\mu = 0.296$ cm^{-1}, $F(000) = 696$, $31.80 \leqslant 2\theta \leqslant 49.92$, $0 \leqslant h \leqslant 20$, $-12 \leqslant k \leqslant 0$, $0 \leqslant l \leqslant 10$, 1337 data collected, 1124 unique data ($R_{int} = 0.0000$), 1124 data with $I > 2\sigma(I)$, 209 refined parameters, $GOF(F^2) = 1.065$, $R_1 = 0.0318$, $wR_2 = 0.0744$. The X-ray crystallographic structure of **2a** is shown in Figure 1. The crystallographic data has been deposited at the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-220320.
12. Brown, J. F., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 2480.
13. Korth, H.-G.; Sustmann, R.; Lommes, P.; Paul, T.; Ernst, A.; de Groot, H.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1994**, *116*, 2767.