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Efficient Hydration of Nitriles Promoted by Simple Amorphous Manganese Oxide Using Reduced Amounts of Water

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Hydration of various kinds of nitriles could efficiently be promoted by amorphous MnO_2 using reduced amounts of water (2 equiv or less), giving the corresponding primary amides in moderate to high yields. The observed catalysis was truly heterogeneous, and the retrieved MnO_2 could be reused without an appreciable loss of its high catalytic performance.

Primary amides are one of the most important chemicals that have widely been utilized as important synthons, producing engineering plastics, detergents, lubricants, pharmaceuticals, agricultural chemicals, and specialty chemicals.[1] Instead of antiquated procedures using activated carboxylic acid derivatives, the development of efficient synthetic routes to primary amides using various kinds of starting materials is a very important subject in modern organic synthesis. Several green catalytic procedures starting from nitriles (hydration),[2,3] aldoximes (rearrangement),[4] primary alcohols (oxidative amidation with aqueous ammonia),[5] and primary amines (oxygenation)[6] have been developed. Very recently, we have successfully developed two new green synthetic routes to primary amides from (i) primary alcohols and aqueous ammonia[5] and (ii) primary amines[6a] via catalytic relay reactions in the presence of manganese-based oxide octahedral molecular sieves (OMS-2, KMn_8O_{16}). One of the most important findings in these studies is that OMS-2 can efficiently catalyze hydration of nitriles (the final step of the above relay reactions).[5,6a]

Hydration of nitriles is an important reaction to produce primary amides in academic as well as industrial laboratories. Many efficient procedures using homogeneous transition-metal-based complexes[2] and microorganisms for enzymatic hydration[7] have been developed, while these systems have disadvantages, i.e., difficulty in catalyst/product separation and necessity of special handling of metal complexes and microorganisms in some cases. Alternatively, several supported catalysts, e.g., MnO_2/SiO_2,[3a] KF/Al_2O_3,[3b] Na/FAP (FAP: fluoroapatite),[3c] AgHAP (HAP: hydroxyapatite),[3d] RuHAP,[3e] and $Ru(OH)_x/Al_2O_3$,[3f] have been developed. Several simple metal oxides have been reported to be active for hydration of nitriles. For example, MnO_2 is known to be effective for limited substrates, e.g., 3-cyanopyridine, in water.[3g–3i] Very recently, CeO_2[3j] and Co_3O_4[3k] have been reported to be active, though their applicabilities were quite limited; for example, CeO_2 for only 2-cyanopyridine and 2-furancarbonitrile derivatives[3j] and Co_3O_4 for only aromatic nitriles.[3k] In most of the reported heterogeneous systems, the hydration has typically been carried out in water (using large excess of water (reactant)),[3] which produces large amounts of waste water containing organic contamination. Therefore, it is desirable to reduce the amounts of water to (near) stoichiometric amounts with respect to nitriles.

Table 1. Hydration of benzonitrile (**1a**) to benzamide (**2a**)[a]

Entry	Catalyst	Solvent	Yield/%
1	Amorphous MnO_2	1,4-Dioxane	62
2[b]	Amorphous MnO_2	1,4-Dioxane	64
3	OMS-2	1,4-Dioxane	27
4[c]	β-MnO_2	1,4-Dioxane	42
5	$KMnO_4$	1,4-Dioxane	<1
6	$MnSO_4{\cdot}H_2O$	1,4-Dioxane	<1
7	Co_3O_4	1,4-Dioxane	3
8[c]	CeO_2	1,4-Dioxane	<1
9[c]	KF/Al_2O_3	1,4-Dioxane	<1
10	$Ru(OH)_x/Al_2O_3$	1,4-Dioxane	<1
11[c]	RuHAP	1,4-Dioxane	<1
12	Amorphous MnO_2	*n*-Heptane	58
13	Amorphous MnO_2	Toluene	48
14	Amorphous MnO_2	DMF	13
15	Amorphous MnO_2	Ethanol	1
16[d]	Amorphous MnO_2	Solvent-free	94
17	None	1,4-Dioxane	<1

[a]Reaction conditions: **1a** (0.5 mmol), catalyst (50 mg), water (2 equiv with respect to **1a**), solvent (2 mL), 140 °C (bath temp), under Ar, 30 min. Yields were determined by GC using naphthalene as an internal standard. [b]Water (1 equiv). [c]Commercially available (see the Supporting Information[13]). [d]1 h.

We demonstrate herein that simple amorphous MnO_2 (with a relatively large BET surface area, $304\,m^2\,g^{-1}$)[8] can promote hydration of various kinds of nitriles using reduced amounts of water and that the activity is much higher than those of several previously reported heterogeneous catalysts including OMS-2 (Table 1).[3] The present procedures have the following significant advantages in comparison with previously reported systems; (i) various structurally diverse nitriles including aromatic, heteroaromatic, unsaturated, and aliphatic compounds can be converted (even under solvent-free conditions), (ii) the amount of water can be much reduced (2 equiv or less), (iii) no ligands or additives are necessary, (iv) catalyst separation and product isolation are very easy, (v) gram-scale hydration is also effective, (vi) MnO_2 is easily prepared (commercially available) and rather inexpensive in comparison with precious-metal-based catalysts, and/or (vii) MnO_2 can be reused without an appreciable loss of its high catalytic performance.

Initially, various kinds of catalysts including previously reported ones were applied to the hydration of benzonitrile (**1a**) to benzamide (**2a**) using "2 equiv of water" with respect to **1a** in 1,4-dioxane (Table 1).[9] Among catalysts examined, only manganese-based oxides such as amorphous MnO_2, OMS-2, and β-MnO_2 gave significant yields of **2a** (27–62% yields). For

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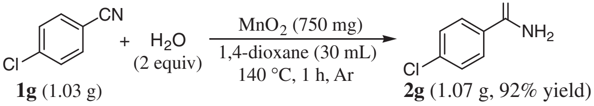
example, when the hydration of **1a** was carried out with amorphous MnO_2 at 140 °C (bath temp), 62% yield of **2a** was obtained in 30 min. Notably, the hydration efficiently proceeded even with "1 equiv of water." The catalytic activity of amorphous MnO_2 was higher than those of OMS-2[5,6a] and β-MnO_2. $KMnO_4$ and $MnSO_4{\cdot}H_2O$ (precursors of amorphous MnO_2[8]) were not effective for the hydration, suggesting that soluble manganese species are not the active species for the present hydration. Previously reported heterogeneous catalysts such as Co_3O_4,[3k] CeO_2,[3j] KF/Al_2O_3,[3b] $Ru(OH)_x/Al_2O_3$,[3f] and RuHAP[3e] did not work well under the conditions described in Table 1 using only "2 equiv of water." 1,4-Dioxane, *n*-heptane, and toluene were good solvents for the hydration, giving 62–48% yields of **2a**. On the other hand, highly polar solvents such as DMF and ethanol were poor solvents. It is emphasized that the hydration also efficiently proceeded even under solvent-free conditions (Entry 16 in Table 1).

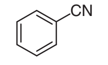
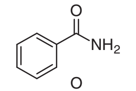
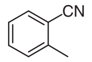
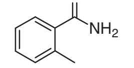
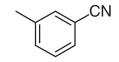
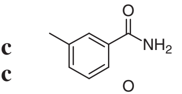
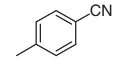
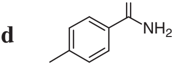
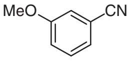
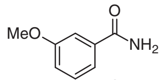
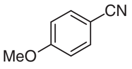
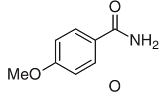
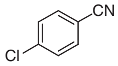
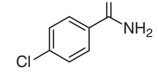
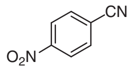
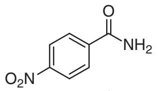
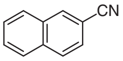
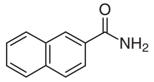
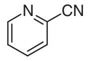
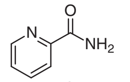
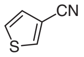
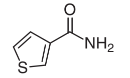
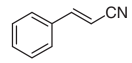
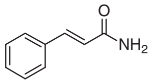
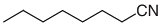
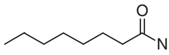
Next, the scope of the present MnO_2-catalyzed system with regard to various kinds of structurally diverse nitriles was examined. Amorphous MnO_2 showed high catalytic activities for hydration of aromatic, heteroaromatic, unsaturated, and aliphatic nitriles, giving the corresponding amides in moderate to high yields (except for **1b**) using only 2 equiv of water (Table 2). Hydration of benzonitrile derivatives **1a** and **1c**–**1i**, which contain electron-donating as well as electron-withdrawing substituents at *m*- and *p*-positions, efficiently proceeded to give the corresponding benzamide derivatives in high yields. In the hydration of *o*-, *m*-, and *p*-tolunitriles (**1b**–**1d**), the reaction rate of *o*-tolunitrile (**1b**) was much smaller than those of *m*- and *p*-derivatives **1c** and **1d**, and the steric effect was very significant. This observation suggests the coordination of nitriles on the surface of MnO_2. A similar steric effect has been reported for $Ru(OH)_x/Al_2O_3$-catalyzed hydration.[3f] Hydration of heteroaromatic nitriles such as pyridine (**1j**) and thiophene (**1k**) carbonitriles efficiently proceeded to afford the corresponding heteroaromatic amides in high yields. An unsaturated nitrile (**1l**) gave the corresponding unsaturated amide. The hydration of a less reactive aliphatic nitrile **1m** also proceeded to afford the corresponding aliphatic amide, though the yield was moderate. Moreover, under the solvent-free conditions, the hydration of various kinds of nitriles also efficiently proceeded even in the case of "solid substrates" such as **1g** and **1h**[10] (see values in the parentheses in Table 2).

The gram-scale hydration was also effective; the hydration of **1g** (1.03 g) efficiently proceeded without any decrease in the performance in comparison with the small-scale transformation in Table 2, and **2g** was produced in 94% yield (by GC). MnO_2 was separated by filtration and washed with ethanol and acetone. Evaporation of the combined filtrate gave a crude product followed by rinsing with *n*-hexane (ca. 10 mL), giving 1.07 g of **2g** (92% isolated yield, >99% purity by GC and NMR) (eq 1).



1g (1.03 g) **2g** (1.07 g, 92% yield) (1)

Table 2. Hydration of various nitriles with amorphous MnO_2[a]

Entry	Substrate		Product		Time / h	Yield / %
1		**1a**		**2a**	1	87 (94[d])
2[b]		**1a**		**2a**	1	88 (93[d])
3[c]		**1a**		**2a**	3	80
4		**1b**		**2b**	1	13
5		**1c**		**2c**	1	82
6[b]		**1c**		**2c**	1	83
7		**1d**		**2d**	1	80
8		**1e**		**2e**	1	94 (93[d])
9		**1f**		**2f**	1	86
10[b]		**1f**		**2f**	1	90
11		**1g**		**2g**	1	97 (>99[d])
12[b]		**1g**		**2g**	1	97
13		**1h**		**2h**	1	99 (>99[d])
14[b]		**1h**		**2h**	1	99
15		**1i**		**2i**	3	96
16		**1j**		**2j**	1	>99 (99[d])
17[b]		**1j**		**2j**	1	>99
18		**1k**		**2k**	1	96
19		**1l**		**2l**	2	93 (96[d])
20[b]		**1l**		**2l**	2	95
21[e]		**1m**		**2m**	12	54

[a]Reaction conditions: substrate (0.5 mmol), MnO_2 (50 mg), water (2 equiv with respect to substrates), 1,4-dioxane (2 mL), 140 °C (bath temp), under Ar. Yields were determined by GC using naphthalene or biphenyl as an internal standard. [b]Reuse experiments. [c]MnO_2 (10 mg). [d]Under the solvent-free conditions. [e]MnO_2 (100 mg), 150 °C (bath temp).

In order to verify whether the observed catalysis is derived from solid amorphous MnO_2 or leached manganese species, the hydration of **1a** was carried out under the conditions described in Table 1, and MnO_2 was removed from the reaction mixture by filtration at 50–60% conversion of **1a**. Then, the filtrate was again heated at 140 °C. In this case, no further production of **2a** was observed. It was confirmed by ICP-AES analysis that no manganese species was detected in the filtrate. All these facts can rule out any contribution to the observed catalysis from manganese species that leached into the reaction solution, and the observed catalysis is intrinsically heterogeneous.[11] In addition, the retrieved MnO_2 catalyst[9] could be reused without an appreciable loss of high catalytic performance for various nitriles (Entries 2, 6, 10, 12, 14, 17, and 20 in Table 2).

The catalytic activities of amorphous MnO_2 for the hydration of *p*-substituted benzonitrile derivatives increased in the

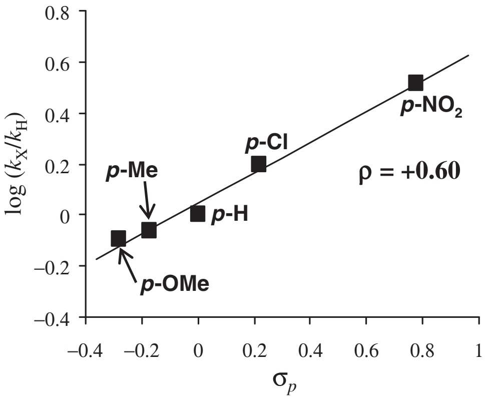


Figure 1. Hammett plot for competitive hydration of benzonitrile (**1a**) and *p*-substituted benzonitrile derivatives **1d**, **1f**, **1g**, and **1h**. Reaction conditions: **1a** (0.25 mmol), *p*-substituted benzonitrile (0.25 mmol), amorphous MnO_2 (50 mg), water (2 equiv with respect to substrates), 1,4-dioxane (2 mL), 140 °C (bath temp), under Ar.

order of **1f** (0.80) < **1d** (0.87) < **1a** (1.00) < **1g** (1.57) < **1h** (3.29), where the values in the parentheses are the relative rates and the rate for **1a** is taken as a unity. The slope of the linear line in Figure 1 gave the Hammett ρ value of $+0.60$. The positive value of the Hammett ρ can be interpreted the formation of a negatively charged transition state. A very similar Hammett ρ value of $+0.58$ has been reported for the CeO_2-catalyzed hydration of substituted 2-cyanopyridine derivatives, where the activation (polarization) of water on the surface of CeO_2 followed by nucleophilic attack of $OH^{\delta-}$ species to a nitrile carbon is proposed.[3j] In the same way, the present MnO_2-catalyzed hydration would proceed through the above-mentioned reaction mechanism.

In the hydration of **1a** with amorphous MnO_2, the reaction rate with D_2O[12] was almost the same as that with H_2O, and no kinetic isotope effect was observed ($k_H/k_D = 0.96$). As mentioned above, the reaction rate was almost independent of water concentrations (Entries 1 and 2 in Table 1). Taking all the above-mentioned results into account, the nucleophilic attack of $OH^{\delta-}$ species to a nitrile carbon is likely included in the rate-limiting step for the present MnO_2-catalyzed hydration.

In summary, simple amorphous MnO_2 could act as an efficient, reusable heterogeneous catalyst for hydration of various kinds of structurally diverse nitriles including aromatic, heteroaromatic, unsaturated, and aliphatic ones even in the presence of reduced amounts of water (2 equiv or less) in 1,4-dioxane or even under solvent-free conditions. Though MnO_2 is known to be effective for hydration of limited nitriles in water,[3g–3i] the above-demonstrated high performance and usefulness of amorphous MnO_2 are previously unknown and new findings.

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8 Amorphous MnO_2 was prepared as follows: $MnSO_4 \cdot H_2O$ (8.8 g) was dissolved in deionized water (30 mL). To this solution, a solution consisting of $KMnO_4$ (5.89 g) in deionized water (100 mL) was added dropwise under continuous stirring. The resulting mixture was stirred at room temperature for 10 min. Then, the solid was filtered off, washed with deionized water (ca. 4 L), and dried in an oven at 150 °C for 12 h, affording 5.0 g of amorphous MnO_2 as a dark brown powder (BET surface area: $304\,m^2\,g^{-1}$).

9 Procedure for nitrile hydration: Amorphous MnO_2 (50–100 mg), 1,4-dioxane (2 mL) (or solvent-free), nitrile (0.5 mmol), and water (1–2 equiv) were placed in a Teflon vessel with a magnetic stirring bar. The Teflon vessel was attached inside an autoclave, and the reaction was carried out at 140–150 °C (bath temp) in 3 atm of Ar. After the hydration was completed, MnO_2 was separated by filtration (>95% catalyst recovery, BET surface area of retrieved MnO_2: $197\,m^2\,g^{-1}$) and washed with ethanol and acetone. The product was isolated by evaporation of volatiles (combined filtrate), followed by rinse with *n*-hexane. The retrieved MnO_2 was washed with water and then dried at 150 °C under air atmosphere for 1 h just before using for the reuse experiment.

10 The melting points of **1g** and **1h** are 91.5 and 145.5 °C, respectively.

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13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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