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Regio- and stereoselective ring opening of aziridines with nitric oxide

Zhong-Quan Liu, Yuan Fan, Rui Li, Bo Zhou and Long-Min Wu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Guansu 730000, PR China

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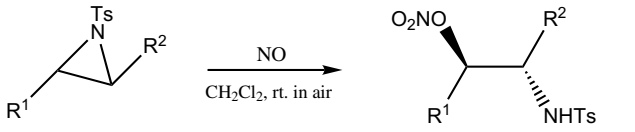
Abstract—Reaction of *N*-tosyl aziridines with nitric oxide affords the corresponding ring-opened products in regio-, stereoselectivities and excellent yields.

Studies on the ring-opening reaction of aziridines with various nucleophiles have been intensively undertaken in the past decades.[1] Generally, the corresponding ring-opened products, *anti*-α-Nu amines are produced in average chemical selectivities. It has rarely been encountered that aziridines ring opening proceeded in highly regio-, diastereo-, and stereoselectivities without any catalyst. Therefore, how to apply the important type of sythons efficiently is the main problem, which researchers are managing to solve.

Nitric oxide (NO) has still been attracting more attention from biologists and chemists.[2,3] Could such a small biological molecular lead to high regio- and stereoselective aziridine ring opening without the aid of any special catalysts? If it were possible, it would be a piece of very exciting news for chemists that some small biological compounds could efficiently take place of complex catalysts in organic transformations. Fortunately, nitric oxide which use to act as the endothelium-derived relaxing factor (EDRF)[4] really did it. In our recent paper, an unbelievable ring-opening reaction of epoxides with NO was spotted that completely *syn*-α-hydroxy nitrates were obtained in high regio- and stereoselectivities.[5] Now we would like to report another interesting but somewhat difficult to understand result upon the ring-opening reaction of aziridines with NO to produce *anti*-α-*N*-tosyl nitrates in similarly high selectivities and excellent yields (Scheme 1).



R^1, R^2 = aryl, alkyl

isolated yields of the *trans*-pair up to 97%
d.r. up to 30:1

Scheme 1.

Additionally, it is well known that hydrolysis of nitrates under strong base can obtain the corresponding alcohols via a S_N2 manner.[6] Therefore, these products can be easily transferred to *syn*-α-amino alcohols, which are very useful to organic synthesis.

As an excellent example, the reaction of **1a** with NO gave a single C-1 opening *anti*-α-*N*-tosyl nitrate **2a** in 97% yield. Its structure along with **2i** is shown in Figure 1. This stereochemical structure corresponds to an energetically most favorable *anti* conformation, in which the relatively large groups (*N*-tosyl and nitrate) are best kept as far from each other as possible. These clearly indicate that the ring opening of **1a** proceeds regiospecifically at C-1 and the preferred formation of **2a** is the *anti* isomer.

However, a mixture of *anti*-pairs (**2b**:**2′b** = 4:1) was obtained when **1b** was treated with NO. The reaction afforded both the C-1 and C-2 opened product with a selectivity of 4:1, although the ring opening still mainly occurred at C-1. Similar phenomena were observed in

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* Corresponding author. Tel.: +86 09318912500; fax: +86 09318625657; e-mail: liuzhongq03@st.lzu.edu.cn

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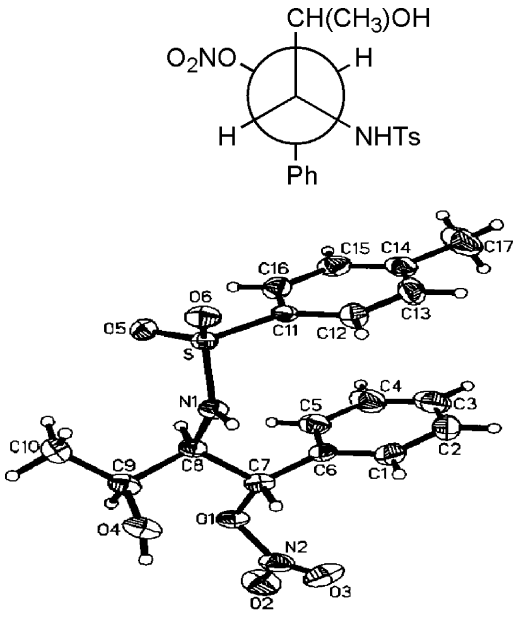
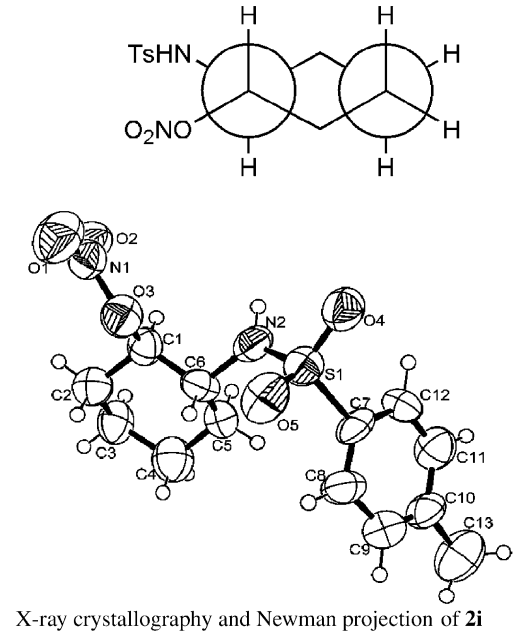


X-ray crystallography and Newman projection of **2a**



X-ray crystallography and Newman projection of **2i**

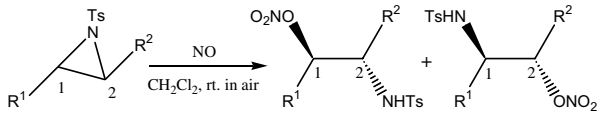
Figure 1. Molecular structures and Newman projections of **2a** and **2i**.

the cases of **1c**–**g**. They clearly demonstrated that the regioselectivity of aziridines ring opening with NO depended upon the ring substituents, with the majority of ring opening at C-1.

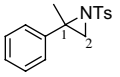
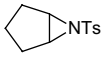
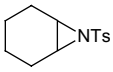
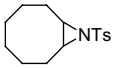
We subjected cyclic aziridines such as **1h**, **1i**, **1j** to ring opening with NO under the same conditions as for **1a**–**g**. Similarly, the ring-opening reaction was completely *anti*-stereoselective, giving only the *anti*-isomers (Table 1).

There existed to the contrary NO-mediated ring-opening stereoselectivities for aziridines and epoxides. In our recent results on ring opening of epoxides,[5] 2,3-epoxy phenyl ketones underwent highly regioselective ring

Table 1. Reaction of nitric oxide with aziridines[11]



1 **2** **2′**

Entry	R^1	R^2	T[a] (h)	Yield[b] (%)	Ratio[c] of **2** and **2′**
1a	Ph	$CHCH_3OH$	14	97	>30:1
1b	Ph	CH_2OH	14	85	4:1
1c	(*p*)MePh	CH_2Ph	17	85	3:1
1d	(*p*)MePh	CH_2CH_2Ph	17	88	3:1
1e	$CH_3(CH_2)_4$	CH_3	18	85	3:1
1f	Ph	H	12	90	>20:1
1g[d]			12	85	>20:1
1h			15	92	—
1i			15	95	—
1j			32	63	—

[a] Reaction time.
[b] Isolated yields after column chromatography.
[c] Determined by ^1H NMR spectroscopy.
[d] Ring opened from the C-1 which was indicated in the substrate.

opening at C-3 with NO allowing only access to *syn*-α-hydroxyl nitrates. In contrast to epoxides, ring opening of aziridines were subjected to *anti*-stereoselective, giving only the *anti*-isomers. In our very recent studies, we found that the *syn*-stereoselectivity in epoxides ring opening reaction related closely to the carbonyl group neighboring to the three member ring. As a matter of fact, ring-opening reactions of general epoxides and aziridines lacking adjoining carbonyl group were performed in an *anti* manner. These results can be found in our later reports.

No reaction occurred when the system was absolutely protected from air. As known, a small amount of oxygen oxidizes NO to nitrogen dioxide (NO_2).[7,8] Since NO is not an effective nucleophile, it leads us to assume the ring-opening reaction under consideration is initiated most likely by NO_2.[9,10] Related studies, including deduction of the reaction mechanism, are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.011.

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