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Reaction of Arylhydrazines with Nitric Oxide in the Presence of Oxygen

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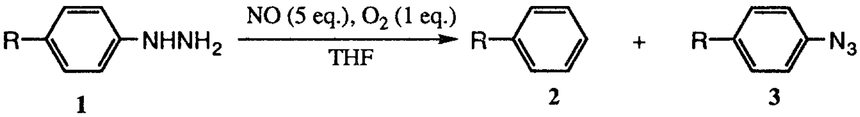
Abstract: Arylhydrazines were treated with nitric oxide in tetrahydrofuran in the presence of oxygen to afford dehydrazinated compounds in good yields accompanied by small amounts of arylazides. © 1997 Elsevier Science Ltd.

Nitric oxide (NO) is a gaseous radical molecule which has been revealed to play a variety of roles in biological functions.[1] Because of the well-recognized importance of NO, extensive research has been carried out from the viewpoints of biochemistry and physiology.

In the area of chemistry, the reactivity of NO has attracted attention only in recent years, and papers concerning the chemistry of NO have been gradually increasing. The published reports seem to be classified into three types: employment of NO as a mild nitrosation or nitration reagent to exploit new organic reactions,[2] development of the detection method of NO in a biological system using organic reactions,[3] and reactions of NO with biologically important molecules.[4] In the course of our study of reactions using NO as a nitrosation reagent, it was revealed that Hantzsch dihydropyridines were readily aromatized by the use of NO as an oxidizing agent.[5] Moreover, aromatic primary amines were found to react with NO in the presence of a catalytic amount of O_2 in THF solution to bring about deamination reaction.[6] These results suggested to us that compounds which contain an N-H bond might react with NO in various ways under the influence of O_2. Thus, other substrates containing an N-H bond were investigated, and it was found that arylhydrazines react with NO in the presence of O_2 to afford benzene derivatives. This paper describes these results.

It was reported that phenylhydrazine was converted to phenylazide by *N*-nitrosation reaction, and various kinds of *N*-nitrosation reagents have been used for this reaction involving nitrous acid,[7] clay-supported ferric nitrate,[8] dinitrogen tetroxide,[9] and nitrosonium tetrafluoroborate.[10] The dehydrazination reaction, however, has never been reported under such *N*-nitrosation conditions.[11] When arylhydrazines **1** reacted with NO in THF solvent in the presence of oxygen, benzene derivatives **2** were obtained accompanied by small amounts of arylazides **3** (Scheme 1 and Table 1).



Scheme 1

In a typical experiment, 0.2 mmol of a substrate **1** was placed in a two-necked flask equipped with a septum rubber and three-way stopcock, one way of which was attached to an Ar balloon, and another joined to a pump. The flask was degassed under vacuo and filled with Ar gas. These operations were repeated five times. Freshly distilled THF (10 ml) was added and the solution was bubbled with dry Ar gas for 20 min, then the flask was sealed. NO gas was passed through a column of soda lime and measured at 22.4 ml using a Hamilton gas-tight syringe, then added to the reaction vessel. Then 4.5 ml of oxygen gas was added and the reaction mixture was allowed to react for 3 h at room temperature. Then Ar was bubbled for degassing of excess NO and O_2, and the product analysis was performed using HPLC or NMR.

Table 1 Reaction of Arylhydrazines **1** with NO in the Presence of O_2[a)]

Entry	Substrate	R	Yield of **2** (%)	Yield of **3** (%)	Ratio **2/3**
1	**1a**	NO_2	61 (60)	25 (18)	2.44 (3.33)
2	**1b**	Cl	77 (73)	13 (11)	5.92 (6.64)
3	**1c**	H	76 (79)	20 (20)	3.80 (3.95)
4	**1d**	Me	82 (76)	10 (14)	8.20 (5.43)
5	**1e**	OMe	72 (69)	8 (12)	9.00 (5.75)

a) The reaction was carried out in 5 eq. of NO and 1 eq. of O_2. The results in the parentheses are obtained in the presence of 4 eq. of NO and 0.5 eq. of O_2.

There seems to be a slight tendency for electron-withdrawing substituents to afford lower selectivity. In the presence of 4 eq. of NO and 0.5 eq. of O_2, the selectivity was improved in these substrates (entries 1 and 2, data shown in parentheses). Considerable solvent effects were observed in the reaction, whose results are shown in Table 2. The data indicate that THF is the best solvent for the formation of **2**, and other ethereal solvents afford moderate yields. These results are in accord with the previous data of the deamination reaction[6] except in the case of chloroform.[12]

Table 2 Solvent Effect on the Reaction of Phenylhydrazine **1c** with NO + O_2[a)]

Solvent	THF	DME	$CHCl_3$	CH_3CN	1,4-Dioxane	CH_2Cl_2	CCl_4
Yield of **2c** (%)	76	53	52	12	47	16	11[b)]
Yield of **3c** (%)	20	21	40	33	23	48	39

a) The reaction was carried out using phenylhydrazine **1c** as a substrate with 5 eq. of NO and 1 eq. of O_2 for 3 h.
b) Chlorobenzene was obtained instead of benzene.

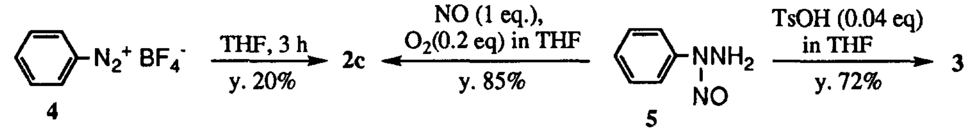
Next, the relationship among the amounts of NO, O_2 and the reaction yields was investigated using **1c** as a substrate. As shown in entries 1-4 in Table 3, 0.5 eq. of O_2 was necessary for the completion of the reaction. The results indicated that the ultimate reactive species is not NO but other nitrogen oxides such as N_2O_3. A further increase of the O_2 amount gradually reduced the yield of **2** (entries 5 and 6). These facts suggest highly oxygenated nitrogen oxide, probably NO_2, has low selectivity in the reaction. The use of NO_2 itself shows low selectivity as expected (entry 7), though the yield of **2** was lower than those of entries 5 and

6. These findings indicate that the formation of NO_2 is incomplete in the mixture of NO and $1/2O_2$. With these results in hand, the amount of NO was varied in the presence of 0.5 eq. of O_2 (entries 8-11). The consumption of the starting material was achieved when 3 eq. of NO was applied (entry 10), but the yield of **2** was higher in the case that more than 4 eq. of NO was used (entries 11, 3).

Table 3 Effect of the Amounts of NO and O_2 on the Reaction of Phenylhydrazine **1c** with NO

Entry	Amount of NO	Amount of O_2	React. Time	Yield of **2** (%)	Yield of **3** (%)	Ratio **2**/**3**
1	5.0 eq.	0	3 h	0	0	-
2	5.0 eq.	0.2 eq.	3 h	20	12	1.67
3	5.0 eq.	0.5 eq.	3 h	75	19	3.95
4	5.0 eq.	1.0 eq.	3 h	76	20	3.80
5	5.0 eq.	2.0 eq.	3 h	52	25	2.08
6	5.0 eq.	3.0 eq.	3 h	55	24	2.29
7	NO_2 (5 eq.)		3 h	35	25	1.40
8	1.0 eq.	0.5 eq.	24 h	24	12	2.00
9	2.0 eq.	0.5 eq.	24 h	31	38	0.82
10	3.0 eq.	0.5 eq.	7 h	74	25	2.96
11	4.0 eq.	0.5 eq.	7 h	79	20	3.95

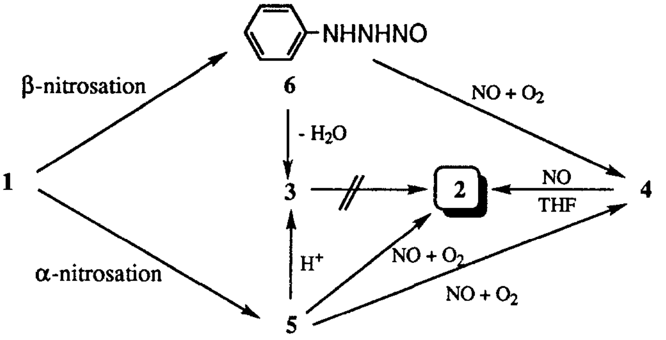
The reaction mechanism was investigated using plausible intermediates in the reaction. It was confirmed that phenylazide **3** was stable under the reaction conditions. Since phenyldiazonium salt **4** was found to be partly dediazoniated to benzene when dissolved in THF,[13] it was assumed the solvent functions as a reductant of **4**. Moreover, α-nitrosophenylhydrazine **5**, which was synthesized according to the reported method,[14] reacted with equimolar NO and 0.2 eq. of O_2 to give **2** in 85% yield. On the other hand, compound **5** afforded azide **3** in the presence of a trace amount of TsOH in THF (Scheme 2).



Scheme 2

Based on these results, the presumed pathways are summarized in Scheme 3. The reaction was assumed to be initiated by α- or β-*N*-nitrosation. β-Nitrosation afforded an intermediate **6** which was reported to lead to phenyldiazonium salt **4** or phenyl azide **3**,[7] whose distribution was probably determined by the nature of the substituent. When there is an electron-withdrawing group on the aryl ring, β-nitrosation might be dominant due to the lowered basicity of α-NH, and the production of **6** brings about the possible formation of **3**. This might be a reason for the relatively lower selectivity in the cases of electron-withdrawing groups (Table 1). Electron-donating substituents render the α-nitrosation advantageous to give **5**. Although **5** was reported to rapidly rearrange to azide **3** in acidic conditions,[14] it was degraded under our conditions to give **2** in good yields, probably through the intermediate **4**. In acidic aqueous nitrosation reaction, the β-amino group was protonated and the nitrosation might ocurr mainly at α-N to give **5**, and the acidic medium should rapidly transform the compound **5** to **3**. Thus, it is inevitable that conventional nitrosation of arylhydrazines afforded only arylazides.

In this paper, we described a new dehydrazination reaction using NO and O_2 in THF solvent. It was revealed that NO in the presence of small amounts of O_2 acts as a mild nitrosating agent in non-acidic medium. The reaction system is thought to be of synthetic use because the reaction and the work-up procedure are quite operationally simple. Elucidation of the detailed reaction mechanism and its application to other compounds are now in progress.



Scheme 3

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12. In the reaction, the solvent acted as a hydrogen donor to a phenyl radical, a presumed intermediate. In the present case, a trace amount of acidic inpurities of $CHCl_3$ might affect the product distributions.
13. When phenyldiazonium tetrafluoroborate was suspended in THF for 3 h, benzene was obtained in 20% yield. The low yield might be due to the effect of a counter cation.
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