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Efficient, metal-free production of succinic acid by oxidation of biomass-derived levulinic acid with hydrogen peroxide†

Saikat Dutta, Linglin Wu and Mark Mascal*

A practical, scalable, metal-free synthesis of succinic acid from the biomass-derived platform chemical levulinic acid is described. Treatment of levulinic acid with the inexpensive, simple oxidant hydrogen peroxide under the catalytic action of trifluoroacetic acid gives succinic acid in high yield and enables facile product isolation by simple distillation of the volatile catalyst and byproducts.

Introduction

Succinic acid (SA) is an organic chemical of major commercial potential. Although the current market for SA is limited by its comparatively high price, it has been proposed as a feedstock for a variety of high-volume commodity chemicals, including 1,4-butanediol (BDO), gamma-butyrolactone (GBL), maleic anhydride (MA), and tetrahydrofuran (THF), among others.[1–3] The recent description of biodegradable polypropylene succinate in the form of a stereocomplex with properties comparable to LDPE may also stimulate new commercial applications.[4] SA is conventionally sourced *via* the C_4 stream of the light naphtha raffinate of petroleum, usually by hydrogenation of MA or maleic acid, or oxidation of BDO, although there are other approaches.[5] Recently, however, a number of companies have begun producing SA *via* fermentative pathways with the goal of becoming competitive with petrochemical routes, such that the global demand for SA has been predicted to increase from the current <100 kT to >700 kT per annum by 2020, representing a *ca.* $1B market.[6,7]

The biological route to succinic acid is centered around native overproducer bacteria and genetically engineered *E. coli*.[8] Carbon sources are typically sugars, which may also be derived from lignocellulose hydrolysates. Although generally good yields and productivity have been reported, challenges associated with downstream processing, including selectivity issues, the use of bases as neutralizing agents, and product isolation complicate the overall economics of the process.[9]

In principle, chemical-catalytic pathways offer much faster and more scalable routes to SA from carbohydrates. Although no practical access to SA directly from raw biomass has yet been developed, approaches *via* furfural and levulinic acid, both one step removed from biomass, have been described. Thus, Choudhary *et al.* recently reported the oxidation of furfural, a derivative of hemicellulose, with H_2O_2 at 80 °C over 24 hours to give SA in up to 74% yield. However, the SA was contaminated with a maleic acid by-product and the reaction is dependent on an ultimately degradable catalyst (Amberlyst-15).[10] Beyond this, the cost of the feedstock and long reaction period give little advantage over fermentative routes. Related methods involving furfural and other furans using a range of oxidants and catalysts generally give SA in lower yields and selectivities, and are described in reviews.[11,12]

Levulinic acid (LA) is a renewable feedstock of exceptional promise. Unlike furfural, LA can be derived both from hemicellulose and the major, cellulosic fraction of carbohydrates. It can be produced in high yield *via* the acidic processing of biomass,[13] and although this is practiced commercially only on a limited scale at present, economic projections have indicated that the production costs of LA could fall as low as $\$0.04–\$0.10\ \mathrm{lb}^{-1}$.[14] LA can also be accessed in high yield by the hydrolysis of the biomass derived platform molecule 5-(chloromethyl)furfural (CMF).[15] As such, the potential of LA to unlock key renewable markets is vast.[16]

Remarkably, the conversion of LA to SA was first described in a paper by Tollens as early as 1879. Nitric acid was employed as the oxidant, resulting in a mixture of organic acids, including SA, albeit in low yield.[17] The first report of the action of hydrogen peroxide on LA was published in 1934, which described a reaction at 60 °C in the presence of a cupric salt catalyst, again giving a mixture of carboxylic acids but only trace SA.[18] A 1954 patent reported the gas phase oxidation of

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Department of Chemistry, University of California Davis, 1 Shields Avenue, Davis, CA 95616, USA. E-mail: mjmascal@ucdavis.edu

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LA with O_2 and a vanadium catalyst at 375 °C, wherein a maximum yield of 83% was claimed.[19] This approach might have been of preparative interest were not the conditions so severe.

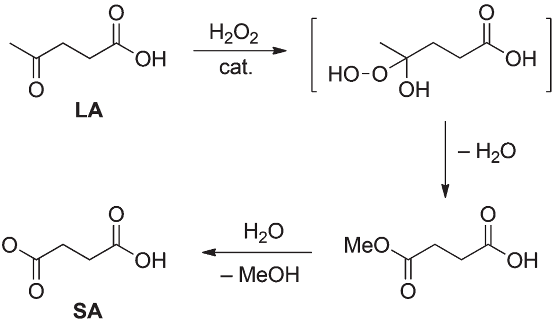
The current emphasis on green chemical production has led to a renewed interest in the conversion of LA to SA, and a flurry of recent publications describing this reaction has appeared. Thus, a 2012 patent describes the heating of LA with nitric acid–$NaNO_2$ at 40 °C for 4 h to give mixtures of SA and oxalic acid, the former in up to 52% yield.[20] Liu *et al.* reported the application of a Mn(III) catalyst in the oxidation of methyl levulinate at 90 °C under 5 bar of O_2 to give a mixture of dimethyl succinate, malonate, and oxalate esters, along with related acetal derivatives.[21] The maximum yield of succinate was 52% in a 20 hour reaction. Podolean *et al.* employed Ru(III) functionalized silica-coated magnetic nanoparticles under 10 bar O_2 at 150 °C for 6 hours in the conversion of LA to SA, where catalyst recycling experiments demonstrated good reusability (×3) at conversions of 54–58% and a 4% loading of ruthenium.[22] Finally, an interesting reaction was reported by Caretto and Perosa that involved simple heating of LA in a dimethylcarbonate–base mixture at 200 °C for 4 h to give dimethyl succinate among a range of other products in up to 20% yield.[23]

In all of the above cases, the conversion of LA to SA involves either modest yields, poor selectivity, severe conditions, and/or potentially foulable catalysts. In the anticipation that LA is poised to become a low-cost feedstock with the potential to supply value to range of chemical markets, we were motivated to explore metal-free catalytic approaches to the oxidation of LA to valuable chemicals such as SA. Below, we report the efficient conversion of LA into SA using an inexpensive, simple oxidant under gentle conditions.

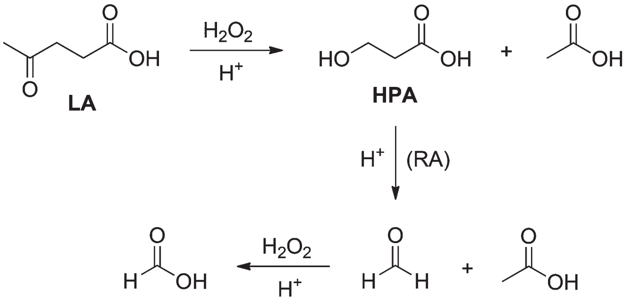
Results and discussion

At the outset, we had identified hydrogen peroxide as a reagent of great and hitherto under-exploited potential for the oxidation of LA due to its well known Baeyer–Villiger type mechanism of action (Scheme 1).

Initial experiments with H_2O_2 in aqueous sulfuric acid showed promise, giving a mixture of SA (48%), acetic acid (50%), formic acid (24%), and methanol (17%) (estimated yields by ^1H NMR integration). Considering the reaction in Scheme 1, methanol is an expected byproduct, and the strong oxidizing conditions also lead to the conversion of LA to acetic acid. This chemistry is precedented – in fact, a recent patent uses LA as a feedstock for producing acetic acid with a range of oxidants, including H_2O_2.[24] Formic acid is also seen in some cases as a byproduct.[24] The observation of acetic acid can be explained as shown in Scheme 2 by invoking the alternative migration product in the Baeyer–Villiger oxidation, *i.e.* 3-hydroxypropanoic acid (HPA), as an intermediate. The conversion of LA to HPA co-produces a molecule of acetic acid on hydrolysis of the initially formed ester. HPA can then undergo a retro aldol cleavage to give acetic acid and formaldehyde, the latter ultimately being oxidized to formic acid.



Scheme 1 Oxidation of LA to SA with H_2O_2.



Scheme 2 Oxidation of LA to acetic and formic acids with H_2O_2. RA = retro aldol.

While the acetic acid, formic acid, and methanol are volatile and can easily be removed from the reaction mixture, separation of the SA product from aq. sulfuric acid is difficult, and the recycle of sulfuric acid is costly. A remarkably simple solution to these issues presented itself in the form of trifluoroacetic acid (TFA) which, with pK_a of *ca.* 0,[25] was found to be sufficiently acidic to catalyze the reaction. Thus, when a mixture of LA and 30% aqueous H_2O_2 in TFA was heated at 90 °C, the starting material was consumed within 2 hours and the result was a 62% yield of SA, alongside 43% acetic acid, 45% formic acid, and 9% HPA (estimated yields by ^1H NMR integration). The initially formed monomethyl ester of SA *trans*-esterifies with TFA to give methyl trifluoroacetate (45%), which is captured in a cold trap. The volatile part of the reaction mixture thus consists of TFA methyl ester (bp 43 °C), TFA (bp 72 °C), the TFA–water azeotrope (79 wt% TFA, bp 105 °C) and finally acetic acid (bp 118 °C). The residual, white solid mass could be triturated with ether, in which SA is largely insoluble, to give pure SA (60% isolated yield). A scaled up reaction starting with 10.0 g of LA provided 6.0 g of SA (59%). The triturate consists of HPA, a small amount of SA, and a mixture of unidentified, minor products.

The management of the TFA would be an important aspect of this process from an applied perspective. Taking the larger scale reaction (processing 10.0 g LA feedstock) as an example, the total 50 mL of 30% H_2O_2 used is capable of delivering a maximum of 48 g H_2O at the completion of the reaction. The 200 mL of TFA used corresponds to 298 g, of which 180 g

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will combine with the 48 g of H_2O to form 228 g of the azeotrope, with a remainder of 118 g TFA. While we used 30% aq. H_2O_2 in this work, 50% H_2O_2 is generally available, with industrial concentrations up to 70%. For the 50% and 70% grades, the delivery of less water with the same quantity of H_2O_2 would result in the formation of 121 g and 76 g of the azeotrope, respectively, from which only 25.5 and 16 g of water would need to be removed. Recycling of TFA is accomplished by dehydration of the azeotrope by membrane pervaporation.[26] We have performed the above reaction using 50% H_2O_2 with no significant variation in outcome.

Conclusions

In summary, we have described an efficient, one-step, non-fermentative, metal-free process for the conversion of biomass-derived levulinic acid into succinic acid under mild conditions and in short reaction times. The mass balance of the reaction consists mainly of acetic and formic acids, which are themselves useful commodity chemicals. TFA is an unfoulable organic acid catalyst which can be fully recycled, involving the minimal removal of co-produced water if industrial strength solutions of H_2O_2 are used. This simple, practical method paves the way for the commercial production of renewable SA and its many useful derivatives.

Experimental section

TFA-catalyzed oxidation of levulinic acid with hydrogen peroxide

Levulinic acid (2.00 g, 17.2 mmol) was dissolved in TFA (40 mL) and 30% aq. H_2O_2 (2.0 mL) was carefully added. The flask was mounted with a water-cooled condenser and −78 °C volatiles trap, and the colorless mixture was placed in an oil bath at 90 °C and stirred for 20 min. Additional 30% aq. H_2O_2 (8.0 mL) was added portionwise at a rate of 2 mL every 20 min. The reaction was allowed to stir a further 20 min after the final addition, at which point the LA had been completely consumed as indicated by ^{1}H NMR analysis. The mixture was cooled to room temperature and a measured amount of 1,4-dioxane was added as an internal standard. The ^{1}H NMR spectrum was measured and the yields were estimated as follows: succinic acid (62%), acetic acid (43%), 3-hydroxypropanoic acid (9%), and formic acid (45%). Methyl trifluoroacetate (45%) was obtained in the cold trap. The volatiles were evaporated to give a white solid (1.70 g) which was triturated with Et_2O (2 × 2 mL) to give pure succinic acid (1.22 g, 60%). Experimental details of the scale-up of this reaction and the sulfuric acid-catalyzed oxidation of levulinic acid are given in the ESI.†

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