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Lipase-Mediated Selective Oxidation of Furfural and 5-Hydroxymethylfurfural

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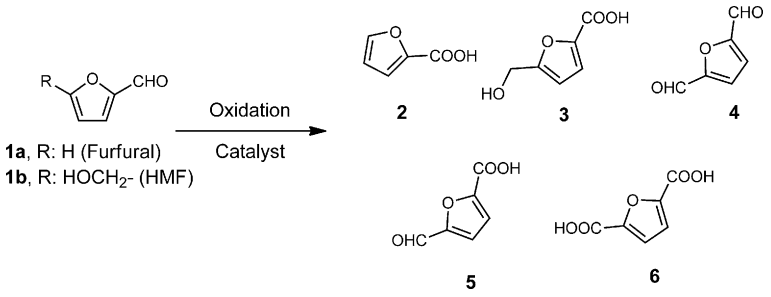
Furfural and 5-hydroxymethylfurfural (HMF) are important biomass-derived platform chemicals that can be obtained from the dehydration of lignocellulosic sugars. A possible route for the derivatization of furanics is their oxidation to afford a broad range of chemicals with promising applications (e.g., diacids, hydroxyl acids, aldehyde acids, monomers for novel polymers). Herein we explore the organic peracid-assisted oxidation of furanics under mild reaction conditions. Using lipases as biocatalysts, alkyl esters as acyl donors, and aqueous solutions of hydrogen peroxide (30% *v/v*) added stepwise, peracids are formed in situ, which subsequently oxidize the aldehyde groups to afford carboxylic acids with high yields and excellent selectivities. Furthermore, the use of an immobilized silica-based 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) affords the selective oxidation of the hydroxymethyl group of HMF to afford 2,5-diformylfuran. That product can be subsequently oxidized using again lipases for the in situ peracid formation to yield 2,5-furandicarboxylic acid, which is considered to be a key building block for biorefineries. These lipase-mediated reactions proceeded efficiently even with high substrate loadings under still non-optimized conditions. Overall, a proof-of-concept for the oxidation of furanics (based on in situ formed organic peracids as oxidants) is provided.

Introduction

The acid-catalyzed triple dehydration of lignocellulosic-based sugars (mostly C_5 xylose and C_6 glucose) leads to the formation of biomass-derived furanics, namely furfural and 5-hydroxymethylfurfural (HMF) from xylose and glucose, respectively. These chemicals are considered promising building blocks for their subsequent derivatization and valorization into a broad range of useful chemicals and biofuel constituents.[1–3] The quest for more selective and environmentally friendly catalytic manufacturing of those biomass-derived furanics is challenging due to their high propensity to trigger, for example, oligomerizations, rehydrations, or humin formation, which ultimately reduce the overall selectivities and yields, often with an unacceptable level of waste formation. Recent literature provides an excellent overview of these efforts.[4]

Among many other promising options,[1–3] an important valorization of the aforementioned biomass-derived furanics is their selective oxidation to a number of highly functionalized carboxylic acids, dialdehydes, hydroxyl acids, among others, which may well serve as monomers for innovative biobased products, such as polymers or resins (Scheme 1).[1–3]



Scheme 1. Possible products derived from the oxidative valorization of furfural and HMF.

For the oxidation of biomass-derived furanics, several chemocatalytic strategies have been reported for the conversions of furfural (**1a**)[5] to furoic acid (**2**) and of HMF (**1b**) to 5-hydroxymethylfuroic acid (**3**),[6] as well as to 2,5-diformylfuran (**4**)[7] and to 5-formylfuroic acid (**5**).[8] Furthermore, the full oxidation of HMF to afford 2,5-furandicarboxylic acid (**6**) is highly relevant to many promising applications (e.g., as monomer for new polymeric materials).[1,3] Chemocatalytic approaches for its synthesis have been extensively studied as well.[3b,7e,8a,9] Several strategies using whole-cells (biotransformations) and enzymes have also been reported. Resting cells of *Nocardia corallina* displayed the oxidation of **1a** to **2**[10] and growing cells of *Pseudomonas putida* can perform the selective oxidation of HMF to

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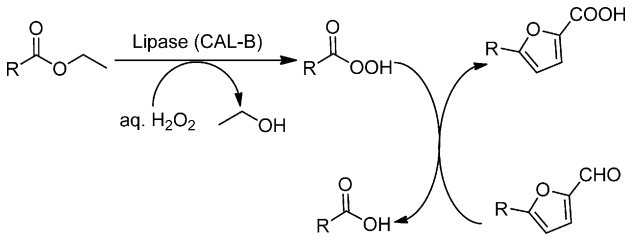
6.[11] Likewise, several enzymatic methods involving oxidases and chloroperoxidases have been assessed.[12]

Overall, the oxidation of furfural and HMF is challenging due to the high reactivity of both substrates and formed products and intermediates. Oxidative conditions must be strong enough to allow oxidations to occur, but mild enough to secure an acceptable selectivity and a diminished by-product formation. On this basis, a broad number of oxidants have been reported in the literature (O_2, CO_2, H_2O_2, *t*BuOOH) for the aforementioned catalytic systems.[5–12] Surprisingly, to our knowledge organic peracids (derived from carboxylic acids) have never been reported for the oxidation of furanics. A possible explanation might be the high reactivity of peracids, which hampers its storage and transportation. Remarkably, the expected oxidative mechanism of peracids (based on a Baeyer–Villiger-type reaction over a carbonylic group)[13] might lead to the selective oxidation of biomass-derived furanics, whereby aldehydes (sp^2) would be prone to such peracid-driven oxidation, whereas alcohols (sp^3) would not.

To probe this idea, peracids were generated in situ in catalytic amounts using lipases as biocatalysts and alkyl esters as acyl donors upon addition of aqueous hydrogen peroxide (30% *v/v*) under very mild reaction conditions (Scheme 2). The biocatalytic promiscuity of lipases enables them to accept hydrogen peroxide as a nucleophile (instead of water or alcohols) in non-aqueous solutions, affording organic peracids. Subsequently, these peracids may perform in situ oxidations. Several oxidative processes have been reported using this strategy (e.g., epoxidations, Baeyer–Villiger reactions),[14] as well as for the selective oxidative delignification of lignocellulose to afford enriched polysaccharide fractions and oxidized and dearomatized lignin oil.[15]

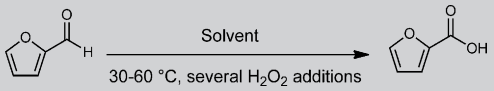


Scheme 2. Envisaged lipase-catalyzed peracid formation to perform a chemoenzymatic oxidation of biomass-derived furanics. Instead of esters, carboxylic acids may also be directly used as substrates, thus leading to the in situ regeneration of the acyl donor.[14,15]

Results and Discussion

Commercially available immobilized lipase B from *Candida antarctica* (Immo-CAL-B) was used. In a first set of experiments, the oxidation of **1** to **2** was assessed by adding stepwise different amounts of aqueous hydrogen peroxide (diluted, 30% *v/v*) and varying other parameters, such as the reaction media and temperature (Table 1).

Table 1. Lipase-mediated oxidation of furfural to furoic acid. Conditions: furfural (50 mM), CAL-B (10 mg mL^{-1}), different solvent ratios and temperatures, 24 h reaction time. Reactions without CAL-B did not show any conversion of furfural to furoic acid.



Entry	Solvent	Addition of H_2O_2[a]	*T* [°C]	Yield[b] [%]
1	EtOAc (neat)	3×1 equiv	30	5
2	EtOAc (neat)	3×1 equiv	60	33
3	EtOAc/*t*BuOH 3:1 (*v/v*)	3×1 equiv	40	50
4	EtOAc/*t*BuOH 1:1 (*v/v*)	3×1 equiv	40	60
5	EtOAc/*t*BuOH 1:1 (*v/v*)	6×1.6 equiv	40	91
6	EtOAc/*t*BuOH 1:100 (*v/v*)	3×1 equiv	40	27
7	*t*BuOH (neat)	3×1 equiv	40	0

[a] Addition of aqueous H_2O_2 (30% *v/v*), performed each hour until the number of additions was completed. [b] Yield determined upon crystallization of furoic acid.

Peracetic acid, which is formed in situ using CAL-B, is able to mildly oxidize furfural to afford furoic acid in moderate to excellent yields. Reactions conducted in neat ethyl acetate (EtOAc), acting both as acyl donor and solvent, led to lower yields in furoic acid than processes performed with a mixture of *tert*-butanol (*t*BuOH, as inert solvent for CAL-B)[16] and ethyl acetate (Table 1, entries 1 and 2 vs. entries 3–6). Moreover, further addition of higher amounts of oxidant (Table 1, entry 5) led to even higher yields in furoic acid ($\approx$5 g L^{-1}, 91%) with excellent selectivity (100%). It must be noted that reaction conditions can still be further optimized, for example, by assessing enzyme loading, type of reactor, frequency of additions of hydrogen peroxide. Likewise, the recent development of highly robust immobilized lipases provides promising prognosis for its implementation in the production of low-added-value products in an economic fashion because those immobilized enzymes are largely stable for their reuse along prolonged reaction times.[17] Moreover, the immobilization of the lipase may contribute to deliver more resistant biocatalysts to the action of hydrogen peroxide as recent literature has shown.[18]

Encouraged by these successful results, the same reaction media (acyl donor/*tert*-butanol, 1:1 *v/v*) and stepwise additions of diluted hydrogen peroxide (30% *v/v*) were then applied for the lipase-mediated oxidation of HMF using in this case either ethyl acetate or ethyl butyrate as acyl donors. As a difference in this case, HMF has two functional groups (alcohol and aldehyde), upon which a potential peracid-assisted oxidation might in principle proceed (Figure 1).

Accordingly, the enzyme-mediated setup resulted successfully also in the oxidation of HMF, notably yielding **3** (with excellent yields) and its corresponding acetyl or butyl ester (99% overall oxidative yield considering both products). The observed esterification of **3** may be considered as a second reaction catalyzed by CAL-B as well.[19] The use of different acyl donors (acetate or butyrate) did not lead to significant changes in yields or in product distribution (Figure 1). Remarkably, no

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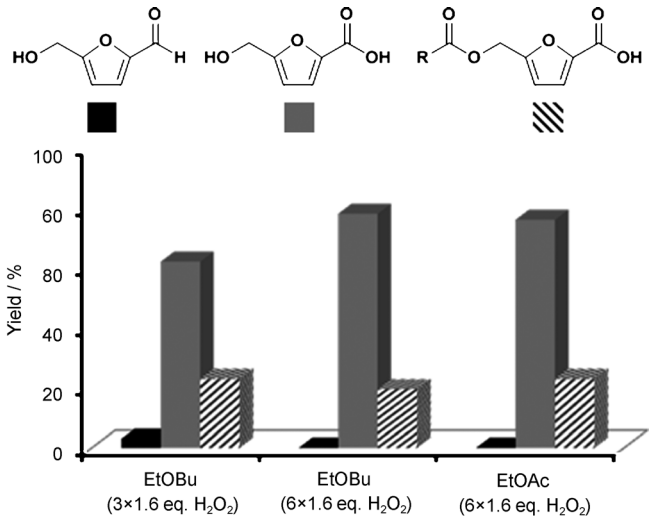

Figure 1. Lipase-mediated oxidation of HMF. Conditions: HMF (50 mM), CAL-B (10 mg mL^{-1}), addition of aqueous H_2O_2 (30% *v/v*) hourly. Reaction media: acyl donor (ethyl acetate or butyrate)/*t*BuOH (1:1 *v/v*), 40 °C, 24 h. A blank reaction without CAL-B did not show any conversion of HMF. Yield was determined by ^{1}H NMR analysis upon evaporation of the solvent (see the Supporting Information).

traces of **4**, **5**, or **6** were found, thus proving the peracid-assisted oxidative process to be chemoselective for the oxidation of the aldehyde group of HMF. This lipase-mediated oxidation of HMF is highly useful when challenging "semi-oxidized" structures such as **3** are pursued. Overall, results suggest that in situ formed peracids are able to oxidize aldehyde groups but not hydroxyl ones. Upon further optimization, the production of **3** might become relevant for future biomass-based processes, in which efficient and selective reaction systems under mild conditions are needed. A number of new uses (e.g., monomers for polyesters) may be easily envisaged for such a compound.

Proceeding with our oxidative studies, the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalyzed organocatalytic oxidation of HMF to **4** was subsequently assessed.[7f] TEMPO is an air-stable nitroxide radical,[20] and oxidative conditions for the conversion of alcohols to aldehydes using KBr and aqueous NaOCl in dichloromethane are typically regarded as "Anelli conditions".[21] Herein, with emphasis on sustainable chemistry, a heterogeneous silica-based immobilized TEMPO[22] was used for the oxidation of HMF. In addition, dichloromethane was replaced by ethyl acetate with a dual purpose: first, the replacement of chlorinated solvents by a biobased one was carried out; and second, the anticipation of a potential combination of the organocatalytic step with a subsequent lipase-mediated oxidation of **4** in ethyl acetate as reaction media (Figure 2).

Under non-optimized conditions, TEMPO could selectively oxidize HMF to **4**, albeit still in low yields. The replacement of dichloromethane by ethyl acetate led to an improvement in yields when free TEMPO was used. The incorporation of immobilized silica-based TEMPO in ethyl acetate turned out to be successful as well. Although yields were slightly lower than those observed for free TEMPO (under the same reaction conditions) the heterogeneous catalysts could be reused

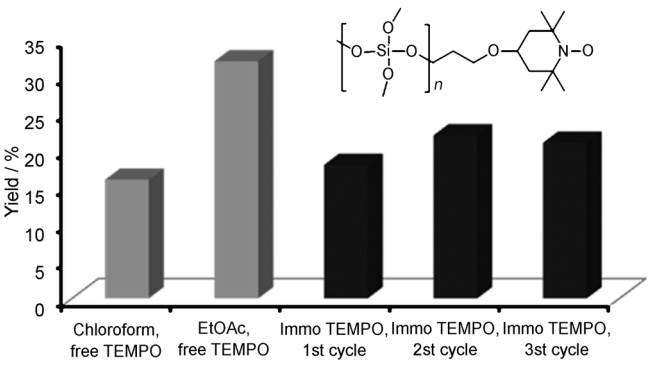

Figure 2. Performance of TEMPO-catalyzed oxidation of HMF to yield **4**. Conditions: dichloromethane or ethyl acetate mixed with aq. NaOCl and KBr (2 M), TEMPO (0.2 mmol), and HMF (10 mmol); reaction for 1 h at room temperature (see the Supporting Information).

a number of times without observing loss in its catalytic activity (Figure 2). Therefore, a further heterogeneous flow-integrated process for producing **4** through this route may be envisaged to provide more sustainable tools for future biomass-based processes.

Once **4** was obtained (non-optimized conditions), the subsequent lipase-mediated oxidation of **4** to afford **6** was studied. Reaction conditions analogous to those previously reported (Table 1 and Figure 1) were used. The reaction was extremely efficient and selective under these conditions, and quantitative yields (with 100% selectivity) in **6** were achieved at concentrations of 50 mM for **4**. After such successful results, substrate loadings were increased to assess whether industrially sound conditions could be realistic within this approach (Figure 3).

Accordingly, the reaction proceeded successfully with higher yields in **6** even at substrate loadings of 150–200 mM. Nevertheless, low amounts of the intermediate oxidized acid alde-

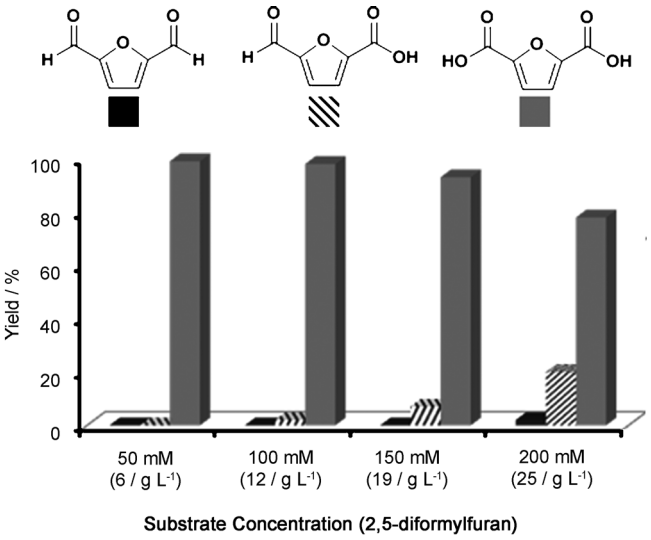

Figure 3. Product distribution of scaleup experiments with increasing concentrations of **4**. Conditions: **4** (50–200 mM), CAL-B (10 mg mL^{-1}), H_2O_2 (6×0.4 mmol, added after 0, 1, 2, 3, 4, and 5 h, up to 400 mM in total), EtOAc/*t*BuOH (1:1 *v/v*); reaction for 24 h at , 40 °C.

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hyde **5** were detected. Because the concentration of H_2O_2 was the same in all experiments (400 mM in total), a plausible reason for the lower conversion at higher substrate loadings may be an insufficient amount of oxidant.

Remarkably, the organocatalytic–enzymatic approach provides a new entry for the synthesis of **6**, which is a promising building block.[1] Envisaging further steps in this area for a more sustainable chemical process, a combined one-pot two-step TEMPO–lipase approach was preliminarily assessed (Table 2).

Table 2. Proof-of-concept of an integrated TEMPO–lipase one-pot two-step approach for the synthesis of **6** from HMF using **4** as substrate, either commercial or formed through the TEMPO pathway. Conditions for the enzymatic process are analogous to that of Figure 3 (with a concentration of 50 mM for **4**).

Origin of substrate **4**	Yield [%]	
	5	**6**
commercial, solid	0	100
isolated (TEMPO), purified, solid	7	93
non-isolated (TEMPO), dissolved	52	48
non-isolated (TEMPO), washed	17	83

The integration of the organocatalytic TEMPO-based oxidation in ethyl acetate may be compatible with a further lipase-mediated oxidation of **4**. When a workup step was included between the two reactions high yields were achieved, thus showing that a reaction based on the isolated product formed through the organocatalytic route proceeded as well as that which involved the use of commercial **4**. When the EtOAc phase of the TEMPO reaction was directly separated from the aqueous solution (NaOCl, KBr) and directly applied into the next CAL-B-based approach, full conversion of **4** was observed, albeit at the cost of forming only 52% of intermediate **5** and 48% of **6**; the low selectivity towards **6** might be due to the existence of impurities resulting from the TEMPO reaction. By looking from a different perspective (not solely focusing on **6**) that option might provide new leads to produce **5** selectively. Remarkably, when the EtOAc–TEMPO phase was washed twice with water before implementing it in subsequent enzymatic reactions, improved yields of 83% in **6** were achieved (Table 2). Overall, this proof of concept demonstrates that a one-pot two-step process for the production of **6** starting from HMF may be feasible, once pertinent optimizations are carried out.

Conclusions

Herein, we successfully explored the use of lipases as biocatalysts for the in situ production of organic peracids, which may subsequently perform the selective oxidation of biomass-derived furanics and finally afford a range of useful building blocks. Under mild and non-optimized conditions, furfural could be readily oxidized to furoic acid, whereas HMF yielded its acidic alcohol derivative with excellent selectivities and yields. Upon TEMPO-catalyzed oxidation of HMF to selectively afford 2,5-diformylfuran, a further lipase-mediated peracid-assisted oxidation led to 2,5-furandicarboxylic acid (a promising building block) in high yields and selectivities, even at high substrate loadings. Overall, results reported herein present a new peracid-based route for the oxidative valorization of biomass-derived furanics, which may bring innovative approaches in the field once optimization and process-development considerations are taken into account.

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Keywords: biocatalysis · enzymes · oxidation · supported catalysts · synthetic methods

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