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DEAMINATION OF 2-AMINOTHIAZOLES AND 3-AMINO-1,2,4-TRIAZINES WITH NITRIC OXIDE IN THE PRESENCE OF A CATALYTIC AMOUNT OF OXYGEN

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2-Aminothiazoles, 2-aminobenzazoles, and 3-amino-1,2,4-triazines were deaminated using nitric oxide (NO) in the presence of a catalytic amount of oxygen to afford corresponding unsubstituted heterocycles in good yields.

KEYWORDS nitric oxide; deamination; 2-aminothiazole; 3-amino-1,2,4-triazine

Recently, research concerning nitric oxide (NO) has become widespread[1] since NO has been found to have a variety of bioactivities. In the area of chemistry, NO has been known as an air pollutant for many years,[2] but the detailed reactivity of NO remained unclear. Recent discoveries of the diverse bioactivities of NO prompted chemists to investigate its reactivity, and several studies have been published in the past few years.[3] The development of organic syntheses using NO as a specific reagent, however, has seldom been reported.[4]

In the course of our studies on the reactivity of NO, it was shown that aromatic primary amines such as aniline reacted with NO in the presence of a catalytic amount of O_2 to give corresponding deaminated products in moderate to good yields.[5] We thought that the reaction system might be of synthetic use because the work-up procedure is quite simple, and the reactivity can be controlled by the ratio of NO and O_2. Therefore we have been studying applications of the reaction system, and found that 2-aminothiazoles, 2-aminobenzazoles, and 3-amino-1,2,4-triazines were readily deaminated to give corresponding unsubstituted heterocycles in good yields. This paper describes these results.

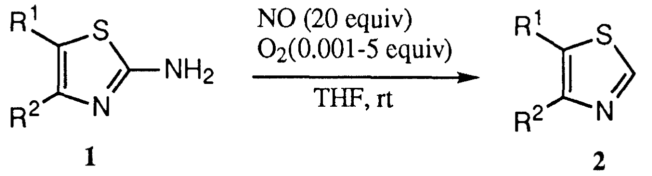

Chart 1

Table 1. Deamination of 2-Aminothiazoles with NO in the Presence of O_2[a)]

Entry	Substrate	R^1	R^2	Amount of O_2 (equiv)	Reaction time (h)	Yield of **2** (%)
1	**1a**	H	H	0.1	8	87
2	**1b**	Me	H	0.1	2	86
3	**1c**	Me	Me	0.01	2	84
4	**1d**	H	Ph	1.0	8	40
5	**1e**	NO_2	H	0.5	8	54
6	**1f**	Benzo		0.1	2	92
7	**1g**	6-Methoxybenzo		0.1	3	86
8	**1h**	6-Methylbenzo		0.1	2	95
9	**1i**	6-Chlorobenzo		0.1	1	88
10	**1j**	6-Nitrobenzo		1.0	6	83

a) All reactions were carried out using 20 equiv of NO gas.

2-Aminothiazole **1a** was allowed to react with 20 equiv of NO in the presence of 0.1 equiv of O_2 in tetrahydrofuran (THF) for 8 h to afford thiazole **2a** in 87% yield (Chart 1).[6] Other 2-aminothiazoles were also subjected to the reaction, and the results are summarized in entries 1-5 of Table 1. THF is used not only as a solvent but also as a hydrogen donor.[5] Thiazole itself can be obtained by condensing chloroacetaldehyde and thioformamide.[7] The reaction is explosive and proceeds

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in low yield because of the instability of the thioformamide under acidic conditions. On the contrary, of all the methods described for the formation of thiazole rings, the most efficient involves formation of 2-aminothiazoles.[8] Therefore an alternative method for thiazole synthesis comprises deamination of **1a** with nitrous acid and hypophosphorus acid (13%),[9] and with amyl nitrite in THF (16%),[10] but the reaction yields and reproducibilities are quite low.[9] Thus we think that our reaction system is superior to the previous methods for the preparation of the parent thiazole.

Table 2. The Reaction Yields of **2a** and **2f** in the Presence of Various Amounts of NO and O_2

Entry	Substrate	Amount of NO (equiv)	Amount of O_2 (equiv)	Reaction time (h)	Yield of **2a** or **2f** (%)
1	**1a**	20	0	8	0
2	**1a**	20	0.001	8	62
3	**1a**	20	0.1	8	87
4	**1a**	20	0.1	2	80
5	**1a**	5	0.1	5	78
6	**1a**	5	0.5	5	83
7	**1a**	5	1.0	5	70
8	**1a**	5	2.5	5	54
9	**1a**	5	5.0	5	53
10	**1f**	20	0.001	5	92
11	**1f**	20	0.1	2	92
12	**1f**	5	1.0	1	86
13	**1f**	5	2.5	1	83
14	**1f**	5	5.0	1	67
15	**1f**	3	1.0	24	69

The same reaction was applied to 2-aminobenzothiazoles **1f**-**1j**, for which the results are shown in entries 6-10 of Table 1.[11] An electron-deficient substrate **1j** required an increased amount of O_2 for the completion of the reaction. The conventional method for the synthesis of benzothiazoles[12] uses the deamination of 2-aminobenzothiazoles with HNO_2/H_3PO_2 in 41-56% yields.[13] In our reaction, the yields are improved, and the work-up procedure is quite simple.[14]

Since the above results indicate the catalytic activity of O_2 on the reaction, the reaction conditions were investigated using various amounts of NO and O_2. Table 2 shows the results. In the absence of oxygen, the product was not obtained.[15] Although the decrease in the NO amount necessitated an increase in additive O_2, further addition of O_2 gradually decreased the yields instead. These facts indicate that the real reaction species is higher oxidized N_2O_3 or NO_2,[16] and that it might react with the substrate in a catalytic manner in the presence of excess NO.

Other heteroaromatics were investigated in the above reaction, and 3-amino-1,2,4-triazine **3** was also found to be a suitable substrate for the reaction. The reaction of **3a** with NO (20 equiv) and O_2 (0.3 equiv) gave parent 1,2,4-triazine **4a** in 60% yield. 6-Phenyl, 5-phenyl, and 5,6-diphenyl derivatives (**3b**, **3c**, and **3d**) also afforded corresponding deaminated triazines, although the reaction with the 5,6-dimethyl derivative **3e** brought about decomposition, probably due to reaction of the activated methyl group with NO (Chart 2 and Table 3). The previous reports[17] concerning the synthesis of **4a** showed that overall yields were 16% to 30% from readily accessible starting materials.[18] In our reaction, **4a** was obtained in one step from commercially available **3a**,[19] and therefore our reaction system is of synthetic use for monocyclic 1,2,4-triazines.

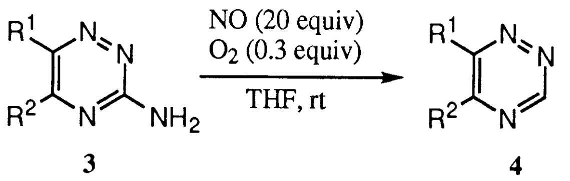

Chart 2

Table 3. Deamination of 3-Amino-1,2,4-triazines with NO in the Presence of O_2[a)]

Entry	Substrate	R^1	R^2	Reaction time (h)	Yield of **4** (%)
1	**3a**	H	H	4	60
2	**3b**	Ph	H	6	83
3	**3c**	H	Ph	5	70
4	**3d**	Ph	Ph	4	65
5	**3e**	Me	Me	5	0

a) All reactions were carried out using 20 equiv of NO gas in the presence of 0.3 equiv of O_2.

In this paper, we report the new deamination reaction of 2-aminothiazoles and 3-amino-1,2,4-triazines using NO in the presence of O_2 in THF solvent. By applying this method, monocyclic thiazoles and 1,2,4-triazines were synthesized in improved yields, and the deamination yields of 2-aminobenzothiazoles were considerably improved. The results suggest that deamination with NO is milder and more selective than the conventional methods, and that NO is a promising reagent for mild nitrosation in the presence of a controlled amount of oxygen. The mechanism and the application of the above reaction are now under investigation.

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6) In a typical procedure, the substrate (50 μmol) was dissolved in THF (3 ml) and Ar gas was bubbled through a gas inlet tube for 30 min. Then 22.4 ml of NO and 112 μl of O_2 were added to the reaction vessel at room temperature, and the mixture was allowed to react for 8 h.

7) Metzger J.V., "Comprehensive Heterocyclic Chemistry," ed. by Katritzky A. R., Rees C. W., Pergamon Press, Oxford, 1984, Vol. 6, pp 235-331, and references cited therein.

8) The reaction involves condensation of equimolar quantities of thiourea and α-halo ketones or aldehydes; see King L., Hlavacek R., *J. Am. Chem. Soc.*, **72**, 5221-5225 (1950), and references cited therein.

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11) 2-Amino-1-methylbenzimidazole and 2-amino-5-chlorobenzoxazole were treated under the same conditions to afford the corresponding deaminated products in 96% and 45% yields, respectively.

12) The most general method for the synthesis of benzothiazoles is the deamination of corresponding 2-amino derivatives **1**, because compounds **1** are readily prepared.

13) Chedekel M. R., Sharp D. E., Jeffery G. A., *Synth. Commun.*, **10**, 167-173 (1980).

14) Only the solvent evaporation afforded almost pure benzothiazoles.

15) Partial consumption of the starting material was observed even in the absence of O_2. This may be due to the formation of amine-NO complex; see *a)* Drago R. S., Paulik F. E., *J. Am. Chem. Soc.*, **82**, 96-98 (1960). *b)* Drago R. S., Karstetter B. R., *J. Am. Chem. Soc.*, **83**, 1819-1822 (1961).

16) It is well known that NO reacts rapidly with O_2 to give NO_2, and that NO_2 thus formed is transformed in the presence of excess NO to bring about the formation of N_2O_3; see von Graetzel M., Taniguchi S., Henglein A., *Ber. Bunsenges. Phys. Chem.*, **74**, 488-492 (1970).

17) *a)* Paudler W. W., Barton J. M., *J. Org. Chem.*, **31**, 1720-1722 (1966). *b)* Neunhoeffer H., Hennig H., *Chem. Ber.*, **101**, 3952-3956 (1968). *c)* Paudler W. W., Chen T.-K., *J. Heterocycl. Chem.*, **7**, 767-771 (1970). *d)* Krass D., Paudler W. W., *Synthesis*, **1974**, 351-352.

18) Deamination of 3-amino-1,2,4-triazines by other methods has never been reported.

19) It was reported that commercially available **3a** was synthesized in 60% yield from glyoxal and aminoguanidine; see Erickson J. G., *J. Am. Chem. Soc.*, **74**, 4706 (1952).

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