A Novel Catalysis of *N*-Hydroxyphthalimide in the Oxidation of Organic Substrates by Molecular Oxygen

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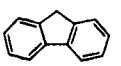
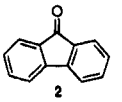
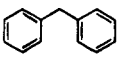
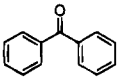
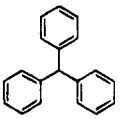
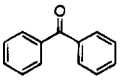
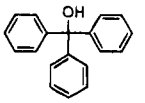
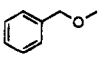
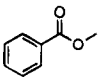
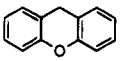
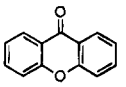
The oxidation of organic substrates is a primary, essential tool in organic synthesis. The utilization of dioxygen in oxidation processes will become increasingly important in the future in response to environmental policies, although several transition metal-catalyzed autoxidations have been applied to industrial processes (e.g., oxidation of cyclohexane, *p*-xylene, and cumene, etc.).[1] The finding of novel, selective oxidation catalysts that utilize molecular oxygen (dioxygen) as the primary oxidant is therefore an endeavor important to both synthetic and industrial chemistry. In recent years, it has been reported that transition metals catalyze the oxidations of organic substrates by the combined use of molecular oxygen and reducing agents such as H_2,[2] $NaBH_4$,[3] and RCHO.[4]

N-Hydroxyphthalimide (NHPI) has been used as an efficient electron carrier for the electrochemical oxidation of alcohols.[5] We now find that NHPI efficiently catalyzes the aerobic oxidation of various organic substrates to oxygen-containing compounds, under nonelectrochemical conditions.

In order to evaluate the features of NHPI catalysis, the oxidation of fluorene (**1**) was examined under various reaction conditions. These results are summarized in Table 1. Treatment of **1** in the presence of a catalytic amount of NHPI (10 mol %) in benzonitrile solution under oxygen (1 atm) at 100 °C for 20 h gave an oxidized product, fluorenone (**2**), in 80% yield (run 1 in Table 1). The yield of **2** was markedly affected by the reaction temperature (run 2), but not by light.[6] The same procedure with **1**, in the absence of NHPI, produced a trace amount of **2** (run 3). When NHPI analogs *N*-hydroxysuccinimide (NHSI) and *N*-hydroxymaleimide (NHMI) were employed in place of NHPI, **1** was oxidized to **2** in 62% and 41% yields, respectively (runs 4 and 5). 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO), which serves as an efficient catalyst for the dehydrogenation of alcohols by dioxygen in the presence of cupric chloride,[7] has no catalytic activity in this transformation (run 6).

Table 1. NHPI-Catalyzed Aerobic Oxidation of Benzylic Derivatives[a]

Run	Substrate	Catalyst	Products (Yield, %)[b]
1	 (1)	NHPI	 (2) (80)
2[c]	1	NHPI	2 (15)
3	1	—	2 (trace)
4	1	NHSI[d]	2 (62)
5	1	NHMI[e]	2 (41)
6	1	TEMPO[f]	2 (0)
7		NHPI	 (73)
8		NHPI	 (34)
9		NHPI	 (64)  (8)
10		NHPI	 (20)  (30)
11		NHPI	 (37)  (13)
12		NHPI	 (42)  (7)
13		NHPI	 (60)
14		NHPI	 (83)
15		NHPI	 (99)

[a] Substrate (2 mmol) was reacted in the presence of NHPI (10 mol %) in PhCN (5 mL) under a dioxygen atmosphere at 100 °C for 20 h. [b] GLC yields. [c] 80 °C for 20 h. [d] NHSI, *N*-hydroxysuccinimide. [e] NHMI, *N*-hydroxymaleimide. [f] TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl.

To survey the generality of the present oxidation, various benzylic compounds were allowed to react in the presence of a catalytic amount of NHPI (10 mol %) under an atmosphere of oxygen (1 atm) at 100 °C for 20 h (runs 7–15 in Table 1).[8] For diphenylmethane and ethylbenzene, oxygenations took place at the benzylic positions to give the corresponding ketones in fair to good yields (runs 7 and 8). In the case of isopropylbenzene, with its tertiary carbon, demethylation took place in preference to hydroxylation to give acetophenone in 64% yield (run 9). In the oxidation of 1,1,1-triphenylmethane, 1,1,1-triphenylmethanol was obtained together with dephenylated product, benzophenone (run 10). Tetraline and

(1) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidation of Organic Compounds*; Academic Press: New York, 1981. Hill, C. L. In *Activation and Functionalization of Alkanes*; Academic Press: New York, 1989. Hill, C. L. In *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum Press: New York, 1993. Mennier, B. *Chem. Rev.* **1992**, *92*, 1411. Busch, D. H.; Alcock, N. W. *Ibid.* **1994**, *94*, 585. Sosnovsky, G.; Zaret, E. H. In *Organic Peroxide*, Vol. 1; Swern, D., Ed.; John Wiley and Sons: 1969; Chapter VIII and references cited therein.

(2) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1981**, *103*, 7371.

(3) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1979**, *101*, 6456.

(4) Kaneda, K.; Hamana, S.; Imanaka, T.; Kawamoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1467. Murahashi, S.-I.; Oda, Y.; Naota, T. *J. Am. Chem. Soc.* **1992**, *114*, 7913. Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17.

(5) Masui, M.; Ueshima, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1983**, 479.

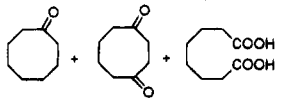
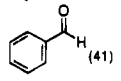
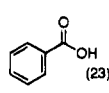
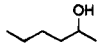
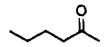
(6) **2** was obtained in 78% yield by the reaction in the dark.

(7) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374.

(8) **General Procedure.** A benzonitrile (5 mL) solution of alkane (2 mmol) and NHPI (33 mg, 0.2 mmol) was placed into a three-necked flask and equipped a balloon filled with O_2. The mixture was stirred at 100 °C for 20 h. After the reaction, the catalyst was filtered off and the resulting solution was extracted with diethyl ether (20 mL × 3). The combined extracts were dried over $MgSO_4$ and analyzed by GLC with an internal standard. Removal of the solvent under reduced pressure afforded a clean liquid, which was purified by column chromatography on silica gel (*n*-hexane/AcOEt) to give the corresponding ketones and alcohols.

0022-3263/95/1960-3934$09.00/0

Table 2. NHPI-Catalyzed Aerobic Oxidation of Various Substrates[a]

Run	Substrate	Temp, °C	Time, h	Conv., %	Product (Yield, %)[b]
1		100	6	24	 (12)
2		100	6	trace	 (trace) +  (0)
3[c]		100	6	14	(9) (3)[d]
4[c,e]		100	6	37	(17) (5)[d]
5[f]		100	6	37	 (23) (3) (6)[d]
6[c,f]		100	6	62	(34) (5) (13)[d]
7		70	7	70	 (35) +  (8)
8		100	5	62	 (41) +  (23)
9[g]		75	20	82	 (80)
10		100	5	54	 (49)
11		100	5	80	 (56)

[a] Substrate (2 mmol) was reacted in the presence of NHPI (10 mol %) in PhCN (5 mL) under a dioxygen atmosphere. [b] GLC yields based on the substrates used. [c] O_2 (10 atm). [d] GLC yield as dimethyl ester. [e] NHPI (20 mol %) was added. [f] AcOH (5 mL) was used as a solvent instead of PhCN. [g] CH_3CN (5 mL) was used as a solvent instead of PhCN.

indan were similarly oxygenated by this system, giving 1-tetralone (37%) and 1-indanone (42%), respectively, with small amounts of the corresponding alcohols (runs 11 and 12). It is interesting that oxygen-containing substrates such as benzyl methyl ether, isochroman, and xanthene were smoothly oxidized by the NHPI–O_2 system to produce methyl benzoate, 1-isochromanone, and xanthone in 60%, 83%, and 99% yields, respectively (runs 13–15).

Table 2 shows the oxidation of cycloalkanes and alcohols by the NHPI–O_2 system under these conditions. The oxidation of adamantane proceeded sluggishly to form adamantanol in which the tertiary C–H bond was exclusively oxidized (run 1). In addition, NHPI catalyzed the aerobic oxidation of cyclohexane under 10 atm of dioxygen to afford a 9% yield of cyclohexanone and a 3% yield of adipic acid, with 14% conversion (run 3). When NHPI (20 mol %) was used under these conditions, cyclohexanone was obtained in 17% yield along with adipic acid (5%), with 37% conversion (run 4). However, the oxidation of cyclohexane under a dioxygen atmosphere (1 atm) afforded a trace amount of cyclohexanone (run 2).[9] In contrast, cyclooctane even under 1 atm of dioxygen was oxidized to cyclooctanone (23%), 1,4-octanedione (3%), and suberic acid (6%), in 37% conversion (run 5). Under a higher pressure of dioxygen (10 atm), cyclooctane was satisfactorily converted into cyclooctanone (34%), 1,4-octanedione (5%), and suberic acid (13%) in 62% conversion (run 6). On the other hand, the oxidation of cyclohexene by the NHPI–O_2 system gave 2-cyclohexen-1-one (35%) and 2-cyclohexen-1-ol (8%), in which the allylic carbons were selectively oxidized (run 7).

To obtain information on the reaction mechanism of the present oxidation, the effect of a radical inhibitor on the oxidation of **1** was examined. The oxidation was found to be completely inhibited by addition of hydroquinone (5 mol %). This suggests that the present oxidation proceeds via a radical process.

Perkins *et al.* have reported that an *N*-oxyl radical such as benzoyl *tert*-butyl nitroxide smoothly adds to the 2-norbornene double bond to form 2,3-bis(*N*-benzoyl-*N*-*tert*-butylaminooxy)bicyclo[2.2.1]heptane in good yield.[10] Thus, 2-norbornene was allowed to react with NHPI (0.5 equiv) under an oxygen atmosphere at 60 °C. As expected, an addition product, *N*-(2-hydroperoxybicyclo-[2.2.1]heptan-2-yloxy)phthalimide (**3**), was obtained in 52% yield (eq 1).[11] However, the same procedure under an argon atmosphere resulted in the recovery of the starting materials. Treatment of triphenylphosphine with **3** thus obtained afforded triphenylphosphine oxide in 94% yield along with *N*-(2-hydroxybicyclo[2.2.1]heptan-2-yloxy)phthalimide (**4**) (83%) (eq 2).[12] The formation of the hydroperoxide **3** from 2-norbornene and NHPI under an oxygen atmosphere suggests that the present aerobic oxidation proceeds via a reaction pathway similar to a free radical autoxidation (Scheme 1). The first step of the reaction is thought to involve the generation of phthalimide *N*-oxyl radical **5** from NHPI and dioxygen.[13] The **5** thus generated abstracts a hydrogen atom from substrates to form alkyl radicals on which subsequent oxygenations by dioxygen produce peroxy radicals, which are converted into ketones or dicarboxylic acids.

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Supplementary Material Available: Equations 1 and 2, Scheme 1, general procedures, and characterization data (9 pages).

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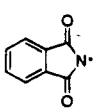
(9) For the substrates such as cyclohexane, we found that the oxidation was considerably accelerated by the addition of a small amount of $Co(acac)_3$ to the NHPI–O_2 system. The oxidation of cyclohexane with dioxygen (1 atm) by NHPI (10 mol %) in the presence of $Co(acac)_3$ resulted in cyclohexanone (16%) and adipic acid (18%) in 45% conversion of cyclohexane.

(10) Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2803.

(11) Spectral data of **3**: ^1H NMR ($CDCl_3$) δ 1.41–1.16 (m, 2H), 1.65–1.48 (m, 2H), 2.04 (d, J = 10 Hz, 1H), 2.31 (s, 1H), 2.94 (s, 1H), 4.14 (d, J = 5.3 Hz, 1H), 4.36 (d, J = 5.3 Hz, 1H), 8.55–7.79 (m, 4H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.3, 134.9, 128.6, 123.9, 93.6, 89.0, 41.7, 39.8, 33.6, 25.9, 22.9; IR (NaCl) 3381, 2950, 1789, 1732, 1379, 1188, 993, 878, 699, 520 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.17; H, 5.18; N, 4.82.

(12) The spectral data of **4** were fair agreement with literature values: Ozaki, S.; Hamaguchi, T.; Tsuchida, K.; Kimata, Y. *J. Chem. Soc., Perkin Trans. 2* **1989**, 951.

(13) The generation of phthalimide radical **6** by the nitrogen–oxygen bond cleavage of NHPI is improbable as the radical species, since the reaction of norbornene with O_2 using *N*-isoproponylphthalimide (**7**) in place of NHPI under these conditions was not observed.



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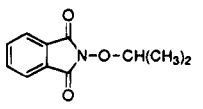

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