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Alkane Oxidation with Air Catalyzed by Lipophilic *N*-Hydroxyphthalimides without Any Solvent

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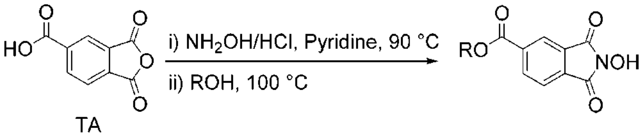
Introduction

Although there have been major advances in the oxidation of saturated hydrocarbons with molecular oxygen, the development of effective and selective methods for the catalytic functionalization of hydrocarbons still remains a major challenge in oxidation chemistry. In particular, selective oxidation of alkanes with dioxygen to oxygen-containing compounds such as alcohols, ketones, and carboxylic acids is a very important industrial process from both economical and environmental aspects.[1] Traditional alkane oxidation with dioxygen, which is referred to as autoxidation, often suffers from relatively harsh conditions and limited conversion and selectivity.[2] For instance, autoxidation of cyclohexane to a mixture of cyclohexanone and cyclohexanol (K/A oil) is now carried out using a soluble cobalt catalyst in industrial scale worldwide. The drawback of this process is that the oxidation must be operated in 3−6% conversion of cyclohexane to maintain higher selectivity (75−80%) to the K/A oil. In the 1940s, DuPont first industrialized this process for the purpose of the production of adipic acid from the K/A oil.[3] Although much effort has been made to develop an effective oxidation system of cyclohexane with molecular oxygen, the DuPont process is currently employed without major modification.

Recently, we have developed a novel method for alkane oxidation with dioxygen using the *N*-hydroxyphthalimide (NHPI) as a catalyst under mild conditions.[4] Thus, cyclohexane can be converted into adipic acid in higher conversion (70%) and selectivity (70%) by a combined catalyst of NHPI with $Mn(OAc)_3$ under normal pressure of dioxygen in acetic acid at 100 °C.[5] Previous work from our laboratory focused on the aerobic oxidations of hydrocarbons must be carried out in an appropriate solvent such as acetic acid or benzonitrile, since NHPI is difficult to dissolve in nonpolar solvents such as hydrocarbons. Therefore, it is interesting to develop NHPI derivatives that easily dissolve in hydrocarbons such as cyclohexane. If such a catalyst can be prepared, the aerobic oxidation of alkanes can proceed without any solvent. This study is focused on the preparation of NHPI derivatives not requiring the use of solvents for the oxidation of alkanes with dioxygen under mild conditions.

Scheme 1. Preparation of NHPI Derivatives



1a (R=H)
1b (R=C_6H_{13})
1c (R=$C_{12}H_{25}$)
1d (R=$C_{14}H_{29}$)

Results and Discussion

To employ NHPI derivatives as catalysts, it is important to use cheap starting materials readily available from commercial sources. Thus, we chose trimellitic anhydride (TA) available from Aldrich Chemical Co. as the starting material and prepared a series of 4-alkyloxycarbonyl *N*-hydroxyphthalimides **1a**−**d** (Scheme 1). Treatment of TA with hydroxylamine afforded *N*-hydroxyphthalimide 4-carboxylic acid (**1a**) on which subsequent esterification with hexyl alcohol led to 4-hexyloxycarbonyl *N*-hydroxyphthalimide (**1b**) in good yield. Similarly, a series of NHPI derivatives substituted by 4-alkyloxycarbonyl moieties having a different alkyl chain were prepared and used for the aerobic oxidation of cyclohexane (**2b**).

Table 1 shows the representative results for the oxidation of **2b** catalyzed by 4-laulyloxycarbony *N*-hydroxyphthalimide (**1c**) under various reaction conditions. As expected, **1c** anchoring a long alkyl chain was cleanly dissolved in the substrate **2b** under the reaction conditions to form a transparent solution. The reaction of **2b** (4 mL, ca. 37 mmol) under air (10 atm) in the presence of **1c** (30 μmol), $Co(acac)_2$ (3 μmol), and $Mn(OAc)_2$ (0.3 μmol) in the absence of solvent at 100 °C for 14 h gave cyclohexanone (**3b**), cyclohexanol (**4b**) and adipic acid (**5b**) in a ratio of 61:28:7 with 56 turnover number (TN) (Table 1, run 1). It is interesting to note that the sum of these oxidation products, **3b**, **4b**, and **5b**, was very high (96%). Removal of **3b**, **4b**, and **5b** from the reaction mixture under reduced pressure left a white solid involving **1c**. It was found that a part of the catalyst **1c** was changed to the corresponding phthalimide, but about 50% of **1c** was recovered unchanged. The oxidation of the alkyl chain contained in **1c** was not observed at all. The oxidation of **2b** by NHPI under these conditions proceeded very slowly to afford **3b**, **4b,** and **5b** in a 51:43:3 ratio in lower conversion (11.7 TN) (Table 1, run 2). In a previous paper, we showed that the NHPI-catalyzed oxidation of **2b** with dioxygen in acetic acid produced **3b** and **5b** as major products, but cyclohexanol **4b** was scarcely formed (Scheme 2). In this oxidation, however, a considerable amount of **4b** was obtained. This is

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(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Mennier, B. *Chem. Rev.* **1992**, *92*, 1411. (c) Busch, D. H.; Alcock, N. W. *Chem. Rev.* **1994**, *94*, 585.

(2) (a) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; John Wiley and Sons: New York, 1992; p 246. (b) Simandi, L. *Catalytic Activation of Dioxygen by Matal Complexes*; Kluwer Academic Pablisher: Dordrecht, The Netherlands, 1992; p 84.

(3) Davis, D. D. *In Ullman's Encyclopedia of Industrial Chemistry*, 5th ed.; Gerhartz, W., Ed.; John Wiley and Sons: New York, 1985; Vol. A1, 270.

(4) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.

(5) (a) Iwahama, T.; Shojyo, K.; Sakaguchi, S.; Ishii, Y. *Org. Proc. Res. & Dev.* **1998**, *2*, 255. (b) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934.

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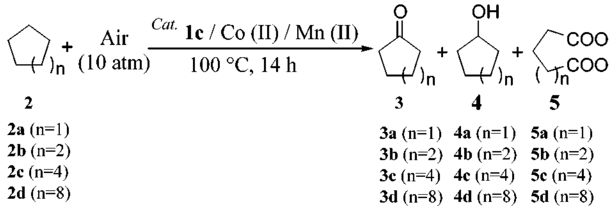
Table 1. Aerobic Oxidation of Cyclohexane (2b) by 1c under Various Conditions[a]

			product distribution/%			
run	catalyst	TN[b]	**3b**	**4b**	**5b**	others[c]
1	**1c**/Co(II)/Mn(II)	56	61	28	7	4
2	NHPI/Co(II)/Mn(II)	11.7	51	43	3	3
3	**1c**/Co(II)	41	65	25	7	3
4	**1c**/Mn(II)	7.7	57	35	4	4
5[d]	**1c**/Co(II)/Mn(II)	33	53	20	26	1
6[e]	**1c**/Co(II)/Mn(II)	28	2	1	85	12

[a] **2b** (37 mmol) was reacted in the presence of **1c** (30 μmol), $Co(acac)_2$ (3 μmol), and $Mn(OAc)_2$ (0.3 μmol) under air (10 atm) at 100 °C for 14 h. [b] Turnover number. [c] Others contain glutaric acid as a major compound. [d] **2b** (19 mmol) was used. [e] **2b** (9 mmol) was used.

Scheme 2



believed to be due to the presence of a large excess of **2b**, although the alcohol **4b** is much more reactive than alkane **2b**. Therefore, when the amount of **2b** employed was reduced from 37 to 9 mmol under these conditions, the formation of **3b** and **4b** decreased markedly, and adipic acid **5b**, which is a further oxidation product of **3b** and **4b**, was crystallized as a white solid from the reaction solution in high selectivity (85%), although the TN of the catalyst decreased from 56 to 28 (Table 1, run 6). Removing the $Mn(OAc)_2$ from the catalytic system resulted in a slight decrease of the total yield of the oxygenated products, but the product distribution was almost the same as that by the **1c**/$Co(acac)_2$/$Mn(OAc)_2$ system. By contrast, oxidation lacking $Co(acac)_2$ in the catalytic system led to a considerably lower amount of the oxidation products (Table 1, run 4). In a previous paper, we showed that the aerobic oxidation of **2b** by NHPI in the absence of a Co species was not induced, since the Co(II) species reacts with dioxygen to give a Co(III)-oxygen complex that assists the hydrogen atom abstraction from the NHPI to form phthalimide *N*-oxyl (PINO), which is a key species in the alkane oxidation.[5] In this oxidation of **2b** by **1c**, the generation of the corresponding PINO from **1c** is necessary to promote the oxidation.

Figure 1 shows the oxidation results of **2b** by several alkoxycarbonyl NHPI derivatives **1a**−**d** having different alkyl chains. It is attractive that the total yields of oxygenated products increased with increasing the alkyl chain length in **1a**−**d**.

It is rather difficult to explain rationally the effect of the alkyl chain length of **1a**−**d** on the oxidation of **2b**. Although the catalytic activity of **1a**−**d** is not fully explained by the solubility of these in **2b**, the solubility seems to be an important factor governing the oxidation activity. The reaction solution involving **1b** bearing the hexyl moiety became turbid under the operated reaction conditions. As a result, the catalytic activity of the **1b** was undoubtedly low compared with that of the **1c**.

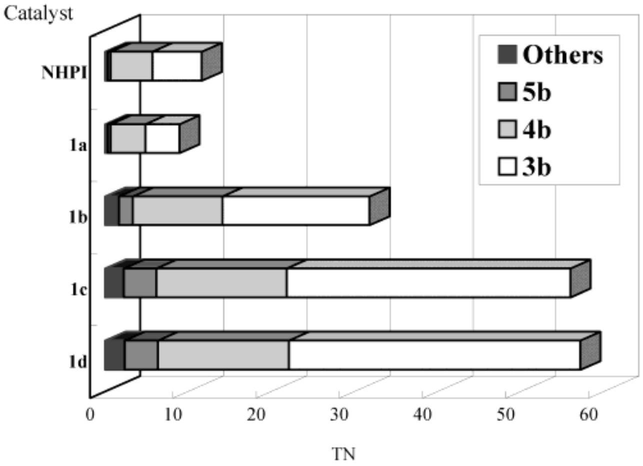
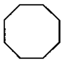
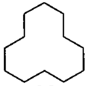
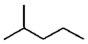
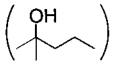


Figure 1. Aerobic oxidation of cyclohexane (2b) by NHPI derivatives. Compound **2b** (37 mmol) was reacted in the presence of NHPI derivatives (30 μmol), $Co(acac)_2$ (3 μmol), and $Mn(OAc)_2$ (0.3 μmol) at 100 °C for 14 h.

Table 2. Aerobic Oxidation of Various Alkanes[a]

			Product distribution / %		
Substrate	Catalyst	TN	**3**	**4**	**5**
 **2a**	**1c**	20	41	13	46
	NHPI	9	19	11	70
 **2c**	**1c**	110	68	29	2
	NHPI	22	77	22	1
 **2d**	**1c**	140	63	37	<1
	NHPI	48	64	36	<1
 **6**	**1c**	33.5	 **7**		
	NHPI	9.7			

[a] Substrate (37 mmol) was reacted in the presence of **1c** (30 μmol) or NHPI (30 μmol), $Co(acac)_2$ (3 μmol), and $Mn(OAc)_2$ (0.3 μmol) at 100 °C for 14 h.

Table 2 summarizes a comparison of the oxidation of various alkanes catalyzed by **1c** in the presence of small amounts of $Co(acac)_2$ and $Mn(OAc)_2$ with that by NHPI under the same conditions.

The oxidation of cyclopentane (**2a**) occurred in lower yield than that of **2b** to give cyclopentanone (**3a**), cyclopentanol (**4a**), and glutaric acid (**5a**) in 31:13:46 ratio with 20 TN. The low TN in the oxidation of cyclopentane **2a** by **1c** may be due to the easy cleavage of the C−C bond to glutaric acid **5a**. Replacing **1c** with NHPI under these conditions, the TN of the catalyst decreased to 9. Large-membered cycloalkanes such as cyclooctane (**2c**) and cyclododecane (**2d**) were easily oxidized by **1c** to afford the corresponding cyclic ketones, **3c** and **3d**, and alcohols, **4c** and **4d**, respectively in good yields. The TN of the catalyst **1c** for the oxidation of **2c** and **2d** reached 110 and 140, respectively. In the oxidation of large-membered cycloalkanes by **1c**, cleavage to α,ω-dicarboxylic acids, **5c** and **5d**, was considerably suppressed compared with the oxidation of cyclopentene **2a**. 2-Methylpentane (**6**) led to 2-methyl-2-pentanol (**7**) in which the tertiary C−H bond was exclusively oxidized. The TN of the NHPI in the oxidation of these alkanes decreased to 1/5 to 1/2 of those of **1c**.

In conclusion, we have succeeded in the oxidation of alkanes with air under mild condition in the absence of any solvent by the use of the lipophilic NHPI derivatives, which are easily dissolved in alkanes. This method would provide an interesting approach to alkanes oxidation with air in industrial chemistry.

Experimental Section

General Procedure. The starting materials were commercially available and used without purification. GC analysis was performed with a flame ionization detector using a 0.2 mm × 30 m capillary column (OV-17). ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in methanol-d_4 with Me_4Si as the internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. GC-MS spectra were obtained at ionization energy of 70 eV. The yields of products were estimated from the peak areas on the basis of the internal standard technique by the use of GC.

Typical Procedure for the Oxidation under Air (10 atm). Cyclohexane (4 mL, ca 37 mmol), NHPI derivatives (30 μmol), $Co(acac)_2$ (3 μmol) and $Mn(Oac)_2$ (0.3 μmol) were placed in a 50-mL Teflon-coated autoclave, and 10 atm of air was charged. After removal of the solvent under reduced pressure, a catalytic amount of *conc.* sulfuric acid and ethanol (10 mL) were added to the resulting mixture, and the solution was stirred at 100 °C for 15 h. The resulting solution was extracted with diethyl ether (5 mL × 3). Removal of the solvent afforded a clean liquid which was subjected to column chromatography on silica gel (*n*-hexane/AcOEt = 5/1) to give the corresponding oxygenated products.

Preparation of Catalysts. *N*-Hydroxylphthalimde-4-carboxylic Acid (1a).[6] To a pyridine (50 mL) was added NH_2OH/HCl (44 mmol) under stirring followed by TA (40 mmol). The mixture was stirred 15 h at 90 °C and poured into 50 mL of water. After cooling, the mixture was acidified by slowly adding hydrochloric acid (50 M) until it becomes acidic to pH 2−3. The precipitate was filtered and washed with water. The solid was filtered off and dried under vacuum to give **1a** (5.2 g) in 70% yield.

1a: ^{1}H NMR (CD_3OD/TMS) δ 7.05 (d, 1H), 8.31 (s, 1H), 8.40 (d, 1H); ^{13}C NMR (CD_3OD/TMS) δ 167.4, 164.9, 137.7, 136.7, 133.8, 130.7, 124.7, 124.2; IR (neat) 2793, 1726, 1191, 709 cm^{-1}.

Preparation of 4-Alkyloxylcarboxyl-*N*-hydroxyphthalimdes 1b−d. Compound **1a** (10 mmol) and *p*-toluenesulfonic acid (0.1 equiv) were dissolved in lauryl, hexyl, or myristyl alcohol (30 mL) and *n*-hexane (10 mL). The mixture was stirred under refluxing temperture for 6 h and cooled to 10 °C. The product was obtained as a white crystal. Recrystallization from methanol gave pure **1b−d**.

1b: ^{1}H NMR (CD_3OD/TMS) δ 0.82 (t, 3H), 1.37 (m, 8H), 1.79 (q, 2H), 4.37 (t, 2H); ^{13}C NMR (CD_3OD/TMS) δ 166.4, 164.9, 137.7, 136.5, 134.1, 131.0, 124.5, 124.3, 67.2, 32.0, 29.7, 26.8, 23.6, 14.4; IR (neat) 2915, 2361, 1786, 1738, 1188, 711 cm^{-1}.

1c: ^{1}H NMR (CD_3OD/TMS) δ 0.88 (t, 3H), 1.2 (m, 18H), 1.8 (q, 2H), 4.37 (t, 2H), ^{13}C NMR (CD_3OD/TMS) δ 166.4, 164.9, 137.4, 136.6, 134.1, 131.0, 124.5, 124.2, 67.2, 33.0, 30.7, 30.6, 30.4, 30.3, 29.7, 27.1, 23.7, 14.4; IR (neat) 2915, 2361, 1786, 1728, 1188, 711 cm^{-1}.

1d: ^{1}H NMR (CD_3OD/TMS) δ 0.88 (t, 3H), 1.27 (m, 22H), 1.8 (q, 2H), 4.37 (t, 2H), ^{13}C NMR (CD_3OD/TMS) δ 166.4, 164.9, 137.7, 136.7, 134.1, 131.1, 124.6, 124.4, 67.2, 33.0, 30.7, 30.6, 30.5, 30.4,30.3, 29.7, 27.1, 23.7, 14.4; IR (neat) 2915, 2361, 1786, 1728, 1188, 711 cm^{-1}.

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