Letter

Heterogeneous *N*-oxidation of pyridines using a combined oxidant of hydrogen peroxide and nitriles catalysed by basic hydrotalcites

Kazuya Yamaguchi, Tomoo Mizugaki, Kohki Ebitani and Kiyotomi Kaneda*

Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan. Phone/fax: +81 6 6850 6260; e-mail: kaneda@cheng.es.osaka-u.ac.jp

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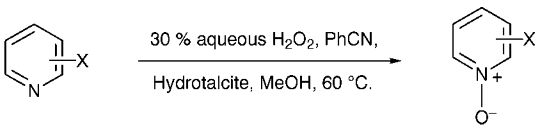
The oxidation of pyridines using a combined oxidant of hydrogen peroxide and benzonitrile catalysed by a basic hydrotalcite, $Mg_{10}Al_2(OH)_{24}CO_3$, gave high yields of the corresponding pyridine *N*-oxides. This solid hydrotalcite catalyst was easily separated from the reaction mixture and could be reused with retention of its high catalytic activity and selectivity.

Recently, we have developed a series of hydrotalcite-catalysed oxidation reactions such as the Baeyer–Villiger oxidation of ketones,[1] oxidative dehydrogenation of alcohols,[2] oxygenation of aromatic compounds,[3] and epoxidation of olefins,[4] using hydrogen peroxide and molecular oxygen as oxidants. The basic hydrotalcite, $Mg_{10}Al_2(OH)_{24}CO_3$, in the presence of a combined oxidant of hydrogen peroxide and nitriles, had especially high catalytic activity for the epoxidation of terminal olefins.[4a] Here, we report the efficient heterogeneous oxidation of various pyridines to yield pyridine *N*-oxides using this same mono-oxygenation catalyst system.



(1)

Pyridine *N*-oxides are versatile synthetic intermediates and are usually prepared by oxidation of pyridines using peracids such as *meta*-chloroperbenzoic acid (*m*-CPBA) and peracetic acid.[5] Catalytic methods for oxidation processes using *aqueous* hydrogen peroxide and molecular oxygen as oxidants in place of stoichiometric reagents are, however, now more desirable because of the need for the chemical industry to minimize waste production associated with stoichiometric reagents.[6] Over the years, many researchers have studied the *N*-oxidation of pyridines using hydrogen peroxide in the presence of metal complex catalysts.[7] However, such homogeneous catalysts are typically not easily recovered from the reaction mixture, are not reusable, and sometimes require halogenated solvents to obtain high yields of *N*-oxides. The heterogeneous *N*-oxidation system using hydrotalcite catalysts we describe here has the following advantages: (1) simple work-up procedures and reusable catalysts, (2) use of non-polluting natural mineral catalysts, and (3) use of non-halogenated solvents.

Various hydrotalcite catalysts were obtained from $Mg(NO_3)_2 \cdot 6H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, NaOH, and Na_2CO_3 (or Na_2SO_4) by the coprecipitation method, according to literature procedures.[8] A typical hydrotalcite-catalysed *N*-oxidation of pyridines was accomplished as follows. Into a reaction vessel with a reflux condenser were successively placed the hydrotalcite, $Mg_{10}Al_2(OH)_{24}CO_3$ (0.10 g), methanol (20 cm^3), pyridine (8 mmol), benzonitrile (16 mmol), and 30% aqueous hydrogen peroxide (4.0 cm^3). After the reaction mixture had been stirred at 60 °C for 24 h, the hydrotalcite was separated by filtration. The recovered hydrotalcite could then be reused as a catalyst. The filtrate was treated with MnO_2 to decompose the remaining hydrogen peroxide. The solution was poured into brine (10 cm^3) and extracted with ethyl acetate (4×10 cm^3). The combined organic layers were dried over $MgSO_4$ and the crude product was purified by column chromatography on silica gel (Wako Gel C-200) with ethyl acetate–methanol (9 : 1) as eluent to give 0.61 g of pyridine *N*-oxide (80% yield).

Nitriles, hydrogen peroxide, and hydrotalcites were indispensable components of this oxidation and methanol was the best solvent. Water-immiscible solvents like benzene, toluene, and cyclohexane were poor solvents. A survey of various base catalysts and nitriles for the *N*-oxidation of pyridine is shown in Table 1. Among the nitriles used (entries 1–3), benzonitrile was the most effective. The yields of pyridine *N*-oxide increased with increasing calorimetric heats of benzoic acid adsorption on the hydrotalcites. The calorimetric heat of benzoic acid adsorption is a measure of the basicity of the

Table 1 *N*-Oxidation of pyridine using H_2O_2, nitriles and various base catalysts[a]

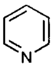
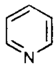
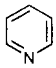
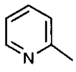
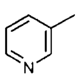
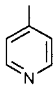
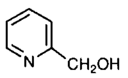
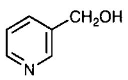
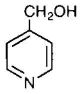
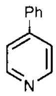
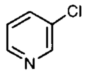
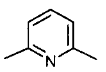
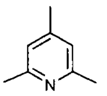
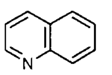
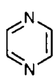
Entry	Catalyst	Nitrile	Convn of pyridine[b] (%)	Yield of *N*-oxide based on pyridine[b] (%)	Heat of adsorption[c]/ $J\ g^{-1}$	Surface area/ $m^2\ g^{-1}$
1	$Mg_{10}Al_2(OH)_{24}CO_3$	Benzonitrile	98	92	14.2	44.3
2	$Mg_{10}Al_2(OH)_{24}CO_3$	Acetonitrile	50	49	14.2	44.3
3	$Mg_{10}Al_2(OH)_{24}CO_3$	Propionitrile	47	42	14.2	44.3
4	$Mg_6Al_2(OH)_{16}CO_3$	Benzonitrile	75	75	6.3	43.5
5	$Mg_6Al_2(OH)_{16}SO_4$	Benzonitrile	38	38	5.1	57.0
6	MgO[d]	Benzonitrile	35	32	8.4	119.3
7	$Mg(OH)_2$	Benzonitrile	84	79	6.4	24.9
8	None	Benzonitrile	0	0	—	—

[a] Reaction conditions: pyridine (4 mmol), nitrile (8 mmol), catalyst (0.05 g), MeOH (10 cm^3), 30% aq. H_2O_2 (2 cm^3), 60 °C, 24 h. [b] Determined by HPLC using an internal standard technique. [c] See ref. 1(*d*). [d] MgO calcined at 400 °C was used.

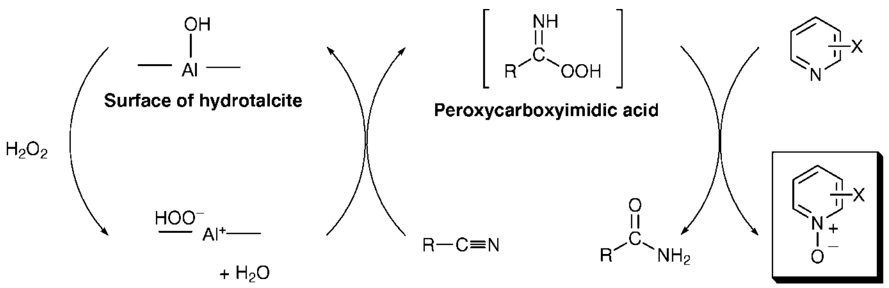
solid surfaces.[1d] $Mg_{10}Al_2(OH)_{24}CO_3$ had much higher catalytic activity than other solid base catalysts such as MgO and $Mg(OH)_2$ (entries 6 and 7), which might be due to the high basicity of its surface. It is likely that the basic hydroxyl functions of the hydrotalcites play an important role in this *N*-oxidation.

Table 2 shows the oxidation of various pyridines using hydrogen peroxide and benzonitrile in the presence of $Mg_{10}Al_2(OH)_{24}CO_3$. In the oxidation of pyridine, the yield of pyridine *N*-oxide based on the consumed hydrogen peroxide reached 70%. *In our oxidation system, the corresponding pyridine* N-*oxides were exclusively obtained without other oxidation*

Table 2 Hydrotalcite-catalysed *N*-oxidation of various pyridines with H_2O_2 and benzonitrile[a]

Entry	Substrate	Convn. (%)[b]	Yield of *N*-oxide based on substrate (%)[b]
1		98	92 (80[c])
2[d]		93	89
3[d]		95	90
4		98	93 (86)
5		99	97
6		96	93 (93)
7		99	92
8		93	87 (87)
9		99	95 (92)
10		84	81 (76)
11		91	89 (84)
12[e]		89	86 (79)
13		99	90 (88)
14		93	89 (87)
15[f]		93	90[g]

[a] Reaction conditions: substrate (4 mmol), PhCN (8 mmol), $Mg_{10}Al_2(OH)_{24}CO_3$ (0.05 g), MeOH (10 cm^3), 30% aq. H_2O_2 (2 cm^3), 60 °C, 24 h. [b] Determined by HPLC using an internal standard technique. Values in parentheses are isolated yields. [c] For the isolation experiment, the amount of reagents was doubled compared to those used in footnote *a*. [d] Same conditions as in entry 1 except that the hydrotalcite catalyst was recovered and used for the following entry (*i.e.*, 1 → 2 and 2 → 3). [e] CH_3CN (10 cm^3) was used as a solvent instead of PhCN. [f] 48 h. [g] Only pyrazine mono-*N*-oxide was formed.

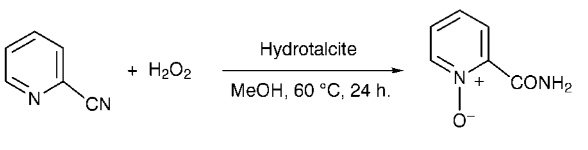


Scheme 1

products. For example, 4-pyridylcarbinol was oxidized to give 4-pyridylcarbinol *N*-oxide without the formation of other oxidation products, pyridinealdehyde and pyridinecarboxylic acid (entry 9), while the use of *m*-CPBA resulted in the formation of a mixture of 4-pyridylcarbinol *N*-oxide and 4-pyridinecarboxylic acid (89 : 11). Pyrazine afforded the mono-*N*-oxide exclusively. No di-*N*-oxide was detected (entry 15).[9] The *N*-oxidation of 3- and 4-substituted pyridines proceeded smoothly and 2-substituted pyridines (except for those with electron withdrawing groups such as 2-chloropyridine and 2-phenylpyridine[10]) gave high yields of the corresponding *N*-oxides (entries 4–13). Recently, Sharpless *et al.* have reported the efficient *N*-oxidation of pyridines using hydrogen peroxide catalysed by methyltrioxorhenium (MTO).[7d] The Sharpless system is not effective for 2-substituted pyridines; it requires a large amount of the expensive rhenium catalyst to attain high yields, even for 2-picoline and 2,6-lutidine. A polysubstituted pyridine like quinoline also could be smoothly oxidized with our hydrotalcite catalysts (entry 14).[11]

The spent hydrotalcite catalyst was easily separated from the reaction mixture by filtration and could be reused without an appreciable loss of catalytic activity and selectivity for the oxidation of pyridine (entries 2 and 3, in Table 2). Furthermore, we found that adding an anionic surfactant, sodium dodecyl sulfate (SDS), to the above reaction system promoted the *N*-oxidation. For example, 4-picoline *N*-oxide was quantitatively obtained within 5 h in the presence of SDS but the reaction required 24 h in the absence of SDS. This *N*-oxidation occurred in three phases: the aqueous, organic and solid phases. We speculate that the main roles of the surfactant are to increase the contact area of the interface between the aqueous and organic phases and to enhance the transfer of the lipophilic benzonitrile from the organic phase to the aqueous phase.

A possible reaction mechanism for this reaction is shown in Scheme 1. Hydrogen peroxide reacts with a basic hydroxyl function on the surface of the hydrotalcite to form HOO^- species, which attacks the nitrile to generate a peroxycarboximidic acid as an active intermediate oxidant. Oxygen transfer from peroxycarboximidic acid to a pyridine then occurs.[4a] *Interestingly, 2-cyanopyridine could react with hydrogen peroxide in the absence of nitriles.* In this case, picolineamide *N*-oxide was formed in high yield without the formation of 2-cyanopyridine *N*-oxide:



(2)

(71 % isolated yield)

presumably *via* intramolecular oxygen transfer by the intermediate peroxycarboximidic acid.

In conclusion, a heterogeneous system consisting of hydrogen peroxide, nitriles, and basic hydrotalcites efficiently oxidize various kinds of pyridines to the corresponding pyridine *N*-oxides. The oxidation proceeds smoothly under mild reaction conditions and the hydrotalcite catalysts are recyclable.[12] At present, we are continuing to study selective oxidations using functionalised hydrotalcites with the aim of developing environmentally benign chemical processes.

References and notes

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9 By contrast, use of the MTO catalyst resulted in 91% yield of di-*N*-oxide.

10 2-Chloropyridine and 2-phenylpyridine afforded the corresponding *N*-oxides in 17 and 63% yields, respectively, under the same reaction conditions as in Table 2.

11 For this substrate, the resultant reaction mixture was poured into ethyl acetate, which was extracted with water. After removal of water, 0.57 g (87%) of quinoline *N*-oxide monohydrate was obtained.

12 In this system, the resultant benzamide could be further employed for the *N*-oxidation: benzamide was also formed as a co-product from benzonitrile, which was recovered quantitatively by column chromatography. By using dehydrating reagents such as P_2O_5 and $SOCl_2$, benzamide could be easily regenerated to benzonitrile.

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