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Catalytic conversion of 5-hydroxymethylfurfural into 2,5-furandiamidine dihydrochloride

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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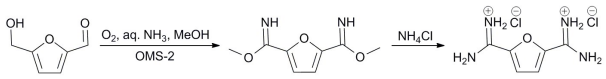
Via **implanting of nitrogen from aq.** NH_3 **into hydroxymethylfurfural (HMF), dimethyl furan-2,5-dicarboximidate was synthesized over manganese oxide catalyst. It was realized by the ammoxidation of HMF followed by methanol addition under mild reaction conditions. The imidate prepared *in situ* was further transformed into 2,5-furandiamidine dihydrochloride by reaction with ammonium chloride.**

In the past decade, catalytic transformation of renewable biomass has received intense global attention, in the interest of developing alternatives to fossil resources-derived chemicals and fuels.[1] Among the strategies for biomass processing, the production of 5-hydroxymethylfurfural (HMF) from hexoses is a typical example.[2] HMF is widely viewed as a versatile platform molecule. It can be selectively oxidized to 2,5-diformylfuran (DFF),[3] 2,5-furandicarboxylic acid[4] and 5-hydroxymethyl-2-furancarboxylic acid.[5] It also can be converted to 2,5-dimethylfuran, 2,5-dimethyltetrahydrofuran, 2,5-dihydroxymethylfuran and 2,5-dihydroxymethyltetra-hydrofuran via selective hydrogenation.[6] In addition, 5-ethoxymethylfurfural[7] and levulinic acid[8] were obtained from HMF via etherification and rehydration, respectively. These kinds of work have been focused on the modulation of the furan ring and adjacent hydroxymethyl/aldehyde group to generate fine chemicals, liquid fuel additives, polymer monomers, surfactants, *etc.*.[9]

Catalytical implanting of nitrogen into HMF is another way to the synthesis of value-added chemicals.[10] Amines were generally used as nitrogen sources as exampled in the synthesis of aminomethylfurans[11] and amide[12] reported by Stevens and Riisager's group, respetively. Starting from aq. NH_3 to directly synthesize nitrogen-containing HMF derivatives remains very challenging.[13] As far as we know, there is no report about the catalytically synthetic strategy of HMF processing with aq. NH_3.



Scheme 1 Catalytic transformation of 5-hydroxymethylfurfural to 2,5-furandiamidine dihydrochloride.

Aromatic diamidines, possessing homobifunctional amidine groups, are of unique biological and pharmaceutical significance.[14] For example, pentamidine was used to treat Pneumocystis-induced pneumonia whcih is the leading cause of morbidity and mortality in AIDS patients.[15] We present our work on the conversion of HMF into unsubstituted diarylamidines, via dimethyl furan-2,5-dicarboximidate (Scheme 1). The conversion of imidate into amidine by the reaction with ammonium chloride is well-established.[16] A major challenge needed in this reasearch is the transformation of HMF into dimethyl furan-2,5-dicarboximidate. The common procedure for imidate synthesis is the Pinner reaction of nitriles with alcohols under anhydrous acidic conditions or through a base-catalyzed process.[16a, 17] The nitriles are either prepared by the cyanation of halogenated compounds using toxic cyanide,[18] or by the ammoxidation of aldehydes or alcohols.[19] From the viewpoint of sustainable development and green chemistry, it is desirable to directly convert readily available aldehydes or alcohols, especially biomass-based aldehydes or alcohols into imidates under mild conditions.

Herein, on continuance of our work on the oxidative transformation of HMF,[3a-b, 4a, 20] we demonstrate a novel strategy to implant nitrogen into HMF to construct diimidate through one pot ammoxidation of HMF followed by methanol addition over manganese oxide under mild conditions. By reaction with ammonium chloride, the imidate prepared *in situ* was further transformed into 2,5-furandiamidine dihydrochloride.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x
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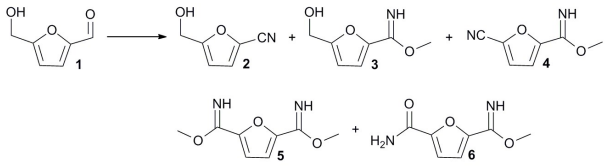


Scheme 2 Products of 5-hydroxymethylfurfural transformation.

The oxidative synthesis of dimethyl furan-2,5-dicarboximidate (**5**) from HMF, methanol and aq. NH_3 was conducted in an autoclave reactor with oxygen pressure up to 0.5 MPa and the products were shown in Scheme 2. Initially, a range of catalysts were explored (Fig. S5). Among the various catalysts examined, only manganese dioxides offered the target product with a complete conversion of HMF and the detailed results were presented in Table 1.

Table 1 Catalytic conversion of 5-hydroxymethylfurfural to dimethyl furan-2,5-dicarboximidate over different manganese oxides.[a]

Entry	Catalyst	Conversion (%)	Yield (%)				
			2	**3**	**4**	**5**	**6**
1	β-MnO_2	>99%	26	4	16	21	-
2	δ-MnO_2	>99%	-	36	7	14	-
3	γ-MnO_2	>99%	-	9	6	54	-
4	OMS-2	>99%	8	11	4	71	5
5[b]	OMS-2	>99%	-	-	-	29	12
6[c]	OMS-2	>99%	-	1	2	73	-
7[d]	OMS-2	>99%	-	5	-	88	6

[a]Reaction conditions: 0.25 mmol HMF, 0.1 g MnO_2, 120 μL aq. NH_3 (6 equiv.), 5 mL MeOH, 0.5 MPa O_2, 30 °C, 12 h. [b]60 °C, 2,5-furandiamide and 2,5-furandicarboxylic acid were identified by HPLC. [c]0.05 g OMS-2, oligomers were detected by MALDI-TOF. [d]30 h.

In the case of β-MnO_2 and δ-MnO_2, 5-hydroxymethyl-furonitrile (**2**) and 5-hydroxymethylfurancarboximidate (**3**) were the main products, respectively, indicating a low activity of hydroxymethyl group transformation (Table 1, entries 1-2). Target product **5** was effectively formed with 54% yield in the presence of γ-MnO_2 (Table 1, entry 3). Manganese oxide based octahedral molecular sieves (KMn_8O_{16}; OMS-2) gave the best result with 71% yield of **5**, as well as a small amount of product **2** (8%), **3** (11%), mononitrile imidate (**4**) (4%) and monoimidate amide (**6**) (5%) (Table 1, entry 4). This partly because OMS-2 is an efficient catalyst for oxidation of the hydroxymethyl group of HMF (Table S1, Entry 4). Subsequently, at increased temperature of 60 °C, the yield of **5** decreased to 29%, meanwhile 12% yield of **6** formed (Table 1, entry 5). In addition, the side-products of 2,5-furandiamide, and 2,5-furandicarboxylic acid were identified by high performance liquid chromatography. And a decreased catalyst loading of 0.05 g gave 73% yield of **5**, as well as a decreased total yield (Table 1, entry 6) due to the formation of oligomers. An 88% yield of **5** was formed upon prolonging reaction time to 30 h (Table 1, entry 7). To show the practical value of the present procedure, a gram-scale transformation of HMF (40-fold scale) was carried out. Subsequent purification gave **5** as white crystalline solid (74% isolated yield, Fig. S6). While only trace aldimine was detected when the reaction was conducted under N_2 atmosphere.

After the reaction was completed, OMS-2 was easily retrieved from the reaction mixture by simple centrifugation. The recovered OMS-2 catalyst could be reused at least five times without obvious loss of its catalytic performance (Fig. S7). There was no remarkable difference in X-ray powder diffraction patterns between the fresh OMS-2 and the recovered OMS-2 after the sixth use, showing the crystal structure of OMS-2 was preserved in the reaction conditions (Fig. S4). Inductively coupled plasma atomic-emission spectroscopy analysis revealed that no Mn species were detected in the reaction mixture, indicating the heterogeneous catalytic nature of OMS-2.

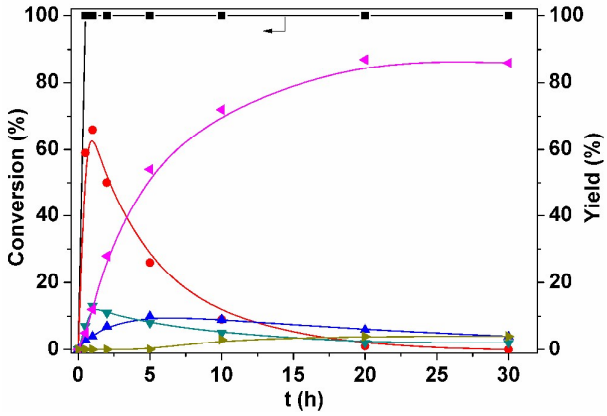


Fig.1 Time course of catalytic conversion of 5-hydroxymethylfurfural to dimethyl furan-2,5-dicarboximidate over OMS-2 (■ = conversion of **1**, ● = yield of **2**, ▲ = yield of **3**, ▼ = yield of **4**, ◀ = yield of **5**, ▶ = yield of **6**). Reaction conditions: 1.5 mmol HMF, 0.6 g OMS-2, 720 μL aq. NH_3 (6 equiv.), 30 mL MeOH, 0.5 MPa O_2, 30 °C.

Following the evolution of the time course, different compounds were detected, and Fig. 1 shows the kinetic curves. Initially, HMF was rapidly converted to **2** with a maximum of ca. 66% yield after 1 h. DFF was not detected. This behavior indicates the high activity of ammoxidation of

aldehyde group over OMS-2. And it is essential on the occasion of DFF ammoxidation (Scheme S1), which largely circumvents the polymerization of DFF with NH_3 by forming methanediamines,[21] with a characteristic absorption of aldimine group at 1636 cm^{-1} (Fig. S8-9). Instead of polymerization, ammoxidation product 2,5-dicyanofuran was detected at 0.5 h and 72% yield of **5** was obtained after 12 h (Fig. S10; Table S2, entry 4). In the case of β-MnO_2, δ-MnO_2 and γ-MnO_2, the polymerization reaction of DFF with NH_3 was obviously detected by real-time in-situ react Fourier transform infrared (React FT-IR, Fig. S11-13), and only trace **5** was detected (Table S2, entries 1-3). It may be attributed to relatively lower activity of ammoxidation of aldehyde group over other manganese oxides.

As the reaction prolonged, **2** was decreased accompanied by the increase of target product **5.** At the same time**,** minor amount of **3** and **4** also appeared. They first increased and then decreased with reaction proceeding. This indicates **3** and **4** were reaction intermediates. It is possible that **2** was first converted to **3** *via* methanol addition to the cyano group. Further ammoxidation of hydroxymethyl group of **3** led to the formation of **4**. **6** appeared after 5 h as a by-product, and kept at low concentration as reaction proceeding. **5** was stable under the reaction conditions, without forming amide **6** (Scheme S2). It is probable that **6** was generated from the **4** via hydrolysis of cyano group. Indeed, the cyano group could be hydrolyzed to acyl group under the reaction condition (Table S3, entry 5). The hydrolysis product of intermediate **2** was not detected. We presume the different reactivity of compound **4** and **2** might be a result of different activation capability on the cyano group by electron-withdrawing imidate and hydroxymethyl group, respectively. The cyano group of product **4** is activated by the strong electron-withdrawing imidate group. In comparison, the electron-withdrawing effect of hydroxymethyl group of intermediate **2** might be too weak to activate the cyano group hydrolysis at the mild reaction condition of 30 °C. The above results show the transformation of HMF to **5** involved the oxidation of hydroxymethyl group to aldehyde group, the ammoxidation of aldehyde group to cyano group and the methanol addition to cyano group.

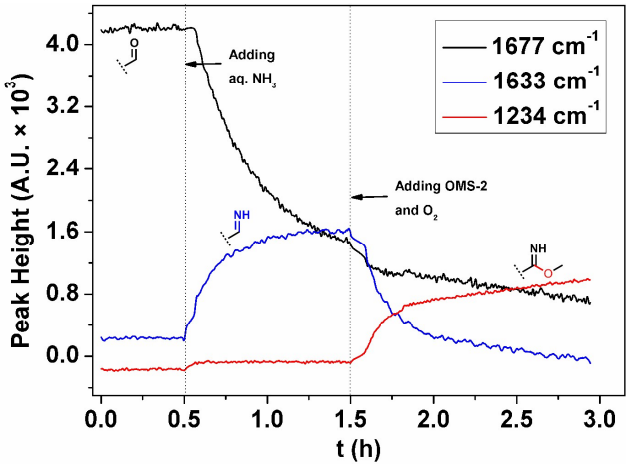


Fig.2 Time course of catalytic conversion of HMF characterized by real-time *in situ* React FT-IR. Reaction conditions: 1.25 mmol HMF, 10 mL MeOH, 30 °C, then 600 μL aq. NH_3 (6 equiv.) added at 0.5 h, 0.5 g OMS-2 and 0.5 MPa O_2 charged at 1.5 h.

In essence, the ammoxidation of aldehyde group to cyano group proceeded via aldimine group as the intermediate (see Fig. S25). Through React FT-IR spectral measurements the dynamic behavior of the aldimine group was clearly observed (Fig. 2 and Fig. S14-15). Initially, the intensity of typical band at 1677 cm^{-1} associated with C=O stretching vibration of aldehyde group of HMF significantly decreased upon adding aq. NH_3. Meanwhile the band at 1633 cm^{-1} associated with C=N stretching vibration of aldimine appeared, and increased its intensity to an equilibrium in 1 h. Afterwards, OMS-2 and O_2 were charged, and the intensity of the band at 1633 cm^{-1} rapidly decreased. Meanwhile, the bands at 1234 and 1197 cm^{-1} associated with C-O stretching vibration of imidate were simultaneously observed.

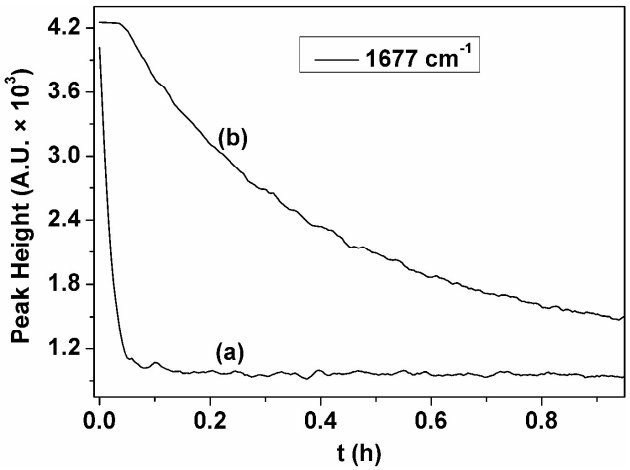
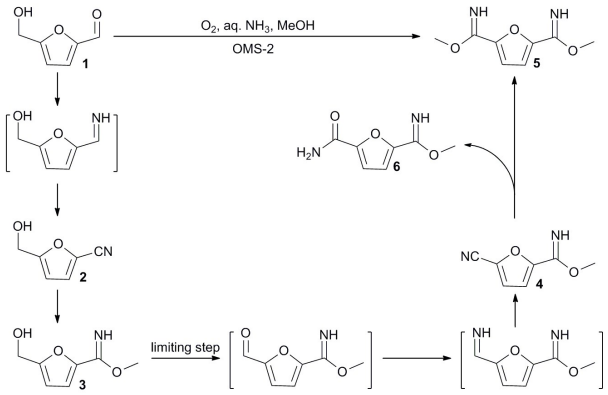


Fig.3 Relationship of peak height at 1677 cm^{-1}ascribed to C=O stretching vibration of the aldehyde group in HMF and reaction time (t) of HMF condensation with aq. NH_3. Reaction conditions: (a): 1.25 mmol HMF,0.5 g

OMS-2, 10 mL MeOH, 600 µL aq. NH_3 (6 equiv.), 30 °C; (b) is the same as (a) except no OMS-2 was added.

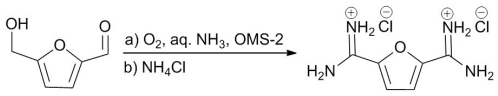
The effect of OMS-2 on the rate of condensation of the aldehyde group with NH_3 can be seen from the results given in Fig. 3. The intensity of peak at 1677 cm^{-1} ascribed to C=O stretching vibration of the aldehyde group in HMF decreased slightly in the absence of OMS-2 (Fig. 3b). While it decreased sharply with the addition of OMS-2 (Fig. 3a). This demonstrated that OMS-2 played an active role in promoting the condensation of aldehyde group of HMF with aq. NH_3.

The rate-limiting step was further investigated. As seen from Fig. 1, the enrichment of **2** in the initial stage suggested that the oxidation of the hydroxymethyl group into aldehyde, or the addition of the cyano group with methanol to imidate was the controlling step. If the latter was the controlling step, 2,5-dicyanofuran accumulation should occur during the further conversion of **2**, which was not detected. On the other hand, OMS-2 played no effect on the addition of 2,5-dicyanofuran with methanol (Fig. S16-18). In fact, the addition of 2,5-dicyanofuran with methanol proceeded smoothly over various manganese oxides, even in the absence of manganese oxide (Table S3). This might be a result of activation on the cyano group by another electron-withdrawing cyano or imidate group.[16a] In addition, the compounds **2** and **3** coexisted in the reaction mixture as shown in Fig. 1. All these results demonstrate that the oxidation of the hydroxymethyl group into aldehyde was the rate-limiting step.



Scheme 3 Proposed reaction pathway of catalytic transformation of 5-hydroxymethylfurfural to dimethyl furan-2,5-dicarboximidate over OMS-2.

Taking into account the kinetic behaviour of the different compounds above-mentioned, a reaction network is presented in Scheme 3. It can be seen that **5** synthesis follows the reactions of hydroxymethyl oxidation, aldehyde condensation with NH_3, aldimine oxidation, and nitrile addition with methanol. The oxidation of hydroxymethyl group to aldehyde was the limiting step. The ammoxidation of aldehyde group of HMF is faster than the oxidation of hydroxymethyl group, making **2** as the main intermediate in the initial period of reaction. **2** was further converted into **3** via methanol addition to the cyano group. The ammoxidation of **3** gave **4**, which was converted to **5** smoothly *via* addition with methanol, as well as trace **6** through hydration.



Scheme 4 One pot transformation of 5-hydroxymethylfurfural to 2,5-furandiamidine dihydrochloride.

In order to examine the reactivity of furan imidate to amidine, 2,5-furandiamidine dihydrochloride was prepared by reaction of the methanolic solution of **5** prepared *in situ* with two equivalent of ammonium chloride to the total imidate groups present. The generated diamidine salts was recrystallized from alcohol-petroleum ether mixture giving yellow powder in 71% yield (Fig. S29-30).

Conclusions

In summary, we reported a novel method of catalytic synthesis of imidate **5** *via* implanting of nitrogen from aq. NH_3 into HMF over manganese oxide under mild conditions. OMS-2 is an efficient catalyst that favours the 1) oxidation of the hydroxymethyl group to aldehyde, 2) condensation of aldehyde with ammonia to aldimine, and 3) oxidation of aldimine to nitrile. The conversions of aldehyde, aldimine and nitrile groups all preferentially proceed rather than the oxidation of hydroxymethyl group. By reaction with ammonium chloride, the imidate **5** prepared *in situ* was further transformed into 2,5-furandiamidine dihydrochloride expediently. This work provides a new and unique strategy to obtain valuable nitrogen-implanted chemicals from biomass resources.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (projects 21233008 and 21303183) and the "Strategic Priority Research Program-Climate Change: Carbon Budget and Related Issues" of the Chinese Academy of Sciences (XDA05010203).

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Catalytic conversion of 5-hydroxymethylfurfural into 2,5-furandiamidine dihydrochloride

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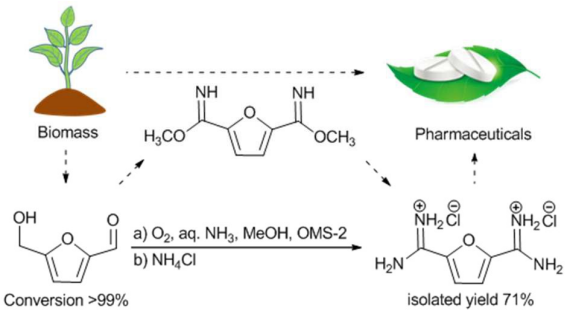

2,5-Furandiamidine dihydrochloride was firstly synthsized from 5-hydroxymethylfurfural by reaction of dimethyl furan-2,5-dicarboximidate prepared in situ with ammonium chloride.