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Reductive Deamination of Aromatic Amines with Nitric Oxide (NO) [1]

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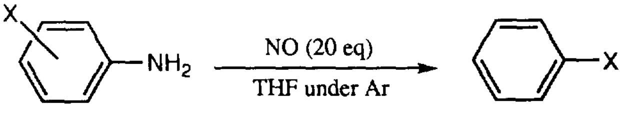
Abstract: Aromatic amines were treated with nitric oxide in tetrahydrofuran or chloroform under argon atmosphere to afford deaminated aromatic compounds in good yields. The reaction is suggested to proceed *via* aryl radicals, which are supposed to be formed by reduction of aryldiazonium salts with NO. Copyright © 1996 Elsevier Science Ltd

Nitric oxide (NO) is a gaseous radical molecule synthesized in the body, and has been revealed to play a variety of roles in biological functions.[2] Blood pressure regulation,[3] inhibition of platelet aggregation,[4] and neurotransmission[5] are among the important biological functions of NO, and extensive research has been carried out from the viewpoints of biochemistry and physiology.

In the area of chemistry, studies of the reactivity of NO were begun only a few years ago, and several results were published recently. Three types of reactions of NO in the absence of dioxygen were reported, that is, the formation of phenoxyl radical from phenol derivatives,[6] the oxidation of Hantzsch dihydropyridines,[7] and the nitration of olefins.[8] The latter report also showed that solvent effects are of primary importance in the reaction.[8] Under aerobic conditions, NO reacts rapidly to give NO_2, and NO_2 thus formed was subjected to the reaction with electron rich organic compounds. It was reported that catecholamines were nitrated with nitric oxide in the presence of O_2,[9] and that tocopherol was oxidized to form a complex mixture of products, one of which was identified as a novel ring contraction product.[10] Recently, Nagano *et al.* reported that aromatic primary amines reacted with NO + O_2 in benzene to give triazene derivatives.[11] In the course of our study of the reaction of NO with amines,[7] we investigated the effects of solvents on the reactivity of NO in the absence of O_2, and found a new reaction of NO where it reacts readily with aromatic amines in ethereal solvents or chloroform to give deaminated products. This paper describes these results.



Scheme 1

p-Methylthioaniline was allowed to react with excess NO gas in tetrahydrofuran for 2 h to give thioanisole in 84% yield. The reaction proceeded via a transient precipitate formation. In a typical procedure, the substrate (0.2 mmol) was dissolved in THF (10 ml) and argon gas was bubbled through the gas inlet tube for 30 min in order to exclude oxygen. Then 90 ml of NO gas was added to the reaction vessel at room temperature, and the mixture was allowed to stand for 2 h under Ar. Then, argon was bubbled again to remove excess NO in the absence of oxygen, and the solvent was evaporated off to leave a residue, which was chromatographed on silica gel to give the product. The results are shown in Scheme 1 and Table 1. The reaction proceeded in moderate to high yields except for anilines which have an electron-donating group at the *meta* position.[12]

Table 1 Deamination of Aromatic Amines with NO in THF under Ar atmosphere

Substituent X	H	NO_2			Cl			OMe			SMe		
		o-	*m*-	*p*-	*o*-	*m*-	*p*-	*o*-	*m*-	*p*-	*o*-	*m*-	*p*-
Yield(%)	85[a)]	85	79	85	92[a)]	86[a)]	88[a)]	55	trace	64	75	16	84

a) Determined by HPLC analysis. Other yields were obtained from the NMR data.

The effect of the solvent was examined for deamination of *p*-methylthioaniline **1a**, and the results are summarized in Scheme 2 and Table 2. Ethereal solvents and chloroform were shown to afford good yields, although the reaction rates varied significantly. Solvents such as 1,2-dichloroethane (DCE),[8] benzene,[11] or acetonitrile,[7] which were reported as suitable for NO reactions, were revealed to be less effective in the deamination. When DCE was used, methyl phenyl sulfoxide was obtained as a side product, which was formed by the oxidation of methyl phenyl sulfide with NO.[13] In benzene, 4-methylthiobiphenyl was obtained in 33% yield instead of **2a**.

Scheme 2

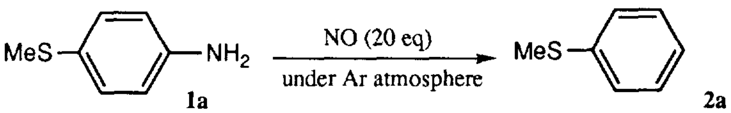
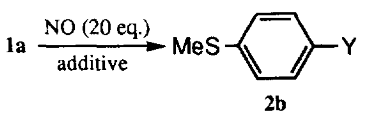


Table 2 Solvent Effects on the Deamination of Methylthioaniline Using NO under Ar

Solvent	THF	$CHCl_3$	1,4-dioxane	EtOEt	DME[a)]	DCE[b)]	benzene	CH_3CN	CH_3OH
Time (h)	2	2	24	24	3	2	2	2	4
Yield(%)	84	79	74	50	80	42[c)]	trace	22	0

a) 1,2-Dimethoxyethane. b) 1,2-Dichloroethane. c) In addition to **2a**, methylphenylsulfoxide was also obtained in 5% yield.

In order to clarify the role of the solvent, reaction of **1a** was performed under various conditions as summarized in Scheme 3 and Table 3. The use of $CDCl_3$ as a solvent decreased the product formation compared to the case with $CHCl_3$, and the product thus formed was *p*-deuteriothioanisole (entry 1). Neither thioanisole nor *p*-chlorothioanisole was formed in the reaction. When carbon tetrachloride was adopted as a solvent, a *p*-chloro derivative was obtained in 43% yield (entry 2). The presence of diphenyl disulfide in benzene afforded a low yield of a phenylthio derivative (entry 3). These results show that a radical source is required to form the deaminated products, and the deuterium isotope effect shown in the experiments with $CHCl_3$ and $CDCl_3$ revealed that hydrogen abstraction from the solvent determined the reaction rate. Therefore, the addition of THF to benzene altered the reaction process with formation of the stated product (Table 3, entry 4).



Scheme 3

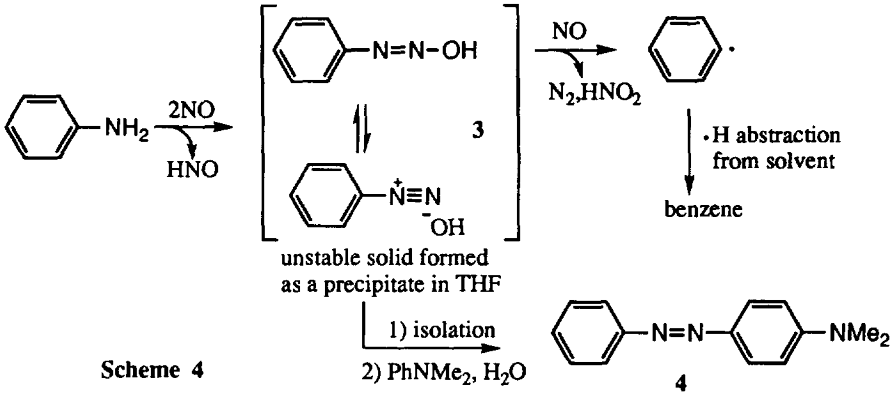
Table 3 The Effect of the Additive on the Formation of **2b**

Entry	Additive	Time (h)	Product (**2b**)	Yield (%)
1	$CDCl_3$ (as a solvent)	27	Y=D	56
2	CCl_4 (as a solvent)	2	Y=Cl	43
3	PhSSPh (2 eq.) in benzene	18	Y=SPh	26
4	THF/benzene(1/4) (as a solvent)	27	Y=H	50

Finally, the relationship between the amounts of NO and the yields of deamination products was investigated. Decrease of the amount of NO necessitated considerable lengthening of the reaction time. That is, *o*-chloroaniline, which is the most susceptible substrate to the reaction, was treated with 3 eq. of NO for 240 h under Ar to give chlorobenzene in 93% yield. While, compound **1a** afforded the product only in 56% yield under the same conditions.[14] Therefore, 3 eq. of NO was supposed to be sufficient for the completion of the reaction, although the reaction rate was too slow for practical use.

Based on these results, the proposed reaction mechanism is shown in Scheme 4. At first, aromatic amine reacts with NO to give a phenyldiazonium salt **3**. In the reaction with THF as a solvent, this compound was formed as a colorless precipitate, which slowly dissolved in the solvent as the reaction advanced to the next step. Some diazonium nitrates were reported to be reduced by NO to form radicals;[15] therefore, the diazonium salt **3** possibly accepts an electron from NO to give the phenyl radical, and the hydrogen abstraction from the solvent gives rise to the deaminated product. The structure of the precipitate was supported by the reported method,[16] that is, its isolation in THF, and the subsequent reaction with *N,N*-dimethylaniline in H_2O afforded dimethylaminoazobenzene **4**.

In this paper, we have described a new type of deamination of aromatic primary amines with NO. A previous report[11] revealed that aniline was transformed to a triazene in benzene under aerobic conditions, thus NO was shown to have different chemical reactivities depending upon its surroundings (in this case, the solvent). These facts might be of interest from a biological viewpoint, because NO is known to have diverse physiological roles in spite of its simple molecular structure. Moreover, its susceptibility to location might enable a selective reaction with NO.[17] Further investigation of the solvent effects and the application to selective chemical reactions is now in progress.



Scheme 4

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1. This paper is dedicated to Professor Masaaki Hirobe on the occasion of his 60th birthday.
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12. PM3 calculations suggest that *m*-methoxy and *m*-methylthiophenyl radicals are more stable as compared to the corresponding *o*- and *p*- isomers, thus the reason for this substituent effect remains unclear.
13. When methyl phenyl sulfide was allowed to react with NO (20 eq.) in DCE under Ar for 15 h, methyl phenyl sulfoxide was obtained in a quantitative yield. Use of other solvents such as THF, DME, and MeOH, resulted in a complete recovery of the substrate.
14. In the case of **1a** as a substrate, relationships between the amount of NO, the reaction time, and the yield are as follows; 84% (NO 20 eq. 2 h); 81% (NO 10 eq. 20 h); 80% (NO 5 eq. 30 h); 70% (NO 4 eq. 67 h); 56% (NO 3 eq. 240 h).
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17. In THF, the nitration reported in ref.8 was slow; therefore, 4,4'-diaminostilbene was deaminated by NO without nitration of the double bond moiety. The detailed results will be reported in the near future.

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