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Reaction of Amides with Nitric Oxide (NO)

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Abstract: Amides were allowed to react with nitric oxide in aprotic and non-ethereal solvents to give the corresponding *N*-nitroso derivatives. The reaction was accelerated by addition of oxygen. The solvent effect revealed that the reaction did not proceed in the presence of protic media.
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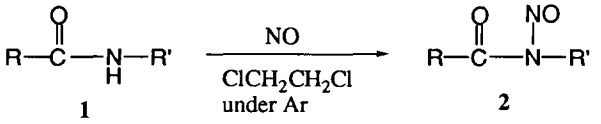
Nitric oxide (NO) is a gaseous radical molecule which has been revealed to play a variety of roles in biological functions.[1] On the other hand, NO is supposed to have cytotoxic effects when it exists in high concentration.[2] Therefore, extensive research has been carried out in the areas of biochemistry and physiology to clarify the mechanisms of both the positive and negative actions of NO.

From the viewpoint of chemistry, papers concerning the reactivity of NO have been gradually increasing.[3] One class of these reports deals with the reaction of NO with biologically important molecules, which involve tocopherol,[4] catecholamine,[5] retinal,[6] β-carotene,[7] unsaturated fatty acid[8] and so on. However, the amide structure, which is an ubiquitous moiety in the biological system, has never been reported as a target of NO reaction. We have been investigating the reaction of NO with organic compounds which contain an N-H bond,[9] and it has been found that amide is nitrosated by NO in aprotic nonethereal solvents. This paper describes these results.

There has been much interest in *N*-nitrosoamides since certain *N*-nitroso compounds are known to be potent carcinogens.[10] Thus, there are many reports[11] concerning the synthesis of *N*-nitrosoamides and *N*-nitrosoureas. Nitrosation by the use of NO, however, has never been reported. In the course of our study on the reactivity of nitric oxide, aromatic primary amines were found to react with NO in the presence of a trace amount of oxygen to give a deaminated product. In this reaction, the addition of 1μl of O_2 in 22.4 ml of NO was revealed to be crucial.[9c] This result also suggests that our reaction system can exclude oxygen at least to the order of 1μl. With these results in hand, we investigated the reaction of NO with amides (Scheme 1).



1 2 **Scheme 1**

In a typical experiment, 0.05 mmol of the substrate **1** in $ClCH_2CH_2Cl$ (2.5 ml) was placed in a two-necked flask (ca. 65 ml) 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 cooled to -78°C to freeze the solvent, and degassed under vacuo and filled with Ar gas. Then the frozen solvent was melted at room temperature,

and refrozen to reiterate the evacuation-Ar purge procedure. The series of operations was repeated three times. NO gas was passed through a column of soda lime and measured at 5.0 ml using a Hamilton gas-tight syringe, then added to the reaction vessel. The reaction mixture was allowed to react with stirring for several hours at room temperature. Then Ar was bubbled to expel excess NO and the product analysis was performed by ^{1}H-NMR using mesitylene as an internal standard. The results in Table 1 show that the substituents R' affect the reaction yields, that is, branched substituents R' retard the reaction considerably (entries 5, 6, 10, 11, and 13).[12]

Table 1 Reaction of Amides with NO in 1,2-Dichloroethane

Entry	Substrate	R	R'	Amount of NO (equiv)	Time (h)	Yield of **2** (%)
1	**1a**	Ph	CH_2Ph	4.0	20	77
2	**1b**	Ph	Me	4.0	20	95
3	**1c**	Ph	Et	4.0	20	80
4	**1d**	Ph	n-Bu	4.0	20	83
5	**1e**	Ph	t-Bu	4.0	20	0
6	**1f**	Ph	$-CH_2-CMe_3$	4.0	20	11
7	**1g**	Me	CH_2Ph	4.0	20	85
8	**1h**	Me	n-Bu	4.0	20	83
9	**1i**	Ph	CH_2CO_2Me	4.0	8	92
10	**1j**	Ph	$CHMeCO_2Me$	4.0	20	10
11	**1k**	Ph	$CH(CH_2Ph)CO_2Me$	4.0	18	19
12	**1l**	Pht-Et[a]	CH_2CO_2Me	20	20	93
13	**1m**	Pht-i-Bu[b]	$CH(CH_2Ph)CO_2Me$	20	22	0

a) 1-phthalimidylethyl. b) 1-phthalimidyl-2-methylpropyl.

Table 2 Solvent Effect on the Reaction of NO with Amide **1a**

Solvent	Yield of **2a** (%)	Solvent	Yield of **2a** (%)
DCE[a]	77	acetone	0
CCl_4	94	THF	0
CH_2Cl_2	88	CH_3OH	0
benzene	62	DMF	0
CH_3CN	49	DCE/H_2O[c]	0
CH_3CN/H_2O[b]	7		

a) 1,2-Dichloroethane is abbreviated as DCE. b) CH_3CH/H_2O=100/1.
c) Dichloroethane/H_2O=1/1.

The solvent effect was investigated using **1a** as a substrate. The yields shown in Table 2 suggest that oxygen-containing solvents are totally ineffective. On the contrary, the use of non-oxygen solvents such as

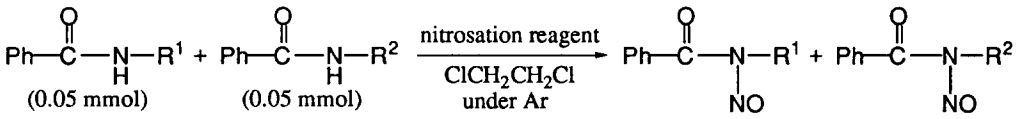
CCl_4 or 1,2-dichloroethane (DCE) resulted in the formation of *N*-nitrosoamides in good yields. When H_2O was added to DCE or CH_3CN, however, the reaction was suppressed drastically. Thus, the selection of solvents has proved to be critical.

Table 3 Effect of O_2 on the reaction of NO with amides **1**

Entry	Substrate	Amount of O_2 (equiv)	Plausible active species (equiv)	Yield of **2** (%)
1	**1b**	0	NO (2.0)	24
2	**1b**	0.02	NO (1.92) + N_2O_3 (0.04)	37
3	**1b**	0.04	NO (1.84) + N_2O_3 (0.08)	53
4	**1b**	0.08	NO (1.68) + N_2O_3 (0.16)	67
5	**1a**	0	NO (2.0)	6
6	**1a**	0.25	NO (1.0) + N_2O_3 (0.5)	58
7	**1a**	0.50	N_2O_3 (1.0)	89
8	**1a**	1.00	NO_2 (2.0)	85
9	**1a**	2.00	NO_2 (2.0) + O_2 (1.0)	58

The reaction was carried out using 0.05 mmol of substrate in the presence of 2 equiv of NO (2.5 ml) and additive O_2 at room temperature in 1,2-dichloroethane (2.5 ml) for 3 h for **1b**, and 1 h for **1a**.

In the reactions using NO as a reagent, there is always a problem that the true active species is unidentified. This is due to the possibility that a trace amount of oxygen or a metal ion can function as a catalyst for the reaction of NO. Thus, the influences of oxygen were investigated for elucidation of the active species of the reaction (Table 3). At first, amide **1b** was allowed to react with 2.0 eq. of NO for 3 h in the absence and the presence of small amounts of O_2, and the results are summarized in entries 1-4 of Table 3. In excess NO, it is known that O_2 can react with NO to give N_2O_3 via NO_2.[13] The addition of O_2 linearly increased the yield of **2b**, and N_2O_3 was estimated to be reused about three times in the reaction for 3 h. Therefore, it is undeniable that the reaction of entry 1 (and the data shown in Table 1 and 2) proceeded by participation of a trace amount of N_2O_3, because N_2O_3 can be catalytic in the reaction.[14] Next, relatively increased amounts of O_2 were applied to the reaction of **1a** (entries 5-9). The yield of **2a** increased with the addition of O_2 until 1.0 equiv. of O_2 was added, but 2 equiv. of O_2 lowered the yield.



Scheme 2

Comparison with other nitrosation reagents was made using NO_2 gas[11a] and nitrosonium tetrafluoroborate,[15] and the results are shown in Scheme 2 and Table 4. NO_2 and NO^+ were found to be more reactive than NO, but the reaction in the presence of two amide compounds revealed that the selectivity of NO was higher than those of other reagents. This high selectivity is interpreted in terms of the lower reactivity of NO to the amide having a large substituent.(Table 4, entries 1 and 4).

Table 4 The Effect of Various Nitrosation Reagents on the Product Ratio of Two Amides

entry	substrate	R^1, R^2	reagent (mmol)	conditions	yield(%)		ratio
					2a	**2b**	**2b/2a**
1			NO (0.1)	rt. 8 h	9	89	9.9
2	**1a + 1b**	R^1=Bn, R^2=Me	NO_2 (0.1)	rt. 20 min.	40	60	1.5
3			$NOBF_4$ (0.05)	rt. 1 h	11	51	4.6
					2a	**2c**	**2c/2a**
4			NO (0.1)	rt. 6 h	17	79	4.6
5	**1a + 1c**	R^1=Bn, R^2=Et	NO_2 (0.1)	rt. 20 min.	42	46	1.1
6			$NOBF_4$ (0.05)	rt. 1 h	22	26	1.2

In this paper, we described the reaction of an amide group with NO in the presence or the absence of oxygen. The reaction proceeded readily in aprotic, non-oxygen solvents, whereas it exhibits no reactivity in protic solvents. These results suggest that nitrosation with NO would occur in the lipophilic site of the biological system. The detailed mechanism of the reaction is now under investigation.

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14. The amounts of oxygen used in the reactions of entries 2 (y. 37%), 3 (y. 53%), and 4 (y. 67%) (Table 3), are 25, 50, and 100 μl, respectively, in the presence of 2.5 ml of NO. In the previous paper,[9c] our reaction system is proved to exclude oxygen at least to the order of 1μl. Thus, we think that the yield of entry 1 (24%) is too high if the reaction of entry 1 (Table 3) could proceed only by participation of 1 μl of O_2, and that NO itself seems to have a weak nitrosation activity. There is a report that showed the reactivity of NO is about 500 times lower than that of NO_2; see, 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*, 2777.
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