Remarkable effect of nitrogen dioxide for N-hydroxyphthalimide-catalyzed aerobic oxidation of methylquinolines

Satoshi Sakaguchi, Akihiro Shibamoto and Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan. E-mail: ishii@ipcku.kansai-u.ac.jp
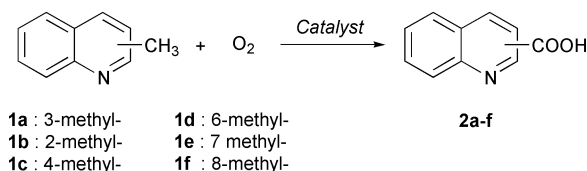
Aerobic oxidation of methylquinolines was successfully achieved by the use of N-hydroxyphthalimide/Co(OAc)$_2$/Mn(OAc)$_2$ as catalyst in the presence of a small amount of nitrogen dioxide as an initiator.

Quinolines and their derivatives are common in natural products, and have attractive applications as pharmaceuticals and agrochemicals.[1] For example, 3-quinolinecarboxylic acid derivatives are reported to be potent inhibitors of bacterial DNA gyrase.[2] So far, there are only limited number of methods for the preparation of quinolinecarboxylic acids despite their potential importance.[2] The synthesis of quinolinecarboxylic acids from the corresponding methylquinolines by direct oxidation seems to be the simplest method, but the reaction is difficult to carry out selectively because of low reactivity of the methyl group bearing the quinoline ring. Classically, the oxidation was conducted using a stoichiometric amount of a metal oxidant like KMnO$_4$,[3] CrO$_3$[3] or nickel peroxide,[4] or by Pd-catalyzed oxidation with H$_2$O$_2$.[5]

From economical and environmental points of view, catalytic aerobic oxidation is highly desirable, in particular, in industrial chemistry, but only limited work has been reported on the oxidation of methylquinolines with O$_2$.[6] In this paper, we wish to report a successful catalytic aerobic oxidation of methyl-quinolines (Scheme 1).

1a : 3-methyl-　**1d** : 6-methyl-
1b : 2-methyl-　**1e** : 7 methyl-
1c : 4-methyl-　**1f** : 8-methyl-

2a-f

Scheme 1

Previously, we reported the aerobic oxidation of methylpyr-idines such as 3-methylpyridine (**3**) by the use of N-hydroxy-phthalimide (NHPI) combined with Co(OAc)$_2$ and Mn(OAc)$_2$ as catalyst to produce pyridinecarboxylic acids (Scheme 2).[7]

In a similar method as used for **3**, 3-methylquinoline (**1a**) was introduced into the NHPI–Co–Mn system. However, no oxidation took place, and **1a** was recovered unchanged (Scheme 2). It was found that the color of the AcOH solution of NHPI–Co–Mn changed from pink, based on Co(II), to light purple on addition of **1a**. A similar color change was observed when **1a** was added to an AcOH solution of Co(OAc)$_2$, but the addition of **3** to this solution led to almost no color change. These observations may suggest that the activation of O$_2$ by Co(II) becomes difficult on addition of **1a** to the AcOH solution of
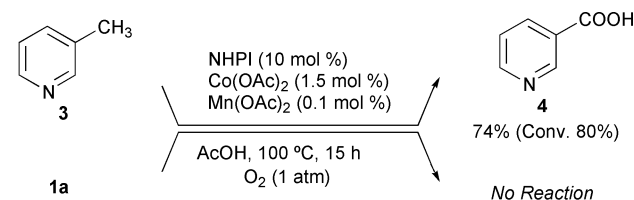
Co(II), probably because of complexation of Co(OAc)$_2$ with **1a**.

In previous work, we have shown that the NHPI-catalyzed oxidation of alkanes proceeds through the formation of phthalimide N-oxyl (PINO) as an active catalytic species, generated *in situ* from NHPI by the action of Co(III)–dioxygen complexes derived from Co(II) and O$_2$.[8] Therefore, we believe that the failure of the oxidation of **1a** is due to the difficulty of the formation of PINO from NHPI owing to the complexation of Co(OAc)$_2$ with **1a**. Recently, we reported the NHPI-catalyzed nitration of alkanes with NO$_2$, in which the generation of PINO from NHPI was easily achieved by NO$_2$ without any transition metal.[9] Hence, if the formation of PINO from NHPI were assisted by the addition of a small amount of NO$_2$ in the oxidation of **1a**, the oxidation would be expected to proceed smoothly. Thus, the NHPI-catalyzed oxidation of **1a** in the presence of NO$_2$ was attempted (Table 1).

It is pleasing that the oxidation of **1a** with O$_2$ (1 atm) catalyzed by NHPI (20 mol%), Co(OAc)$_2$ (2 mol%) and Mn(OAc)$_2$ (0.1 mol%) in the presence of NO$_2$ (10 mol%) gave 3-quinolinecarboxylic acid (**2a**) in 75% yield along with small amounts of several unidentified products at 90% conversion (Run 1).† This is the first successful catalytic oxidation of **1a** to **2a** under normal pressure of dioxygen. It is very important to reduce the NHPI employed from the practical synthetic viewpoint. The catalytic potential of several NHPI analogues was compared with that of the NHPI. N,N'-Dihydroxypyro-mellitic diimide (DHPI) and N-acetoxyphthalimide (NAPI)[10] were found to be good catalysts (Runs 3 and 4).

The use of *conc.* HNO$_3$, which can also facilitate the formation of PINO from NHPI,[11] led to **2a** in good yields (Runs 5 and 6). Since the use of air instead of pure oxygen is also important from the industrial viewpoint, the oxidation of **1a** with air was performed. The oxidation of **1a** under 20 atm of air at 120 °C was completed within 5 h even in the absence of NO$_2$, forming **2a** in 76% yield (Run 7). When DHPI combined with NO$_2$ was employed as the catalyst, the amount of the catalyst could be reduced to 5 mol% (Run 8).

NHPI (10 mol %)
Co(OAc)$_2$ (1.5 mol %)
Mn(OAc)$_2$ (0.1 mol %)

AcOH, 100 °C, 15 h
O$_2$ (1 atm)

74% (Conv. 80%)

No Reaction

Scheme 2

Table 1 Oxidation of **1a** to **2a** with O$_2$ (1 atm) catalyzed by the NHPI–Co–Mn system[a]

Run	NHPI derivative (mol%)	Initiator	Conv. (%)	Yield[b] (%)
1	NHPI (20)	NO$_2$	90	75
2	NHPI (10)	NO$_2$	76	63
3	DHPI (5)	NO$_2$	90	80
4	NAPI (10)	NO$_2$	89	72
5	NHPI (10)	HNO$_3$	70	61
6	NAPI (10)	HNO$_3$	81	70
7[c]	NHPI (20)	—	95	76
8[c]	DHPI (5)	NO$_2$	78	68

[a] **1a** (1 mmol) was allowed to react with 1 atm of O$_2$ in the presence of NHPI derivative, Co(OAc)$_2$ (2 mol%), Mn(OAc)$_2$ (0.1 mol%) and initiator (10 mol%) in AcOH (5 mL) at 110 °C for 15 h. [b] Based on **1a** used. [c] **1a** (2 mmol) was allowed to react with 20 atm of air in the presence of Co(OAc)$_2$ (2 mol%), Mn(OAc)$_2$ (0.1 mol%) in acetic acid (5 mL) at 120 °C for 5 h.
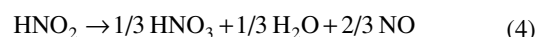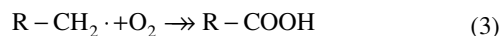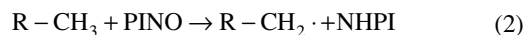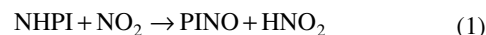
Table 2 Oxidation of several methylquinolines (**1b–f**) with dioxygen[a]

Run	Substrate	Catalyst[b]	Method[c]	Conv. (%)[d]	Product	Yield (%)[d]
1	**1b**	**A**	**D**	42 (0)	**2b**	32 (0)
2	**1b**	**B**	**D**	70 (0)	**2b**	64 (0)
3	**1c**	**A**	**E**	98 (21)	**2c**	87 (10)
4	**1c**	**C**	**E**	65 (0)	**2c**	61 (0)
5	**1d**	**A**	**E**	89 (67)	**2d**	81 (50)
6	**1e**	**A**	**D**	75 (35)	**2e**	60 (26)
7	**1f**	**A**	**D**	40 (2)	**2f**	35 (< 1)

[a] Substrate (2 mmol) was allowed to react with O_2 in the presence of catalyst in AcOH (5 mL). [b] **A**: NHPI (20 mol%), $Co(OAc)_2$ (2 mol%), $Mn(OAc)_2$ (0.1 mol%), NO_2 (10 mol%); **B**: NHPI (10 mol%) NO_2 (30 mol %); **C**: NHPI (20 mol%) NO_2 (10 mol%). [c] **D**: O_2 (1 atm), 110 °C, 15 h; **E**: Air (20 atm), 150 °C, 5 h. [d] The number in parenthesis shows the conversion or yield in the reaction without NO_2.

Next, the oxidation of 2-methylquinoline (**1b**) was run (Table 2). No reaction took place under 1 atm of O_2 at 110 °C in the absence of NO_2. Although the oxidation of **1a** occurred under 20 atm of air without NO_2, the oxidation of **1b** was difficult under these conditions. However, when 10 mol% of NO_2 was added to the reaction system, the oxidation furnished 2-quinolinecarboxylic acid (**2b**) in 32% yield (Run 1). Surprisingly, the oxidation of **1b** was efficiently promoted by NHPI in the presence of NO_2 without any metal salt. Treatment of **1b** with O_2 (1 atm) under the influence of NHPI and NO_2 in the absence of any metal salt produced **2b** in 64% yield (Run 2). It is important to note that no nitrated products were formed. This finding provides a new aerobic oxidation system of methylquinolines by NHPI without the use of a transition metal catalyst. Other methylquinolines (**1c–f**) used were successfully oxidized by the NHPI–Co–Mn–NO_2 or NHPI–NO_2 systems giving the corresponding carboxylic acids in moderate to good yields.

A plausible reaction pathway for the oxidation by the NHPI–NO_2 system is outlined in Eqns (1)–(5). It is possible to assume that the reaction would be initiated by the hydrogen abstraction from NHPI by NO_2 to form PINO and HNO_2 [Eqn. (1)]. The PINO thus formed abstracts the hydrogen atom from the methyl group of the substrate to produce R-CH_2· (R- = quinolyl-) and NHPI [Eqn. (2)]. The R-CH_2· is readily trapped by O_2 affording a peroxy radical which is eventually converted into the corresponding carboxylic acid [Eqn. (3)]. On the other hand, HNO_2 may be converted into HNO_3, H_2O and NO [Eqn. (4)].[12] The resulting NO was oxidized with O_2 to generate NO_2, which is reused for the formation of PINO from NHPI [Eqn. (5)].

$$NHPI + NO_2 \rightarrow PINO + HNO_2 \tag{1}$$

$$R - CH_3 + PINO \rightarrow R - CH_2 \cdot + NHPI \tag{2}$$

$$R - CH_2 \cdot + O_2 \Rrightarrow R - COOH \tag{3}$$

$$HNO_2 \rightarrow 1/3\ HNO_3 + 1/3\ H_2O + 2/3\ NO \tag{4}$$

$$NO + 1/2\ O_2 \rightarrow NO_2 \tag{5}$$

Notes and references

† *A typical reaction was carried out as follows*: To a solution of NHPI (0.1 mmol) and transition metal salts in AcOH (5 mL) were added **1a** (1 mmol) and NO_2 (0.1 mmol, using a Hamilton gas-tight syringe). The flask was equipped with a balloon filled with O_2 (1 atm). The mixture was stirred at 110 °C for 15 h.

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