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Facile synthesis of nitriles *via* manganese oxide promoted oxidative dehydrosulfurization of primary thioamides†

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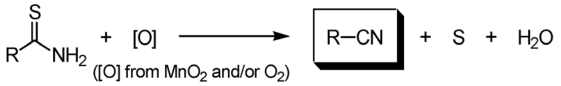
In the presence of manganese oxides, dehydrosulfurization of various kinds of primary thioamides including aromatic, heterocyclic, and aliphatic ones efficiently proceeded to give the corresponding nitriles in high yields. The observed catalysis was truly heterogeneous, and manganese oxides could be reused.

Nitriles have widely been utilized in production of pharmaceuticals, agricultural chemicals, and fine chemicals.[1] Classically, nitriles have been synthesized by non-green procedures using hazardous inorganic and organic cyanides.[1] Instead of these antiquated procedures, several efficient catalytic procedures for nitrile synthesis from methylarenes (ammoxidation),[2] alcohols (ammoxidation),[3] and amides (dehydration)[4] have been developed until now though these systems have several shortcomings such as harsh reaction conditions (typically $\geq$ 130 °C) and/or limited substrate scope.[2–4] In order to expand possible choices of nitrile synthesis, the development of efficient catalytic procedures from a variety of starting materials is a very important subject.

Thioamides have attracted considerable attention in organic synthesis as versatile synthons due to their unique reactivity and wide availability.[5] For example, various important chemicals including nitriles,[6] amides,[7] amidines,[8] and sulfur-containing heterocycles (*e.g.*, thiazoles, thiazolins, and thiazolinons)[5a] have been synthesized from thioamides in the presence of stoichiometric reagents and/or transition metal catalysts. With regard to synthesis of nitriles *via* dehydrosulfurization of primary thioamides, metal carboxylates,[6a,b] butyltin oxide,[6c] organotelluroxides,[6d–f] organotellurinic acids,[6d–f] organoselenoxides,[6f,g] diphosphorus tetraiodide,[6h] and organic halides/inorganic bases[6i] have generally been utilized in stoichiometric amounts because these reagents are irreversibly converted into the corresponding sulfides.[5b,6] Thus, to date there have been no reports on efficient "catalytic" dehydrosulfurization of primary thioamides, as far as we know.

Herein, we demonstrate for the first time heterogeneously catalyzed selective dehydrosulfurization of primary thioamides to nitriles with simple manganese oxides [eqn (1)]. In the presence of amorphous MnO_2, various kinds of primary thioamides including aromatic, heterocyclic, and aliphatic ones could be converted into the corresponding nitriles in high yields under very mild conditions.



(1)

Initially, 28 kinds of (metal) oxides (except for expensive platinum group metal oxides, Table S1, ESI†) were examined for the dehydrosulfurization of thiobenzamide (**1a**) to benzonitrile (**2a**) in chloroform at 30 °C.‡ Among oxides examined, amorphous MnO_2 showed the highest performance for the dehydrosulfurization; 98% yield of **2a** was obtained in only 15 min (Fig. S1, ESI†). Amounts of amorphous MnO_2 could be reduced; even when the dehydrosulfurization of **1a** was carried out using a reduced amount of amorphous MnO_2 (9 mg, 41 mol% with respect to **1a**), 87% yield of **2a** was obtained in 1 h (at 100 °C in toluene). Other oxides gave much lower yields of **2a** ($\leq$10% yields, Fig. S1, ESI†). The activities of a series of manganese oxides (amorphous MnO_2, α-MnO_2, β-MnO_2, and δ-MnO_2) for the dehydrosulfurization of **1a** increased with an increase in their specific surface areas (Table 1), and the reaction rates were approximately proportional to their specific surface areas (Fig. S2, ESI†). While $KMnO_4$ was converted into amorphous MnO_2 during the dehydrosulfurization under the conditions described in Table 1, **2a** was obtained in 97% yield. Probably, **1a** and/or the hydrogen sulfide formed would act as reductant(s) for $KMnO_4$, and the dehydrosulfurization was likely promoted by the *in situ* generated MnO_2. $MnSO_4{\cdot}H_2O$ and

Table 1 Dehydrosulfurization of thiobenzamide (**1a**) to benzonitrile (**2a**) by various manganese oxides and salts[a]

Entry	Oxide or salt	BET surface area ($m^2\ g^{-1}$)	Yield of **2a** (%)
1	Amorphous MnO_2	304	98
2	α-MnO_2	97	51
3	β-MnO_2	54	42
4	δ-MnO_2	36	24
5	$KMnO_4$	—	97
6	$MnSO_4{\cdot}H_2O$	—	4
7	MnS	—	3
8	None	—	<1

[a] Reaction conditions: **1a** (0.2 mmol), oxide or salt (50 mg), chloroform (3 mL), air (1 atm), 30 °C, 15 min. Yields were determined by GC using naphthalene as an internal standard. See also Fig. S2, ESI.

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† Electronic supplementary information (ESI) available: Experimental details, Tables S1 and S2, and Fig. S1–S4. See DOI: 10.1039/c2cc36635e

MnS were not effective for the dehydrosulfurization. Chloroform, toluene, acetonitrile, and acetone were good solvents, giving **2a** in moderate to high yields (65–98% yields, Table S2, ESI†). On the other hand, 1,4-dioxane and *N*,*N*-dimethylformamide (DMF) were not effective for the present dehydrosulfurization (≤21% yields, Table S2, ESI†).

To verify whether the observed catalysis is derived from solid amorphous MnO_2 or leached manganese species, the dehydrosulfurization of **1a** to **2a** was carried out under the conditions described in Table 1, and MnO_2 was removed from the reaction mixture by filtration at *ca.* 30% conversion of **1a**. When the reaction was again carried out with the filtrate, no further production of **2a** was observed (Fig. S3, ESI†). It was confirmed by ICP-AES analysis that no manganese species was detected in the filtrate. Thus, the above-mentioned results show that the observed catalysis for the present dehydrosulfurization is truly heterogeneous.[9]

After the dehydrosulfurization of **1a** was completed, amorphous MnO_2 was easily retrieved from the reaction mixture by simple filtration with >95% recovery. The retrieved MnO_2 could be reused for the dehydrosulfurization of **1a**; for the fifth reuse, 70% yield of **2a** was still obtained, while the formation rates of **2a** were gradually decreased by repeating reuse experiments (Fig. 1). The main reason for the deactivation of amorphous MnO_2 is probably a decrease in the specific surface area during the transformation and/or the drying step before reuse (after the fifth reuse: 153 $m^2\ g^{-1}$, *cf.* fresh one: 304 $m^2\ g^{-1}$, Fig. S2, ESI†). When prolonging the reaction time to 40 min (from 15 min), **2a** was obtained in 98% yield even for the sixth reuse (Fig. 1). The total turnover number based on total amount of manganese species in amorphous MnO_2 reached up to 2.6 after the sixth reuse.

In contrast, stable crystalline α-MnO_2 could be reused without any loss of its performance; when the dehydrosulfurization of **1a** was carried out with the retrieved α-MnO_2, the reaction rate and the final yield of **2a** were almost the same as those with fresh α-MnO_2 (Fig. S4, ESI†).

Next, the scope of the present MnO_2-promoted dehydrosulfurization of primary thioamides was examined (Table 2). The dehydrosulfurization of thiobenzamide derivatives (**1a–1g**), which contain electron-donating as well as electron-withdrawing substituents, efficiently proceeded to give the corresponding substituted benzonitrile derivatives in high yields (≥ 82% yields). In the case of **1e**, no dechlorination proceeded. Notably, a phenolic thioamide of **1b** was selectively converted into the corresponding cyanophenol without any side reactions. Heterocyclic thioamides (**1h–1j**) gave the corresponding heterocyclic nitriles in high yields (≥ 83 yields). Less reactive aliphatic thioamides (**1k–1m**) could also be converted into the corresponding aliphatic nitriles (≥ 71% yields). In the case of **1m**, the dehydrosulfurization efficiently

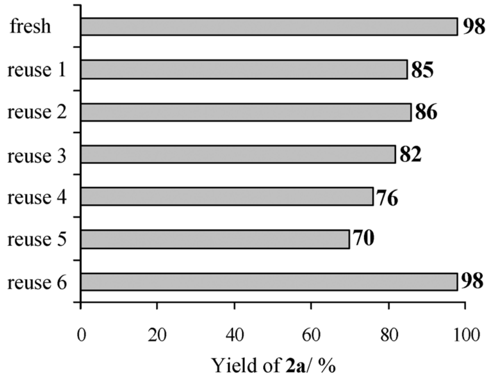
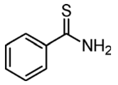
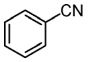
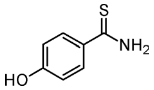
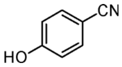
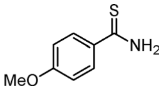
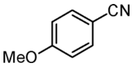
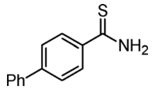
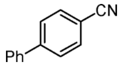
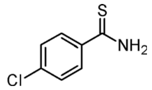
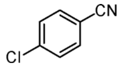
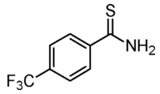
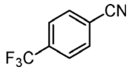
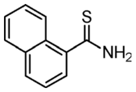
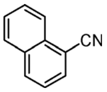
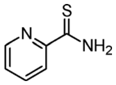
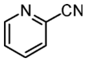
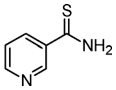
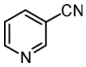
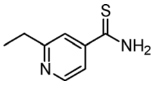
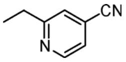
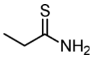
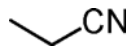
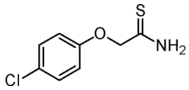
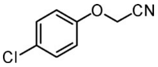
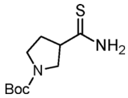
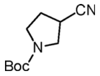
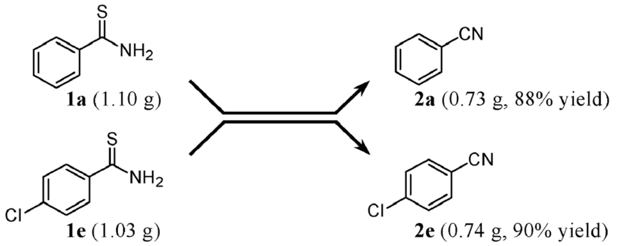


Fig. 1 Reuse of amorphous MnO_2. Reaction conditions: **1a** (0.2 mmol), amorphous MnO_2 (50 mg), chloroform (3 mL), air (1 atm), 30 °C, 15 min. For the sixth reuse experiment, the reaction time was prolonged to 40 min.

Table 2 Dehydrosulfurization of various nitriles[a]

Entry	Substrate		Time (min)	Product		Yield (%)
1		**1a**	15		**2a**	98
2[b]		**1b**	30		**2b**	82
3		**1c**	45		**2c**	86
4[c]		**1d**	60		**2d**	90
5		**1e**	15		**2e**	92
6		**1f**	15		**2f**	86
7		**1g**	15		**2g**	86
8[d]		**1h**	30		**2h**	83
9[d]		**1i**	30		**2i**	97
10[d]		**1j**	15		**2j**	97
11		**1k**	20		**2k**	81
12[e]		**1l**	60		**2l**	71
13		**1m**	15		**2m**	>99

[a] Reaction conditions: substrate (0.2 mmol), amorphous MnO_2 (50 mg), chloroform (3 mL), air (1 atm), 30 °C. Yields were determined by GC using naphthalene as an internal standard. [b] Acetone (3 mL). [c] Toluene/acetone (4 mL/2 mL). [d] MnO_2 (100 mg), acetone (5 mL). [e] Substrate (0.1 mmol), MnO_2 (25 mg). Boc = *tert*-butoxycarbonyl.



Scheme 1 Gram-scale dehydrosulfurization. Reaction conditions for **1a**: **1a** (1.10 g), amorphous MnO_2 (2 g), chloroform (120 mL), air (1 atm), room temp. (*ca.* 25 °C), 30 min. Reaction conditions for **1e**: **1e** (1.03 g), amorphous MnO_2 (1.5 g), chloroform (90 mL), air (1 atm), room temp. (*ca.* 25 °C), 30 min. In the dehydrosulfurization of **1a** and **1e**, elemental sulfur was also isolated in 83% (0.21 g) and 74% (0.19 g) yields, respectively.

proceeded without deprotection of the *tert*-butoxycarbonyl group.

In order to demonstrate practical usefulness of the present dehydrosulfurization, the gram-scale transformations of **1a** (1.10 g) and **1e** (1.03 g) were carried out at room temperature (Scheme 1). These transformations also efficiently proceeded without any decrease in the performance in comparison with the small-scale transformations. After the reaction was completed, amorphous MnO_2 was separated by filtration and washed with chloroform. Evaporation of chloroform gave crude mixtures containing nitriles and elemental sulfur (S^0).§ Elemental sulfur is intrinsically insoluble, and the desired nitriles are soluble in acetone. Thus, acetone was added to the crude mixtures, followed by filtration to retrieve elemental sulfur (> 99.99% purity by elemental analysis). Finally, evaporation of acetone afforded 0.73 g of **2a** (88% isolated yield) and 0.74 g of **2e** (90% isolated yield). The purities of isolated **2a** and **2e** were > 95% (by GC and NMR analyses).

In the previously reported dehydrosulfurization systems, the reagents are irreversibly converted into the corresponding sulfides possibly by reaction with S^{2-} species such as H_2S, HS^-, and S^{2-}.[5b,6] Thus, at least one equivalent (two equivalents in some cases) of reagents is required in the previous systems, and their repeated use is intrinsically impossible.[6] In contrast, it was confirmed by XPS analysis that no manganese sulfide was detected in the retrieved amorphous MnO_2 after the dehydrosulfurization of **1a**.¶ In addition, almost equimolar amounts of elemental sulfur with respect to nitriles could be isolated, as shown in Scheme 1. These results clearly indicate that S^{2-} species can be oxidized to S^0 species in the presence of manganese oxides even under the present mild reaction conditions. It is known that the electron transfer from S^{2-} species to manganese oxides smoothly proceeds to form oxidized sulfur species, *e.g.*, S^0.[10] The oxidizing ability of manganese oxides would enable their catalytic and repeated use for dehydrosulfurization (Fig. 1, Fig. S4, ESI†).

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Notes and references

‡ A typical procedure for dehydrosulfurization: **1a** (1.10 g, 8 mmol), amorphous MnO_2 (2 g), and chloroform (120 mL) were placed in a Pyrex-glass reactor with a magnetic stir bar, and the reaction was carried out at room temperature (*ca.* 25 °C) in 1 atm of air. After 30 min, MnO_2 was separated by filtration and washed with chloroform (> 95% recovery). Evaporation of chloroform gave crude mixtures containing **2a** and elemental sulfur. Then, acetone was added to the crude mixtures, followed by filtration to retrieve elemental sulfur (0.21 g, 83% yield). Evaporation of acetone afforded 0.73 g of **2a** (88% yield). The retrieved MnO_2 was washed with deionized water and dried at 150 °C prior to being used for the reuse experiment.

§ In the presence of nitriles, elemental sulfur (S_8) is soluble in chloroform but almost insoluble in acetone.

¶ The elemental analysis revealed that only a small amount of sulfur species was detected in the retrieved amorphous MnO_2 after the dehydrosulfurization of **1a** (below 1.1 wt%). It was confirmed by XPS analysis that the average oxidation state of the sulfur species was +4 (binding energy $2p_{3/2}$: 167.4 eV, *e.g.*, SO_2 and SO_3^{2-}). This sulfur species could completely be removed by simple washing with deionized water. In addition, the average oxidation of amorphous MnO_2 was preserved after the dehydrosulfurization of **1a**.

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