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Editor's Choice

Manganese Oxide-catalyzed Additive- and Solvent-free Aerobic Oxidative Synthesis of Primary Amides from Primary Amines

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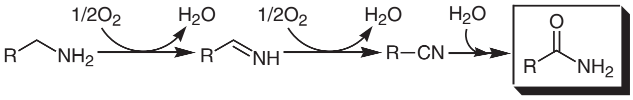
Various kinds of primary amides could be synthesized through indirect aerobic oxygenation of primary amines using simple amorphous MnO_2 under additive- and solvent-free conditions. The catalyst/product separation was very easy, and the retrieved MnO_2 catalyst could be reused without an appreciable loss of its high catalytic performance.

Primary amides are one of the most important chemicals that have widely been utilized as raw materials for engineering plastics, intensifiers of perfume, antiblock reagents, color pigments for inks, detergents, lubricants, and intermediates in peptide and protein synthesis.[1] Even at present, ammonolysis of activated carboxylic acid derivatives with ammonia is still utilized for synthesis of primary amides.[2] However, this procedure requires stoichiometric reagents such as thionyl chloride and carbodiimide for preactivation of carboxylic acids, and at least equimolar amounts of by-products are formed not only during the aminolysis but also the preactivation step.[2] Therefore, instead of this antiquated procedure, the development of efficient green procedures for synthesis of primary amides using various kinds of starting materials is a subject of urgency.[3–5]

Primary amines are candidates as desirable starting materials for primary amides because they are readily available and inexpensive. However, in general, it is very difficult to oxygenate primary amines directly to primary amides, and reactive stoichiometric reagents such as 2,6-di-*tert*-butyl-*p*-benzoquinone[6] and in situ-generated RuO_4 (from $RuO_2{\cdot}nH_2O$ and $NaIO_4$)[7] have typically been used for indirect oxygenation of primary amines. Though oxygenation of primary amines through the dehydrogenation–hydration sequence using molecular oxygen (air) and water (Scheme 1) is one of the greenest procedures, only two systems catalyzed by a supported ruthenium hydroxide ($Ru(OH)_x/Al_2O_3$)[8] and a cryptomelane-type manganese oxide-based octahedral molecular sieve (OMS-2)[9] have previously been reported to date, as far as we know. In the system of $Ru(OH)_x/Al_2O_3$, a large amount of water (reactant) is indispensable because of the very low catalytic activity of $Ru(OH)_x/Al_2O_3$ for nitrile hydration (the last step of the sequence).[8] The OMS-2-catalyzed oxygenation requires "aqueous ammonia" as an indispensable additive to prevent the formation of *N*-alkylimines (by-products) and to promote nitrile hydration.[9]



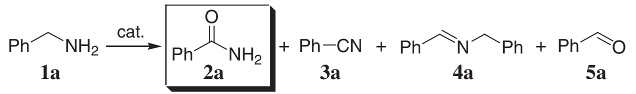
Scheme 1. Reaction path for oxygenation of primary amines to primary amides through the dehydrogenation–hydration sequence.

Very recently, we have reported that amorphous MnO_2 (with a large specific surface area)[10] shows extremely high catalytic performance for nitrile hydration with only reduced amounts of water (2 equiv or less with respect to nitriles, Table S1)[11,19] and that the catalytic activity of amorphous MnO_2 is much higher than that of OMS-2 (Table S2).[11,19] In addition, it is well known that manganese-based oxides possess high dehydrogenation abilities for various substrates including alcohols and amines.[9,12] Therefore, it is expected that amorphous MnO_2 can efficiently promote oxygenation of primary amines through the dehydrogenation–hydration sequence in the absence of any additives (Scheme 1).

As we expected, we herein found that amorphous MnO_2 can promote aerobic oxygenation of various kinds of primary amines to primary amides using molecular oxygen (air) as a sole oxidant "without any additives (even without addition of water)." During the transformation, 2 equiv of water is generated (Scheme 1), and the last step of nitrile hydration proceeds with the in situ-generated water.[11] It is emphasized that the MnO_2-catalyzed oxygenation efficiently proceeds even under "solvent-free" conditions.

Initially, various catalysts including previously reported ones such as $Ru(OH)_x/Al_2O_3$[8] and OMS-2[9] were applied to the oxygenation of benzylamine (**1a**) to benzamide (**2a**) (Table 1).[13] Among them, manganese-based oxides such as amorphous MnO_2 and OMS-2 gave significant yields of **2a** (58–74% yields), and the catalytic activity of amorphous MnO_2 was higher than those of other manganese-based oxides such as OMS-2,[9] β-MnO_2, and birnessite-type MnO_2. When the oxygenation of **1a** was carried out with amorphous MnO_2 at 130 °C (bath temp.) in 1,4-dioxane for 1 h, **2a** and benzonitrile (**3a**) were obtained in 74% and 23% yields, respectively. When the reaction time was prolonged to 3 h, **3a** was completely hydrated to give a quantitative yield of **2a**. Although OMS-2 gave **2a** and **3a** in 58% and 20% yields, respectively, undesirable by-products such as *N*-benzylidenebenzylamine (**4a**) and benzaldehyde (**5a**) were also formed under the conditions described in Table 1 (without aqueous ammonia[9]).[14] In the case of birnessite-type MnO_2, **2a** and **3a** were hardly produced, and **4a** was produced as a major product (54% yield). $KMnO_4$ and $MnSO_4{\cdot}H_2O$ (1 equiv with respect to **1a**, precursors for amorphous MnO_2[10]) were not effective for the oxygenation, suggesting that soluble manganese species are not active for the present oxygenation.[15] Indeed, when amorphous MnO_2 (or OMS-2) was removed from the reaction mixture by filtration at ca. 50% conversion of **1a** and the filtrate was again heated at 130 °C in 6 atm of air, no further production of **2a** and **3a** was observed. Thus, the above-mentioned results can rule out any contribution to the observed catalysis from manganese species that leached into the reaction solution, and the observed catalysis for the present oxygenation is truly heterogeneous.[16]

Table 1. Oxygenation of benzylamine (**1a**) to benzamide (**2a**)[a]

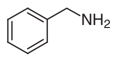
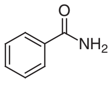
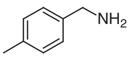
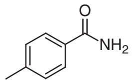
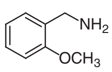
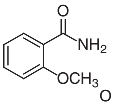
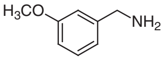
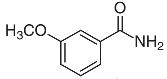
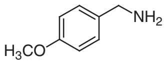
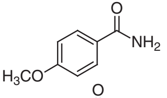
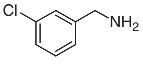
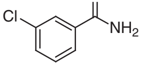
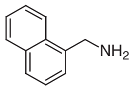
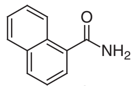
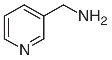
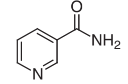
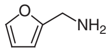
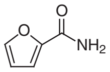
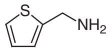
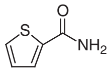


1a **2a** **3a** **4a** **5a**

Entry	Catalyst	Yield/%			
		2a	**3a**	**4a**	**5a**
1	Amorphous MnO_2	74	23	<1	<1
2[b]	Amorphous MnO_2	92	<1	<1	<1
3	OMS-2	58	20	6	5
4[c]	β-MnO_2	4	45	36	4
5	Birnessite-type MnO_2	<1	2	54	<1
6[d]	$KMnO_4$	<1	2	9	<1
7[d]	$MnSO_4 \cdot H_2O$	<1	<1	<1	<1
8	Co_3O_4	<1	3	48	<1
9[c]	CeO_2	<1	<1	9	<1
10	$Ru(OH)_x/Al_2O_3$	<1	15	5	<1
11[c]	RuHAP	<1	28	5	<1
12	None	<1	<1	<1	<1

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (50 mg), 1,4-dioxane (2 mL), 130 °C (bath temp.), air (6 atm), 1 h. Yields were determined by GC using naphthalene as an internal standard. [b] Under solvent-free conditions. Amorphous MnO_2 (100 mg), 3 h. [c] Commercially available (see the Supporting Information[19]). [d] Mn salts (0.5 mmol).

Table 2. Solvent-free oxygenation of various primary amines with amorphous MnO_2[a]

Entry	Substrate		Product		Yield/%
1		**1a**		**2a**	92 (90)
2[b]		**1a**		**2a**	94
3[c]		**1a**		**2a**	81
4		**1b**		**2b**	>99 (94)
5		**1c**		**2c**	91
6		**1d**		**2d**	93
7		**1e**		**2e**	98 (89)
8[b]		**1e**		**2e**	97
9		**1f**		**2f**	87
10		**1g**		**2g**	60
11		**1h**		**2h**	96 (86)
12[b]		**1h**		**2h**	98
13		**1i**		**2i**	40[d]
14[e]		**1j**		**2j**	89

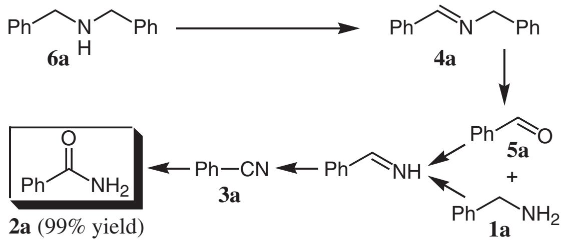
[a] Reaction conditions: substrate (0.5 mmol), amorphous MnO_2 (100 mg), 130 °C (bath temp.), air (6 atm), 3 h. Yields were determined by GC using naphthalene or biphenyl as an internal standard (see Table S4 in more detail[19]). Values in the parentheses are isolated yields. [b] Reuse experiments. [c] Amorphous MnO_2 (20 mg). [d] Unidentified by-products were formed. [e] 2 h.

Co_3O_4 and CeO_2 did not give **2a** as well as **3a**, and the corresponding alkylimine **4a** was formed as a major product (9–48% yields). Supported ruthenium catalysts such as $Ru(OH)_x/Al_2O_3$[8] and RuHAP (HAP: hydroxyapatite)[17] did not work well for the synthesis of **2a** under the conditions described in Table 1. 1,4-Dioxane and toluene were good solvents for the oxygenation of **1a**, giving 54–74% yields of **2a** (Table S3).[19] On the other hand, highly polar solvents such as *N*,*N*-dimethylformamide (DMF) and ethanol gave lower yields of **2a** (1–24% yields) (Table S3).[19] Notably, the oxygenation also efficiently proceeded even under "solvent-free" conditions, affording **2a** in 92% yield without formation of any by-products (Entry 2 in Table 1). We hereafter carried out oxygenation under solvent-free conditions.[13]

Next, the scope of the present MnO_2-catalyzed solvent-free oxygenation of various kinds of structurally diverse primary amines was examined (Table 2). Typically, oxygenation was carried out with 100 mg of amorphous MnO_2. The amount of amorphous MnO_2 could be much reduced. For example, the oxygenation of **1a** with 20 mg of amorphous MnO_2 gave 81% yield of **2a** under the conditions described in Table 2 (Entry 3). Oxygenation of benzylamine derivatives **1a**–**1g**, which contain electron-donating as well as electron-withdrawing substituents at different positions, efficiently proceeded to afford the corresponding benzamide derivatives ($\geq$60% yields). Oxygenation of *ortho*-, *meta*-, and *para*-substituted benzylamine derivatives **1c**–**1e** proceeded well, and the yields of the corresponding substituted benzamide derivatives were almost equal (91–98% yields), suggesting that the steric effect of substituents on the phenyl rings is negligible. Heteroaromatic methylamines such as pyridine (**1h**), furan (**1i**), and thiophene (**1j**) methylamines gave the corresponding heteroaromatic amides in moderate to high yields (40–96% yields). Unfortunately, the oxygenation of an aliphatic amine of *n*-octylamine was unsuccessful (2% yield of *n*-octanamide at >99% conversion of *n*-octylamine) because of formation of many unidentified by-products.

After oxygenation was completed, amorphous MnO_2 was easily retrieved from the reaction mixture by simple filtration with >95% recovery.[13] The retrieved MnO_2 catalyst could be reused without an appreciable loss of its high catalytic performance for oxygenation of various primary amines (Entries 2, 8, and 12 in Table 2).

Furthermore, we also found that primary amides could be synthesized from "secondary amines" and aqueous ammonia (Scheme 2). For example, dibenzylamine (**6a**) could be converted into **2a** in 99% yield in the presence of amorphous MnO_2 under solvent-free conditions. This transformation is composed of six relay steps. The reaction profile showed that an alkylimine **4a** was initially produced. We confirmed that **4a** was quantitatively converted into **2a** under the same conditions in the



Scheme 2. Transformation of dibenzylamine (**6a**) to benzamide (**2a**). Reaction conditions: **6a** (0.25 mmol), amorphous MnO_2 (100 mg), 28% aq. ammonia (50 µL, ca. 2.6 equiv with respect to **6a**), 130 °C (bath temp.), air (6 atm), 3 h.

presence of aqueous ammonia. In addition, an aldehyde **5a** was also quantitatively converted into **2a** under the same conditions in the presence of aqueous ammonia.[18] Therefore, all relay steps in Scheme 2 can be promoted by amorphous MnO_2.[9,11]

In summary, simple amorphous MnO_2 could act as an efficient, reusable catalyst for indirect oxygenation of primary amines through the dehydrogenation–hydration sequence. The present procedure has the following significant advantages in comparison with previously reported systems; (i) oxygenation efficiently proceeds even under additive- and solvent-free conditions, (ii) catalyst separation and product isolation are very easy, (iii) amorphous MnO_2 is easily prepared and rather inexpensive in comparison with precious metal-based catalysts, e.g., $Ru(OH)_x/Al_2O_3$,[8] and/or (iv) MnO_2 can be reused without an appreciable loss of its high catalytic performance for various substrates. This convenient procedure demonstrated herein will provide a green route to primary amides, which can completely avoid utilization of (hazardous) stoichiometric reagents and formation of vast amounts of inorganic by-products, and will be one of the choices for green amide synthesis.

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

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13 A typical procedure for oxygenation: Amorphous MnO_2 (100 mg) and a primary amine **1a** (0.5 mmol) were placed in a Teflon vessel with a magnetic stir bar (conditions described in Table 2). The Teflon vessel was attached inside an autoclave, and the reaction was carried out at 130 °C (bath temp.) in 6 atm of air. After the oxygenation was completed (3 h), MnO_2 was separated by filtration (>95% catalyst recovery, BET surface area of retrieved MnO_2: $190\,m^2\,g^{-1}$) and washed with ethanol. Then, the filtrate was analyzed by GC. The product **2a** was isolated by evaporation of volatiles, followed by rinse with *n*-hexane (54.3 mg, 90% isolated yield). 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.

14 Alkylimines and aldehydes are possibly formed through the hydrolytic decomposition of aldimine intermediates. The amount and density of acidic sites of OMS-2 were $1.23\,mmol\,g^{-1}$ and $12.7\,\mu mol\,m^{-2}$, respectively, and larger than those of amorphous MnO_2 (amount: $1.04\,mmol\,g^{-1}$; density: $3.42\,\mu mol\,m^{-2}$) (Table S5[19]). Therefore, it is likely that OMS-2 has higher ability for decomposition of aldimine intermediates to undesirable by-products such as alkylimines and aldehydes.

15 Under the conditions described in Table 1, $KMnO_4$ and $MnSO_4 \cdot H_2O$ were slightly soluble in the reaction solution. Even when the reaction was carried out under the conditions described in Table 1 with water (1 mL, manganese salts were soluble in this case), the desired amide **2a** was not produced at all.

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