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Hydrogen Gas-Mediated Deoxydehydration/Hydrogenation of Sugar Acids: Catalytic Conversion of Glucarates to Adipates

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S Supporting Information

ABSTRACT: The development of a system for the operationally simple, scalable conversion of polyhydroxylated biomass into industrially relevant feedstock chemicals is described. This system includes a bimetallic Pd/Re catalyst in combination with hydrogen gas as a terminal reductant and enables the high-yielding reduction of sugar acids. This procedure has been applied to the synthesis of adipate esters, precursors for the production of Nylon-6,6, in excellent yield from biomass-derived sources.

The valorization of biomass is an ongoing challenge that has significant implications for sustainability of processes in the chemical industry.[1] Most current commercial processes to utilize biomass focus on chemically simple lipid-based sources.[2] In contrast, carbohydrate feedstocks such as cellulose and starch have a high degree of chemical complexity and can potentially be useful as precursors to complex, industrially relevant molecules.[3] One attractive target that meets this criterion is adipic acid and its derivatives.[4] This C6 monomer is synthesized in quantities of 2.5 M tonnes per year in order to produce Nylon-6,6.[5] Currently, its production employs petroleum-derived starting materials and is responsible for a significant proportion of anthropogenic N_2O emissions.[6] As such, identification of economical routes for adipic acid production from biomass would be a significant development.[7]

Glucose is an attractive choice of starting material for this route, as it is abundant and inexpensive.[4,8] Additionally, it can be readily oxidized to glucaric acid, which contains the carboxylic acid functionality of adipic acid. While the conversion of glucaric acid into adipic acid using hydrogen as the terminal reductant has been reported, the reaction required stoichiometric hydrogen bromide to promote the reaction, which is likely to lead to challenges in reactor materials as well as issues involving removal of brominated byproducts (Figure 1A).[9] The deoxydehydration (DODH) of diols to olefins is a promising alternative, as it offers the possibility of achieving the desired transformation at near-neutral pH without the need for any halogen promoters.[10−12] However, traditional DODH chemistry is not without drawbacks. First, the reaction generally shows a preference for *cis*-diols, deriving from the requirement to form a rhenium diolate intermediate. This constraint is highlighted by the fact that mucic acid, an aldaric acid with two *cis*-diols in its open form, has been converted into adipate esters in a two step process (Figure 1B),[13] while the DODH reaction of glucaric acid gave only 25% of the muconic ester. More importantly, most reported DODH chemistry is mediated by expensive terminal reductants such as triphenylphosphine or secondary alcohols. In recent years, there have been several promising reports of hydrogen-mediated DODH reactions on model systems.[14,15] However, to date, reports of applying such conditions to efficiently convert relevant sugar acids into adipates are absent. Herein, we describe discovery and development of a catalyst system that directly provides adipates from glucose derivatives, in a single operation, using hydrogen as a terminal reductant (Figure 1C).

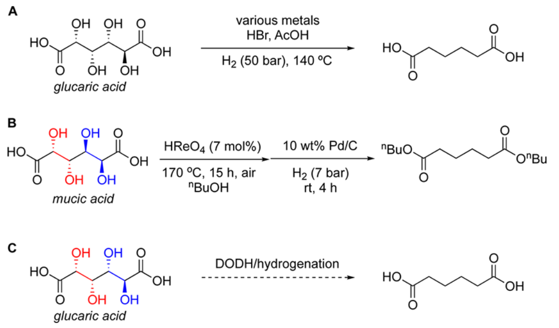

Figure 1. Methods for converting aldaric acids to adipic acid or adipate esters.

We conducted initial studies to assess the viability of adipate production via DODH using the ethyl ester of D-glucarate-6,3-lactone **1**, which can be derived from calcium glucarate. Direct application of literature precedent using a secondary alcohol as reductant/solvent and MTO as catalyst showed promising yields of the initial DODH product **2-Et** (Table 1, entry 1), but with a significant degree of charring and precipitation of solid byproducts.[16] Changing the solvent to ethanol lowered the yield of **2-Et** somewhat, but also produced a homogeneous solution at the end of the reaction. In subsequent experiments, palladium on carbon and H_2 were added with the aim of achieving a one-pot reduction to the saturated lactone **3-Et**.

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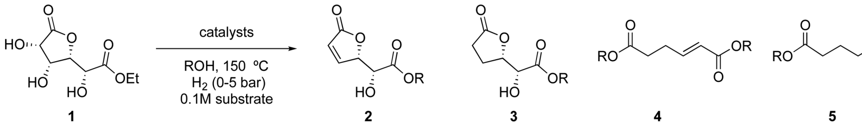
Table 1. Optimization of Reaction Conditions[a]



Entry	Catalyst(s)	Additives	H_2 Pressure	Solvent	Reaction Time	Yield **2**	Yield **3**	Yield **4**	Yield **5**
1	10 mol % $MeReO_3$	-	-	3-octanol	2 h	55%^{b}	-	-	-
2	10 mol % $MeReO_3$	-	-	EtOH	5 h	42%^{c}	-	-	-
3	10 mol % $MeReO_3$, 2.5 mol % Pd/C	-	-	EtOH	5 h	40%^{c}	-	-	-
4	10 mol % $MeReO_3$	-	1 bar	EtOH	5 h	39%^{c}	-	-	-
5	10 mol % $MeReO_3$, 2.5 mol % Pd/C	-	1 bar	EtOH	5 h	65%^{c}	trace	-	-
6	10 mol % $MeReO_3$, 2.5 mol % Pd/C	-	5 bar	EtOH	5 h	-	32%^{c}	-	-
7	10 mol % $MeReO_3$, 2.5 mol % Pd/C	-	5 bar	EtOH	18 h	-	28%^{c}	-	-
8	10 mol % $KReO_4$, 2.5 mol % Pd/C	-	5 bar	EtOH	18 h	-	30%^{c}	-	22%^{c}
9	10 mol % $KReO_4$, 2.5 mol % Pd/C	-	5 bar	MeOH	18 h	-	-	18%^{d}	61%^{d}
10	1 mol % $KReO_4$, 0.75 mol % Pd/C	27 wt % activated C	5 bar	MeOH	18 h	-	-	-	71%^{d,e}
11	1 mol % $KReO_4$, 0.75 mol % Pd/C	3 mol % H_3PO_4, 27 wt % activated C	5 bar	MeOH	18 h	-	-	-	88% (83%)^{d,e,f}

[a]Reactions run at 0.75 mmol scale. [b]3-octyl ester. [c]ethyl ester. [d]methyl ester. [e]Reaction run at 7.5 mmol scale and 1 M concentration. [f]Isolated yield of adipic acid from hydrolysis of crude product with 2 N HCl in parentheses.

Interestingly, while the yield of **2-Et** improved under these conditions, complete reduction to the saturated product was not observed at 1 bar of hydrogen. However, both a hydrogen atmosphere and Pd/C were necessary to observe an improvement in yield, suggesting that in this system the palladium facilitates the reduction of the rhenium catalyst by H_2 (Table 1, entries 2–5).

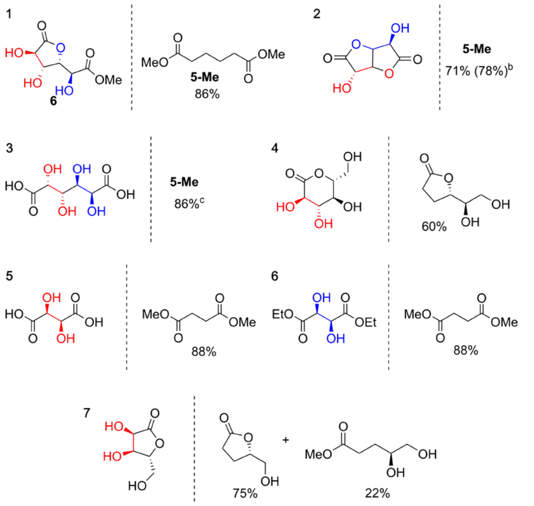
While several factors might result in formation of the fully saturated ester using the combined Pd/Re/H_2 system, we posited the lack of alkene hydrogenation derived from the low hydrogen pressure. Indeed, increasing the pressure of hydrogen to 5 bar provided saturated **3-Et**, but in significantly lower yield (Table 1, entry 6) compared to the amount of **2-Et** produced at 1 bar, even with prolonged reaction times (entry 7). This observation supports a hypotheses the rhenium catalyst is unstable to hydrogen and that the palladium catalyst is still active at higher pressures. Thus, we posited the carbon–rhenium bond in MTO might be problematic to its stability under the reactions conditions, and sought alternative catalysts. Accordingly, replacing MTO with potassium perrhenate resulted in reduction to the saturated lactone **3-Et**, as well as some production of **4-Et** due to ring-opening of this initial product followed by a second DODH/hydrogenation sequence (entry 8).

Spurred on by these promising results, conditions that promoted the ring-opening reaction of **3-Et** were explored in order to improve the yield of the desired diethyl adipate. During the synthesis of various potential substrates, we observed choice of esterifying alcohol had a significant impact on the equilibrium concentrations of various lactonized products based on glucaric acid. In particular, while esterification with ethanol favored isolation of 6,3-lactone **1**, under similar conditions in methanol the 1,4-lactone **6** was isolated almost exclusively.[17] Given the importance of the lactone/ester equilibrium on formation of the final adipate esters, methanol was examined as a solvent for the tandem DODH/hydrogenation reaction, resulting in a good yield of dimethyl adipate (**5-Me**) as well as some unsaturated intermediate **4-Me** (entry 9).

Studying various additives uncovered that addition of activated carbon resulted in full conversion to **5-Me** and allowed the concentration of the reaction to be increased to 1 M. Furthermore, addition of catalytic phosphoric acid to the reaction mixture further improved the process, affording dimethyl adipate in 88% overall yield (entry 11). We propose the Brønsted acid cocatalysts acts to facilitate the ring opening of **3-Et** to the necessary open-form diol, which might increase the rate of the desired reaction and that the activated carbon acts as a scavenger for catalysts poisons or as a support for partially reduced rhenium species.

With these optimized conditions in hand, we explored the substrate scope of the reaction. A variety of polyhydroxylated esters and lactones were competent substrates (Table 2).

Table 2. Substrate Scope[a]



[a]Substrate left/product(s) right. Reaction conditions: 7.5 mmol substrate, 1 mol % $KReO_4$, 3 mol % H_3PO_4, 0.75 mol % Pd/C, 25 wt % activated carbon, 5 bar H_2, 7.5 mL MeOH, 150 °C, 18 h. [b]Substrate prestirred at 120 °C in MeOH for 3 h. [c]48 h reaction time.

Interestingly, under these reaction conditions the DODH reaction was completely selective for vicinal diols in the α,β positions of carboxylic acids and esters; reaction of an equimolar mixture of diethyl tartrate and 1,2-dodecanediol produced diethyl succinate in 89% yield without a trace of dodecane (eq 1). This is in stark contrast to previously reported DODH

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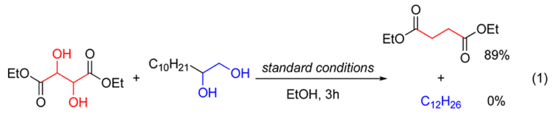
protocols, where substrates primarily consist of electronically neutral aliphatic diols.



The divergent reactivity observed in this system prompted us to investigate the possibility the reaction proceeds via a mechanism that differs from the retro-[3+2]-cycloaddition generally postulated for rhenium-catalyzed DODH reactions.[18] One possibility is the ester moiety promotes a stepwise dehydration[19]/ketone reduction pathway via either an α- or β-ketoester, as palladium-catalyzed hydrogenations of both have been reported previously.[20] However, subjecting ethyl acetoacetate to the reaction conditions resulted in only trace reaction, and while diethyl 2-oxoglutarate was fully decomposed on the time scale of the reaction, only traces of the expected DODH/hydrogenation product were observed (Figure 2A).[21]

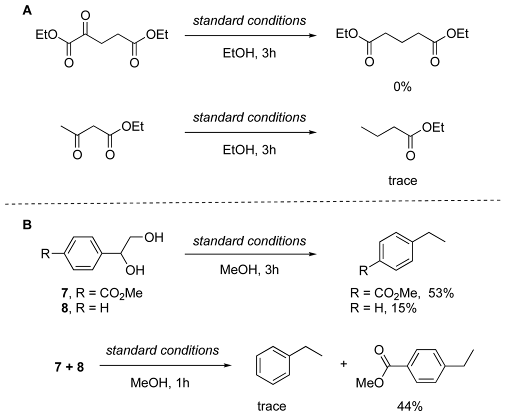
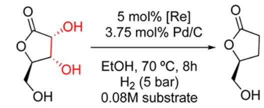


Figure 2. (A) Competence of diol dehydration products. (B) Impact of electronic properties of styrene diols on reaction yield.

Having ruled out the intermediacy of ketonic dehydration products, we reasoned the ester group might facilitate the DODH reaction, either by serving as an electron-withdrawing group or by coordinating to the rhenium catalyst. In order to distinguish between these possibilities, ester-substituted styrene glycol **7** and styrene glycol (**8**) were subjected to the standard reaction conditions for 3 h, producing the fully hydrogenated products in 53% and 15% yield, respectively (Figure 2B). Additionally, a 1-h direct competition experiment between **7** and **8** produced the ester-containing product in 44% yield and only traces of ethylbenzene. We therefore propose the ester (or other electron withdrawing group) facilitates the reaction by accepting electron density from the vicinal carbon−oxygen σ orbital into its π^* orbital. This effect lowers the energy of the transition state for carbon−oxygen bond cleavage.[18a,22]

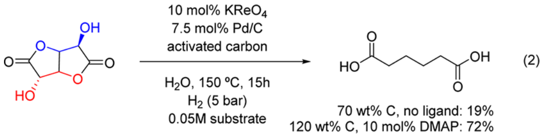
We also examined whether active rhenium catalyst was a soluble species or if surface deposition was responsible for the change in catalytic activity. SEM-EDS analysis indicated that use of $KReO_4$ in the DODH reaction was accompanied by significant precipitation of rhenium-containing species onto the Pd-containing solid support (Table 3). However, when tetrabutylammonium perrhenate was used as precatalyst, essentially no Re could be detected on the residual solids, while still performing at a similar level to the potassium catalyst. Thus, while precipitation of rhenium species occurs to a significant extent over the course of the reaction under typical conditions, the active catalyst is likely a soluble species.

Table 3. Metal Analysis of Residual Solids after DODH Reaction



Catalyst	Deposited Pd:Re (mole ratio)	Yield
$KReO_4$	2.2 : 1	25%
nBu_4NReO_4	>99 : 1	31%

Lastly, we recognized the importance of our catalytic system's reliance on hydrogen as a means of avoiding alcoholic solvents. In contrast to previously reported DODH-based syntheses of adipates, our system had the potential to directly produce adipic acid in water. This would confer several advantages: reduction of solvent cost, generation of the most industrially relevant nylon precursor, and simplification of the purification process. Reaction of glucarodilactone under analogous conditions did indeed produce adipic acid, albeit in only 19% yield. Based on this promising result, we examined strategies to stabilize the catalyst, ultimately finding that prestirring the rhenium precatalyst with DMAP[23] and increasing the amount of activated charcoal used resulted in a 72% yield of adipic acid (eq 2).



The combination of a rhenium(VII) catalyst and a palladium-on-carbon cocatalyst has allowed for the development a catalytic system to effect the high-yielding complete deoxygenation of 1,2-diols using hydrogen gas as the terminal reductant. Key to the success of this chemistry was the choice of a rhenium catalyst sufficiently stable to the strongly reducing conditions, as well as the addition of Pd/C, which acts both as a cocatalyst for the DODH step and the catalyst for the reduction of the resulting olefin. This catalyst system enabled the conversion of glucaric acid into adipate esters, as well as direct conversion into adipic acid using water as the solvent. In the future, we look forward to further investigating and optimizing this system as a means to affect the important goal of converting readily available biomass into valuable chemical feedstocks that have, until now, been derived from petroleum sources.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07801.

Procedures and spectral data (PDF)

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Notes

The authors declare the following competing financial interest(s): A provisional patent has been filed by UC Berkeley and BASF.

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(16) Previously reported DODH systems utilize solvents such as benzenes, dioxane, or long chain alcohols, which tended to lead to undesired condensation of **1** to **2**, effectively eliminating the vicinal diol functionality.

(17) The ratio of 1,4 vs 6,3 lactone is equal in the absence of catalysts in both EtOH and MeOH. The isolation of **1** and **6** appears to result from a dynamic crystallization process wherein **1** selectively crystallizes from the mother liquor in EtOH, while the remaining soluble glucarate re-equilibrates as **1** precipitates. The same holds true for **6** in MeOH. For previous isolation of these lactones, see: Kiely, D. E.; Chen, L.; Lin, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 571.

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(21) Additionally, α,β-dideuterated substrates showed washing out of deuterium at the β position but not the α position. Since formation of either of these intermediates should result in deuterium exchange at the α-position (by direct reduction of that position for the α-ketoester and by facile enolization of the β-ketoester), this observation further supports the idea that ketoester intermediates are not involved in product formation (see SI for details).

(22) Theoretical studies have shown the exact nature of the transition state for deoxydehydration and dihydroxylation can vary significantly depending on the ligand set of the catalytic species. As such, any insight into the specifics of the relevant transition state is challenging to derive from analogy to known catalytic systems. For experimental demonstration of an asynchronous transition state in the [3+2] cycloreversion, see 18a. For a theoretical analysis of the favored dihydroxylation/deoxydehydration transition states for various simple rhenium complexes, see: Deubel, D. V.; Frenking, G. *J. Am. Chem. Soc.* **1999**, *121*, 2021.

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