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Stereoselective nitration of asymmetric hydrazones with nitric oxide

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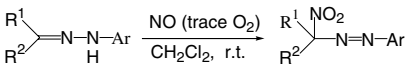
Abstract—Nitration of asymmetric hydrazones with nitric oxide occurred stereoselectively at C1′-atom, giving mono-nitrated trans isomer as a major outcome. The ratio of trans to cis was up to >99. Higher isolated yields of nitrated products and higher trans/cis ratios of isomers suggest that this procedure offers advantages for synthesizing asymmetry nitro compounds.

The remarkable synthetic importance of nitro compounds has ensured long-standing studies of their utilization in organic synthesis.[1] They have proven to be valuable reagents for synthesizing complex target molecules. Their versatility in organic synthesis is largely attributed to their easy availability[2] and transformation into a variety of diverse functionalities.[3] In particular, the azo and the adjacent nitro group will be of great significance in organic synthesis. Otherwise, nitric oxide (NO) has been used as a nitrating reagent in many processes.[4] Recently, we reported that ketone arylhydrazones reacted with NO to give C1′-nitro azo compounds in high yield (Scheme 1),[5] wherein a quaternary carbon center was newly established. Our interest in NO promoted us to explore whether the structural features in cyclic ketone hydrazones will exert a significant influence on stereochemistry.

We started with an enantiopure hydrazone substrate **1a** (Table 1), which derived from naturally occurring L-menthone with a (2*S*,5*R*) configuration, to survey the reaction conditions. An excess of NO was bubbled into a CH_2Cl_2 solution of **1a** at room temperature under an atmosphere of argon. It led to the C1′-mononitration of **1a**, affording the single *trans*-**2a** in 91% yield. The structure of **2a** was identified by standard spectral data.[6] X-ray analysis carried out on single crystals of **2a** slowly grown in a mixed solvent of EtOAc and hexane (1:30, v/v) (Fig. 1, the deposition number: CCDC-241117) clearly shows that **2a** is a (1*R*,2*S*,5*R*) enantiomer, where the (2*S*,5*R*) configuration of L-menthone is known, and that the azo group is at the axial position of the six-membered ring and the nitro group lies along the equator of the molecule. The ratio of trans to cis was up to 99:1 and the ee value up to 99%, estimated by the HPLC analysis. Herein, trans and cis are specified stereochemical relationships between the nitro group at C1 and group R^1 at C2 on the six-membered ring. It was also confirmed that no racemizaton occurred in the course of nitration of **1a**. Other asymmetric cyclic hydrazones bearing different substituents were examined accordingly (Scheme 2). The results are listed in Table 1.



Ar = 2,4-dinitrophenyl

Scheme 1.

Several issues on this nitration could be approached from the above results: (a) The nitration uniquely occurred at C1′-atom, stereospecifically constructing a new quaternary carbon center; (b) the major stereochemical outcome of the nitration is that in which the C1′-nitro group and C2′-substituent lie on opposite sides of the six-membered ring; (c) both the cyclopentanone and cyclohexanone hydrazones gave higher trans/cis ratios, whereas the seven-membered ring hydrazone derivatives afforded a less stereoselectivity (Table 1, entry 8); and (d) the substituent R at C2′-atom with branched chain such as the isopropyl group led to higher trans/cis ratios than those with linear structures.

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Interestingly, the α,β-unsaturated derivatives such as **1c** gave double bond shifting products rather than C1′-nitro products. No reaction occurred with **1i**, a fructose derivative (Table 1, entry 9). The hydroxyl was kept un-reacting with NO (Table 1, entry 2), in contrast to that previously reported.[7]

Table 1. Nitration of asymmetric hydrazones with NO

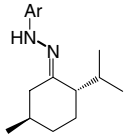
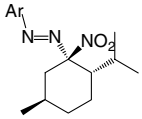
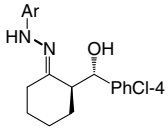
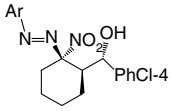
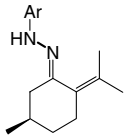
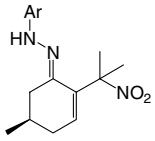
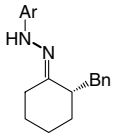
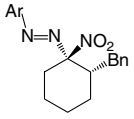
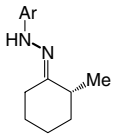
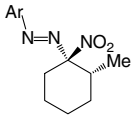
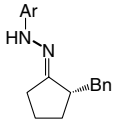
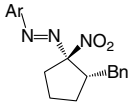
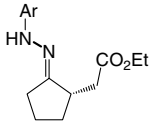
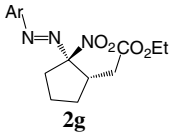
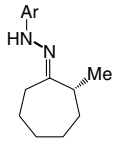
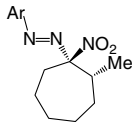
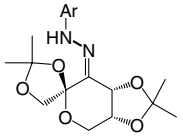
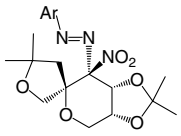
Entry	Substrate	Product	Time (h)	Yield[a] (%)	Trans/cis
1	 **1a**	 **2a**	16	91	>99:1[b]
2	 **1b**	 **2b**	18	95	9:1[c]
3	 **1c**	 **2c**	16	96	—
4	 **1d**	 **2d**	16	98	5:1[c]
5	 **1e**	 **2e**	16	89	6:1[d]
6	 **1f**	 **2f**	16	80	5:1[c]
7	 **1g**	 **2g**	18	95	7:1[d]

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[a] (%)	Trans/cis
8	 **1h**	 **2h**	14	85	2:1[c]
9	 **1i**	 **2i**	48	0[e]	—

[a] Isolated yield after silica gel chromatography.
[b] The ratio of *trans*-**2** to *cis*-**2** was determined by chiral HPLC.
[c] The ratio of *trans*-**2** to *cis*-**2** was evaluated using ^{1}H NMR peaks of the characteristic Ar-H.
[d] Values for trans/cis ratio were estimated based on isolated yields.
[e] Along with >99% recovered substrate.

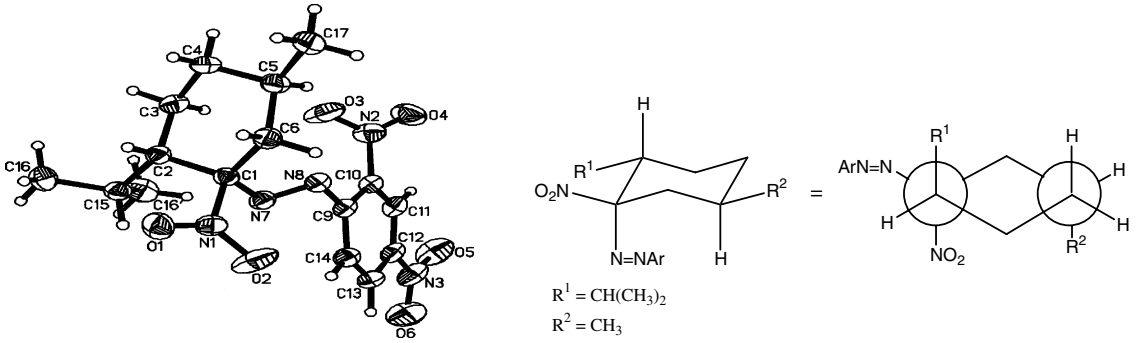
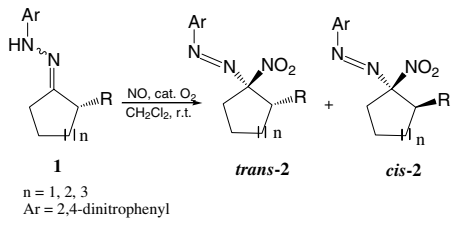


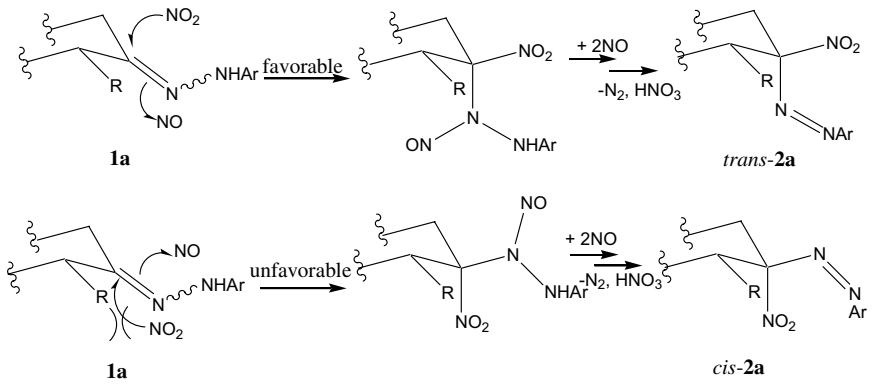
Figure 1. X-ray crystallographic structure of **2a** and its Newman project viewed along the C2–C1 and C4–C5 bonds.

From our previous report,[5] it has been known that NO stereoselectively reacted with asymmetric ketone hydrazones, the reaction was initialized by NO_2, and the nitrated products with a new stereogenic center were obtained as single products. In order to explain the stereoselectivity of the nitration, substrate **1a** is exemplified. In general, the addition of an NO_2 to a C=N double bond will occur equally at two available sides of the $(CH_2)(CH_2)C{=}N$ plane (Scheme 3), leading to a racemic mixture of two diastereoisomers: (1*R*,2*S*,5*R*)- and (1*S*,2*S*,5*R*)-**2a**. Yet, our present results seem to indicate that the moiety of six-membered ring and the axially lying R at C2′ largely favor NO_2 attack from the equatorial direction (Scheme 3). Such a stereoselectivity was not observed in our previous work.[5] Furthermore, the equatorial nitro-compound is normally more stable than axial isomer. As such, higher trans/cis ratios were established.



Scheme 2.

Higher isolated yields of nitrated products and higher trans/cis ratios of isomers of the nitration suggest that this procedure offers advantages for synthesizing asymmetry nitro compounds. Its experimental simplicity and ease execution will be attractive.



Scheme 3.

Acknowledgment

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6. *Representative procedure for the nitration of asymmetric hydrazones with NO*: A stock solution was prepared by dissolving 0.5 mmol of **1a** in 35 mL of anhydrous CH_2Cl_2. The stock solution was previously deaerated with argon for 15 min. In the course of degassing, the argon flow rate was controlled by regulating the flow meter at 0.8 L min^{-1} and the stock solution was kept at a pressure of up to +10 mm H_2O over local atmospheric pressure at room temperature. Purified NO was bubbled through the stock solution until the completion of the reaction, as indicated by TLC. The solution was then concentrated under vacuum and purified by column chromatography on silica gel to give **2a** (91% yield) as orange crystalline needles. Data for **2a**: $[\alpha]_D^{18}$ +573 (*c* 1.3, EtOAc), mp 96 °C; IR (KBr) ν_{max} 3104, 3088, 2957, 2933, 2906, 2874, 1605, 1536, 1463, 1346, 1302, 1151, 1065, 919, 839, 783, 757, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, d, $J = 6.8$ Hz), 0.9 (3H, d, $J = 6.4$ Hz), 1.07 (3H, d, $J = 6.8$ Hz), 1.16 (1H, dd, $J = 14.0$ Hz, $J = 11.6$ Hz), 1.29 (1H, dq, $J = 13.2$ Hz, $J = 3.6$ Hz), 1.76 (1H, dt, $J = 12.8$ Hz, $J = 2.8$ Hz); 1.82–1.90 (3H, m), 2.14 (1H, dqq, $J = 6.8$ Hz, $J = 2.4$ Hz), 2.38 (1H, ddt, $J = 12.8$ Hz, $J = 2.8$ Hz), 2.75 (1H, dt, $J = 13.2$ Hz, $J = 2.4$ Hz), 7.54 (1H, d, $J = 8.4$ Hz), 8.55 (1H, dd, $J = 8.4$ Hz, $J = 2.4$ Hz), 8.95 (1H, d, $J = 2.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 22.1, 22.4, 22.9, 27.9, 29.1, 33.8, 42.5, 50.3, 113.4, 120.4, 120.7, 129.0, 145.5, 148.2, 148.8; HR-ESI-MS *m*/*z* calcd for $C_{16}H_{21}N_5O_6$ ($M+H^+$) 380.1569, found 380.1564; EIMS *m*/*z* 379 (M^+), 333, 317, 291, 195, 110, 93, 81, 67, 55, 41. Trans/cis ratio >99:1, ee >99% [HPLC, Chiralcel OD-H column, hexane/2-propanol, 90:10, v/v, the flow rate, 0.5 mL/min]. Crystal data for **2a**:[8] $C_{16}H_{21}N_5O_6$, $M_r = 379$, monoclinic, space group $P2(1)$, $a = 8.419(2)$ Å, $b = 9.382(2)$ Å, $c = 12.366(4)$ Å, $\beta = 107.46(1)°$, $V = 931.71(47)$ $Å^3$, $Z = 2$, $\rho_{calcd} = 1.352$ g/cm^3, $\mu = 0.105$ mm^{-1}, $F(000) = 400$, $3.5 \leqslant 2\theta \leqslant 56.8°$, $0 \leqslant h \leqslant 11$, $0 \leqslant k \leqslant 12$, $-16 \leqslant l \leqslant 15$, 2739 data collected, 2480 unique data ($R_{int} = 0.0223$), 1397 data with $I > 2\sigma(I)$, 248 refined parameters, GOF(F^2) = 0.839, $R_1 = 0.0823$, $wR_2 = 0.0910$. 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-241117.
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8. (a) Wu, W. T.; Wu, G. L.; Shen, Y. L.; Wu, L. M. *Chin. J. Org. Chem.* **2005**, *25*, 446; (b) Zhao, L. F. *Acta Crystallogr.* **2006**, *E62*, o2160–o2162.