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Manganese Dioxide and *N*-Hydroxyphthalimide. An Effective Catalytic System for Oxidation of Nitrotoluenes with Molecular Oxygen

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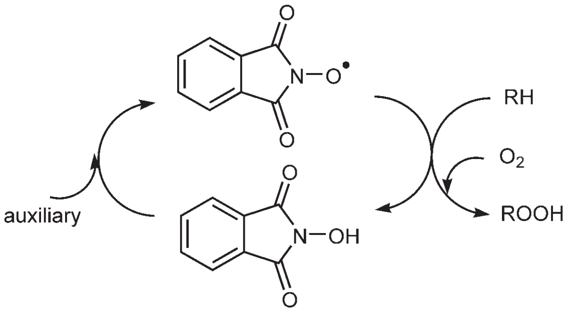
Abstract: The inexpensive manganese dioxide has been proven to be an efficient auxiliary for oxidizing *N*-hydroxyphthalimide (NHPI) to form the phthalimide *N*-oxyl radical *via* reduction and reoxidation. The combination of manganese dioxide and NHPI could catalyze effectively the oxidation of nitrotulenes by molecular oxygen. Thus, the oxidation of *p*-nitrotoluene with molecular oxygen (0.4 MPa) in the presence of manganese dioxide (10 mol %) and NHPI (10 mol %) in acetic acid at 110 °C for 4 h proceeded with 97 % conversion, and gave *p*-nitrotoluene in 89 % isolated yield.

Keywords: aerobic oxidation; catalysis; *N*-hydroxyphthalimide; manganese dioxide; nitrotoluene

The oxyfunctionalization of alkylarenes with molecular oxygen as an ultimate oxidant is a key technology for converting petroleum-based feedstocks to useful primary and special chemicals. The success of these oxygenations always depends largely on the development of catalysts to promote productivity, the rate of reaction, as well as the selectivity of products.[1] Due to its very highly catalytic efficiencies even under mild conditions in the aerobic oxidation of a wide variety of organic substrates, *N*-hydroxyphthalimide (NHPI) is attracting continuous attention.[2] The general consensus for the NHPI-catalysis mechanism is that the one-electron oxidation of NHPI to the phthalimide *N*-oxyl radical (PINO) must take place first.[3] The formed PINO abstracts the hydrogen of a C–H bond in organic substrates to produce carbon-centered radicals, and then propagates the autoxidation. In 1983, Masui et al.[4] had documented that the oxidation of NHPI to PINO occurs on the anode when they employed NHPI as mediator in the electrochemical oxidation of secondary alcohols to ketones. Subsequently, there are many methods reported of NHPI-catalyzed oxygenations, however, PINO generation always relies on the assistance of various auxiliaries (Scheme 1). The reported auxiliaries could include generally two sorts: the cocatalyst and the radical initiator. The transition metal ions,[5] including Co,[2a] Mn,[6] V,[7] Ce,[8] etc., are well-documented cocatalysts. Notably, the combination of NHPI with Co or with Co and Mn together affords an effective catalytic system, known as the Ishii system, for the autooxidation of a broad range of organic substrates. For example, the oxidation of toluene in the presence of NHPI (10 mol %) and $Co(OAc)_2$ (0.5 mol %) in acetic acid afforded benzoic acid with 96 % selectivity in 84 % conversion even at ambient temperature and pressure.[2a,b] Based on the assumption that redox-active organic compounds could oxidize NHPI to PINO, we found that anthraquinones can serve as purely organic cocatalysts for NHPI-catalyzed oxygenations.[9a,b] On the other hand, some radical initiators, such as alkyl hydroperoxide,[10] AIBN,[11] and aldehyde,[12] can also mediate the formation of PINO in the NHPI-based oxidation, although they are consumed during the reactions and are not recoverable.

The investigations revealed that the methyl groups on nitroarenes, due to the strong electron-withdrawing effect of the nitro substituent, are very difficult to



Scheme 1. NHPI-catalyzed aerobic oxidation.

be oxidized with O_2. For example, using the wide-used Amoco MC method (cobalt salt, manganese salt and bromide ion as the catalysts and acetic acid as a solvent), the aerobic oxidation of nitrotoluenes to nitrobenzoic acids was carried out only under high pressure of air and higher reaction temperature (around 175 °C).[13] Despite the fact that the Ishii system displayed more efficiency in this oxidation,[14] affording *p*-nitrobenzoic acid in 78% yield when 10 mol% NHPI, 0.5 mol% $Co(OAc)_2$ and 0.05 mol% $Mn(OAc)_2$ were employed as catalytic system in acetic acid solution at 130 °C, the reaction time still needed as long as 14 h and a pressure as high as 1.0 MPa of air. Under the same conditions, the oxidation of *o*-nitrotoluene gave as little as 3% conversion. An interesting find by Ishii is that the addition of NO_2 (20 mol%) into the oxidation obviously promoted the catalytic efficiency of the Ishii system.[14] Using NO_2, with $Co(OAc)_2$ and $Mn(OAc)_2$ together, the oxidation of *o*-nitrotoluene gave 52% conversion and 46% yield of *o*-nitrobenzoic acid at 150 °C; without NO_2 the reaction gave only 20% conversion and 11% yield. The author suggested that NO_2 would smoothly abstract the hydrogen atom from NHPI to form PINO in the first step, playing a similar role to a radical initiator, and then was reoxidized with dioxygen to accomplish the redox cycle, acting as a cocatalyst. This double function means that when cocatalyst and radical initiator are used together, the NHPI catalysis should be more powerful.

It is known that manganese oxides could be employed as oxidation catalysts based on two transformations: the reduction of Mn species of higher valence to lower ones and the reoxidation of the lower ones to the higher ones by dioxygen.[15,16] Furthermore, a recent study revealed that MnO_2 could stoichiometrically oxidize hydroxylamines to the corresponding nitrones with good to excellent yields even in an ice-cooled solution.[17] These observations inspired us to suggest that MnO_2 could *in situ* oxidize NHPI to PINO, by acting as a radical initiator, and also serve as a cocatalyst for NHPI-catalyzed aerobic oxidation. Hence, it is of interest to suppose that the double function of MnO_2 would enhance the efficiency of NHPI catalysis. Herein, selecting the more inert nitrotoluenes as substrates, we investigate the performance of the inexpensive MnO_2 in combination with NHPI in the aerobic oxidation.

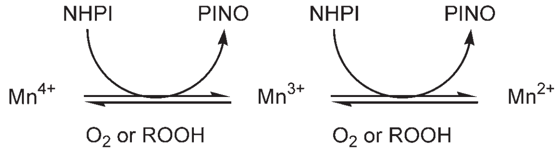
The initial experiment was carried out using *p*-nitrotoluene (8 mmol) as a test substrate with 10 mol% NHPI and 20 mol% MnO_2 in acetic acid (20 mL) under 0.3 MPa of dioxygen at 100 °C for 1 h, affording 58% conversion and 46% isolated yield of *p*-nitrobezoic acid (Table 1, entry 1). In sharp contrast, the reaction could not occur by using MnO_2 alone. And NHPI alone, realizing 37% conversion, was of low efficiency. Prolonging the reaction time to 6 h increased the conversion to 85% and the isolated yield to 77% with MnO_2/NHPI (entry 4). Furthermore, optimization experiments showed that the catalytic system could exhibit much better performance. Using 10 mol% NHPI and 10 mol% MnO_2 at 110 °C under 0.4 MPa for 4 h, the conversion reached 97% and the isolated yield reached 89% (entry 7). Comparably, Co/Mn/NHPI gave 76% conversion and 65% isolated yield at 110 °C under 1.0 MPa of air for 14 h with a same loaded amount of NHPI.[14] To probe further its potential, the new catalyst system was employed to catalyze aerobic oxidations of *o*- and *m*-nitrotoluenes. The oxidation of *m*-nitrotoluene also gave an excellent result, affording 96% conversion and 88% the isolated yield (entry 9). Unfortunately, the conversion of *o*-nitrotoluene reached only 19% (entry 10). *o*-Nitrotoluene is known to be reluctant to oxidation due to the steric hindrance and the strong deactivation of the adjacent bulky NO_2. At 130 °C and 150 °C under 1.0 MPa for 14 h the conversion with Co/Mn/NHPI was as low as 3% and 20%, respectively; An interesting fact was that the conversions could be promoted to 19% at 130 °C and 25% at 150 °C, respectively, by

Table 1. Aerobic oxidation of nitrotoluenes with MnO_2 and NHPI in acetic acid.

Entry	Nitrotoluene	NHPI [mol%]	MnO_2 [mol%]	*T* [°C]	Time [h]	*P* [MPa]	Conversion [%]	Isolated Yield [%]
1	*p*-	10	20	100	1	0.3	58	46
2	*p*-	0	10	100	1	0.3	0	–
3	*p*-	10	0	100	1	0.3	37	–
4	*p*-	10	20	100	6	0.3	85	77
5	*p*-	0	20	100	6	0.3	0	–
6	*p*-	7	10	110	4	0.4	94	87
7	*p*-	10	10	110	4	0.4	97	89
8	*p*-	10	7	110	4	0.4	87	77
9	*m*-	10	10	110	4	0.4	96	88
10	*o*-	10	10	110	4	0.4	19	–
11	*o*-	10	10	150	12	1.0	37	33

the addition of the radical initiator AIBN (1 mol%) into the Co/Mn/NHPI-catalyzed oxidation of *o*-nitrotoluene.[14] Similarly, by promoting the reaction temperature to 150 °C, MnO_2/NHPI realized obvious increases of the conversion to 37% and the isolated yield to 33% in a period of 12 h (entry 11). This contrast showed that the performance of MnO_2 looks like a combined use of cocatalyst and radical initiator in the NHPI-catalyzed oxidation. Hence, it could be concluded that MnO_2/NHPI is an effective system to catalyze the aerobic oxidation of methyl groups on nitroarenes.

Recognizing the successful performance of the first combination of MnO_2 and NHPI, we sought to find the role which MnO_2 played in the oxidation. We noticed that the residual amount of MnO_2 after reaction is obviously less than the loading in the case of using over 10 mol% of MnO_2. On decreasing the loading amount of MnO_2 to 7 mol%, the conversion still was good (entry 8), but black MnO_2 disappeared after reaction, giving a brown solution. Adding a small amount of H_2SO_4 into the solution, the brown color immediately became light yellow. The reduction of MnO_2 by organic compounds, such as ascorbic acid,[18a] fructose,[18b] oxalic acid[18c] etc., has been well studied, revealing that, in these reactions, Mn^{4+} converts finally into Mn^{2+} *via* an intermediate Mn^{3+} following a one-step, one-electron transfer mechanism. It is especially notable that the one-electron oxidation property of ascorbic acid is similar to that of NHPI. The color change and disappearance of MnO_2 in our reaction are quite similar to the above reduction of MnO_2. Therefore, the assumption could be reasonably made that the reaction between MnO_2 and NHPI follows the same route as the reaction between MnO_2 and ascorbic acid, i.e., PINO is formed in the every step of Mn reduction. In order to confirm the reactivity of MnO_2 and NHPI, the reaction of 0.8 mmol MnO_2 (equal to 10 mol% load in reaction) and 1.6 mmol NHPI (equal to 20 mol% load) in 20 mL acetic acid was run at 110 °C. The disappearance of MnO_2 required only 2 h. Under the same conditions no change was observed in the mixture of MnO_2 and acetic acid even after 5 h. These results clearly support our assumption. The role of MnO_2 is similar to that of a radical initiator for NHPI-based catalysis. However, if MnO_2 takes the sole role of radical initiator, in consideration of stoichiometric relation, the load amount of 10 mol% cannot result in as high as 97% conversion. In association with the above reaction phenomena, it could be concluded that Mn species with low valences were reoxidized to ones with higher valences during the course of the oxidation. The oxidants for low-valence Mn species were suggested to be O_2, the intermediate alkyl hydroperoxide, as well as MnO_2[18d]. As a consequence, although all Mn species are not known in detail, the general mechanism of this new catalytic oxidation can be described possibly as in Scheme 2. Both reduction and reoxidation of Mn species take place together to construct the redox cycle in the oxidation. The reduction is less fast than the reoxidation, therefore, MnO_2 could be consumed completely in the case of low load.



Scheme 2. The proposed route of MnO_2-mediated formation of PINO in aerobic oxidation.

In conclusion, we have successfully developed a highly efficient catalytic process for the aerobic oxidation of nitrotoluenes. The oxidation catalyzed by a mixture of MnO_2/NHPI is carried out under comparatively mild conditions in acetic acid. Mechanistically, the concurrence of reduction and reoxidation constructs the redox cycle of Mn species. For inducing PINO formation, MnO_2 plays the double role of the cocatalyst and the radical initiator in the NHPI-catalyzed oxidation. Moreover, the ready availability and low price of MnO_2 makes it feasible for industrial applications. Further studies will focus on the use of this novel catalytic system in the aerobic oxidation of other substrates.

Experimental Section

General Remarks

Gas chromatography measurements were conducted using an Agilent Technologies 6890N Network GC system with a flame ionization detector and a DB-1 capillary column (30 m × 0.535 mm × 3.0 μm). Agilent Chemstation software was used for spectra acquisition and processing. The conversions of substrates were estimated with calibration curves using chlorobenzene as an internal standard. The products were characterized by IR and HPLC in comparison with the authentic sample, respectively. All starting materials and catalysts were purchased from commercial sources and used without further treatment.

General Procedure for the Oxidation

The reaction was carried out in a 150-mL autoclave. Typically, a mixture of *p*-nitrotoluene (8 mmol), NHPI (0.8 mmol), MnO_2 (0.8 mmol), and acetic acid (20 mL) was stirred and heated to 110 °C after the atmosphere over the mixture was replaced with O_2 for three times. The pressure of O_2 was kept under 0.4 MPa for the desired reaction time. After cooling to room temperature, the mixture was diluted with ethanol to a volume of 100 mL, and samples were taken for GC measurement. Then, the ethanol solution was distilled under reduced pressure to dryness. A dilute solution of NaOH was added, the mixture stirred for 30 min, and filtered to remove the insoluble solid. The filtrate was acidified to a pH above 1, and then was filtered to afford *p*-nitrobenzoic acid in 89 % yield.

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