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The Aromatization of Hantzsch Dihydropyridines with Nitric Oxide (NO)

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Abstract: Hantzsch dihydropyridines were readily oxidized by nitric oxide to give corresponding pyridines in quantitative yields. This reaction system required no work-up procedure. In the presence of oxygen, it was possible to reduce nitric oxide to less than an euimolar amount. This is the first reaction of nitric oxide itself that is practical for synthetic use.

In recent years, nitric oxide (NO) has been attracting much attention since it was revealed in 1987 that NO acted as the endothelium-derived relaxing factor.¹ Many researches exhibited that NO has a variety of biological activities² including inhibition of platelet aggregation,³ the relaxation of smooth muscle,⁴ neurotransmission,⁵ and so on.

From chemical viewpoints, NO has been known as an air pollutant along with NO₂ for over thirty years, but few data are available concerning its reactivity. Recently, the reaction of NO with superoxide was reported by some groups,⁶ because peroxynitrite⁷ thus formed may also be a significant cytotoxin.⁸ An application of NO to organic chemistry was performed recently by Ducrocq *et al.*⁹ that catecholamines were nitrated with nitric oxide under an aerobic condition.

In the course of our study of the reaction of heterocycles with superoxide,¹⁰ we were interested in the reactivity of NO, which is an endogeneous radical species as same as superoxide. We have investigated the oxidation potential of NO using dihydroazaaromatics, and it was revealed that Hantzsch 1,4-dihydropyridines¹¹ were oxidized by NO to give corresponding pyridines in quantitative yields. This paper describes these results.

The oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous problems in organic chemistry, and even in recent years several groups have reported the new methods for aromatization including oxidation with ferric or cupric nitrates on a solid support,¹² oxidation with ceric ammonium nitrate,¹³ ultrasound-promoted oxidation by clay-supported cupric nitrate,¹⁴ and oxidation with pyridinium chlorochromate.¹⁵ Moreover, there has been a general method using nitric acid,¹⁶ though all these procedures require the work-up processes. Our reaction system is quite simple and easy to be done because the oxidant is supplied as a gas.

In the typical experiment, Hantzsch dihydropyridine 1a (0.2 mmol) was dissolved in benzene (10 ml), and the reaction atmosphere was displaced with argon. Then 10 ml (ca. 2eq.) of NO was introduced to the reaction system with a syringe, and the mixture was allowed to stir for 8 h at room temperature under argon. Thereafter, the solvent was evaporated to give a pure aromatized pyridine 2a in 98% yield. The results are summarized in Scheme 1 and Table I. Substrates 1g and 1h have poor solubilities in benzene, thus acetonitrile was used in these cases (Table I, entries 7 and 8).



 Table I Aromatization of Hantzsch Dihydropyridines1 with Nitric Oxide under Argon Atmosphere

Entry	Substrate	R ¹	R ²	Amount of NO (eq.)	Conditions	Yield of 2 (%)
1	1a	CO ₂ Et	Н	2.0	benzene, rt., 8h	98
2	1b	CO ₂ Et	Me	13.0	benzene, rt., 4h	91
3	1c	CO ₂ Et	Et	13.0	benzene, rt., 4h	98
4	1d	CO ₂ Et	Pr	13.0	benzene, rt., 4h	99
5	le	CO ₂ Et	3-CH ^{a)}	13.0	benzene, rt., 4h	75 (25) ^{b)}
6	1f	CO ₂ Et	Ph	4.0	benzene, rt., 6h	95
7	1g	CN	i-Pr	3.0	CH ₃ CN, rt.,12h	98
8	1h	CN	3-CH ^{a)}	16.0	CH ₃ CN, rt., 4h	92

a) 3-Cyclohexenyl is abbreviated as 3-CH.

b) In the case of 1e, 2a was obtained in 25% yield other than 2e (75%).

In the case of 1a as a substrate, the reaction was completed in 8h even by the use of 2 eq. of NO. The other substrates required excess amount of NO to complete the reaction in reasonable time. The reaction system was extremely clean, and only evaporation of the solvent was necessary for the isolation of the products except for 1e (entry 5). Substrate 1e afforded a mixture of 4-(3-cyclohexenyl)pyridine 2e (75%) and 4-H-pyridine 2a (25%), which could be separated by silica gel chromatography.

Next, the reaction was carried out in the presence of oxygen,¹⁷ and the results were summarized in Scheme 2 and Table II. In these cases, less than equimolar amount of NO were required for the consumption of the starting material in 10 min. Moreover, there is one noticeable difference between the results of Table I

and II, that is, substrate le afforded 2a as a sole product under oxygen atmosphere (Table II, entry 5), which was different from the result in the absence of oxygen (Table I, entry 5). These facts suggest that the active species of both reactions have different reactivities, though the plausible reaction mechanisms remained unclear.

$$1 \xrightarrow{\text{NO} + \text{ excess O}_2} 2 \text{ Scheme } 2$$

Entry	Substrate	Amount of NO (eq.)	Conditions	Yield of 2 (%)
1	1a	0.2		98
2	1b	0.6	h	84
3	1c	0.7	benzene rt. under O ₂ 10 min	89
4	1d	0.6		97
5	1e	0.5		(97) ^{a)}
6	1f	0.7		95
7	1g	0.7	CH ₃ CN	96
8	1h	0.9	10 min	96

Table II Aromatization of 1 with Nitric Oxide under Oxygen Atmosphere

a) In the case of 1e, 2a was obtained as a sole product.

In this paper, we described the aromatization of Hantzsch 1,4-dihydropyridines with NO both in the absence and presence of oxygen. Under anaerobic condition, NO was reported to react with phenolic antioxidants and phenoxyl radical thus formed.¹⁸ The reaction was supposed to proceed via hydrogen abstraction with NO from phenolic hydrogen or the initial electron transfer from the antioxidant to NO, and this is the only example that revealed the oxidizing ability of NO. Thus the results shown in Table I might be novel examles for exploring the chemical reactivity of NO. In the presence of oxygen, NO is known to be oxidized to NO₂,¹⁹ and NO₂ was reported by Kochi *et al.* as a good oxidant for hydroquinone²⁰ and oximes²¹ in the presence of oxygen. They suggested the presence of NO in the reaction medium, and that NO was reoxidized to NO₂ in the reaction course. Thus it is probable that the active species responsible for the results shown in Table II is NO₂.²² These two systems gave slightly different results, but are both quite effective synthetic methods because there are no needs for the separation of oxidant. The reaction mechanism and the application of the above methods are now under investigation.

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