Biomass Valorization

Synthesis of \( \alpha,\beta \)- and \( \beta \)-Unsaturated Acids and Hydroxy Acids by Tandem Oxidation, Epoxidation, and Hydrolysis/Hydrogenation of Bioethanol Derivatives

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Abstract: We report a reaction platform for the synthesis of three different high-value specialty chemical building blocks starting from bio-ethanol, which might have an important impact in the implementation of biorefineries. First, oxidative dehydrogenation of ethanol to acetaldehyde generates an aldehyde-containing stream active for the production of \( \beta \)-unsaturated acids via base-catalyzed aldol-condensation. Then, the resulting C4 adduct is selectively converted into crotonic acid via catalytic aerobic oxidation (62 % yield). Using a sequential epoxidation and hydrogenation of crotonic acid leads to 29 % yield of \( \beta \)-hydroxy acid (3-hydroxybutyric acid). By controlling the pH of the reaction media, it is possible to hydrolyze the oxirane moiety leading to 21 % yield of \( \alpha,\beta \)-di-hydroxy acid (2,3-dihydroxybutyric acid). Crotonic acid, 3-hydroxybutyric acid, and 2,3-dihydroxybutyric acid are archetypal specialty chemicals used in the synthesis of polyvinyl-co-unsaturated acids resins, pharmaceutics, and bio-degradable/-compatible polymers, respectively.

Polymers play a key role in the creation of a myriad of materials that have contributed to the development of our modern society. The current use of plastics, however, is not sustainable in the long term due to its dependence on non-renewable fossil fuels and the environmental pollution caused by plastic waste.[1] This dilemma has triggered intensive research in the development of environmentally friendly and sustainable bio-based and biodegradable polymers.[2] Polyhydroxyalkanoates (PHAs) are a class of biodegradable isotactic polymers synthesized by bacteria.[3] Until now, these family of polymer building blocks have been synthesized using genetically modified micro-organisms or enzymes.[4] However, the production cost of PHAs is nearly four times larger than its petroleum-based counterparts (circa PHAs[5] and polypropylene[6] prices are 5–6 and 1–2 $/kg, respectively). This is due to the high cost of raw materials, low conversion rates, the complex purification of the fermentation broths, and the large amounts of biomass waste generated (circa 5 kg of raw material per 1 kg of product), and low conversion rates.[7]

Catalytic conversion routes of biomass-derived feedstocks to short \( \beta \)-hydroxy acids (e.g. lactic acid) have shown higher productivities and atom-efficiency at industrially relevant operating conditions,[8] but their application has been limited to short chain (C\(_3\)) molecules. Inspired by nature, we have developed a new catalytic cascade process that mimics the step-wise coupling of C\(_3\) units that occur during the biosynthesis of PHA in bacteria. Accordingly, we have used base-catalyzed aldol-condensation followed by tandem oxidation, epoxidation and hydrogenation or hydration (Scheme 1). This catalytic cascade route has allowed us to generate medium-chain \( \alpha,\beta \)-unsaturated acids (crotonic acid), \( \alpha,\beta \)-di-hydroxy acids (2,3-dihydroxybutyric acid), and \( \beta \)-hydroxy acids (3-hydroxybutyric acid), which are emerging specialty chemicals and building blocks.

The process of converting ethanol into unsaturated and mono- and di-hydroxy acids starts with the catalytic dehydrogenation of ethanol to acetaldehyde (Scheme 1a). This step was accomplished in a flow reactor at 250°C using SiO\(_2\)-supported 10 wt. % Cu and 5 wt. % Ni catalysts (see Table S1 in the Supporting Information). When the reaction was performed at conversions below 20% in the presence of oxygen, the observed rates were 0.67 ± 0.06 and 0.46 ± 0.02 \( \text{molO}_2\text{Cat}^{-1}\text{h}^{-1} \) on the Cu and Ni catalysts, respectively. At these conditions the selectivity on both catalysts in the presence of oxygen was circa 100 %, which is in agreement with previous kinetic studies performed on Cu–SiO\(_2\), Cu–ZnO and Cu–Al\(_2\)O\(_3\) catalysts that indicated that selectivities to acetaldehyde 80% can be obtained below 20% conversion.[9,10] The unreacted ethanol could either be recycled back.
Table 1: Product selectivity and conversions obtained during aerobic oxidation reaction of crotonaldehyde to crotonic acid at 38 bar of synthetic air using 200 mg of catalyst in decalin.[a]

| Catalyst         | Reaction time [h] | Temperature [°C] | Solvent  | Conversion [%] | Crotonic acid yield [%] | STY [mol g⁻¹ h⁻¹] |
|------------------|-------------------|------------------|----------|---------------|--------------------------|------------------|
| Co₃O₄            | 6                 | 100              | Decalin  | 66            | 54                       | 0.03             |
| RuCo₄Ce₂O₇       | 6                 | 100              | Decalin  | 92            | 92                       | 0.09             |
| RuCo₄Ce₂O₇       | 6                 | 100              | Water    | 78            | 9                        | 0.15             |
| RuCo₄Ce₂O₇       | 6                 | 80               | GVL      | 67            | 54                       | 1.53             |
| RuCo₄Ce₂O₇       | 6                 | 60               | Water    | 48            | 2                        | 0.96             |
| ETS-4            | 6                 | 100              | Decalin  | 70            | 58                       | 6.07             |
| ETS-4            | 0.75              | 100              | Acetic acid | 85            | 85                       | 11.33            |

[a] RuCo₄Ce₂O₇ refers to 5 wt. % Ru supported on Co₄Ce₂O₇ oxide. STY refers to the site time yield calculated as the moles of product per mol of catalyst per unit of time.
By changing the solvent to a dipolar aprotic organic solvent such as γ-valerolactone (GVL), we observed similar conversion as that obtained in water (67%), while the yield to crotonic acid increased to 54% (Figure 1). The differences in yield in the two solvent environments was caused by the activation of acid catalyzed condensation reactions. In the aqueous phase crotonic acid can partly dissociate (crotonic acid ionic form) lowering the pH of the reaction media and activating the vinylic bonds of the crotonaldehyde and crotonic acid. Furthermore, acid catalyzed aldol condensation of the vinylic bonds of the crotonaldehyde and crotonic acid. Notably, when the solvent was changed to acetic acid, the conversion and yield significantly increased resulting in quantitative production of crotonic acid (91 mol C%) in the reaction mixture (Figure 2). The high yields to the di-hydroxy acid (37%) in the acidic environment can be ascribed to the hydrolysis of epoxide ring (Table S3). The exact mechanism of this reaction, step e in Scheme 1, is still under debate. Early work on kinetic isotope effects on the hydrolysis of ethylene oxide showed that there are two possible mechanisms (SN1 and SN2).[21–23] In both mechanisms, the first step is the protonation of the epoxide oxygen in a fast equilibrium step.[21,24] The second step is either the decomposition of the conjugated acid followed by rapid reaction of the carbonium ion with water (SN1 mechanism) or the bimolecular substitution of the conjugated acid with water (SN2 mechanism).[25] A similar strategy is applied industrially for the production of ethylene glycol from ethylene oxide, although at higher temperature (200 °C).[26]

To reduce the rate of α,β-di-hydroxy acid formation we decided to increase the pH to 6.4 by adding KOH to the reaction mixture (Figure 2). The 13C-NMR results indicated that the two main species present in the reaction mixture after 3 h of reaction were crotonic acid and the epoxide. At these conditions, the conversion of crotonic acid increased to 89% and the yield of 3-methyloxirane-2-carboxylic acid and 2,3-dihydroxybutanoic acid were 76 and 22%, respectively (see Table S3). Previous reports indicate that increasing the pH beyond 7 leads to faster rates of hydrolysis[21,24] which in our
case would have led to higher selectivity to 2,3-dihydroxybutanoic acid. These results indicate that nearly neutral pH can effectively reduce the rate of epoxide hydrolysis increasing the selectivity towards the epoxide adduct.

The performance of the WO₃ catalyst prepared using the combustion method was compared with commercial WO₃ (Sigma-Aldrich), and SBA-15 doped with WO₃ prepared by incipient wetness impregnation (Figure 3). The molar distribution after 0.5 h of reaction indicates that with the WO₃ combustion catalyst it was possible to obtain up to 54 mol% of the epoxide (3-methyloxirane-2-carboxylic acid), while in the case of commercial WO₃ and WO₃-SBA-15 catalysts these values decreased to 15 and 7%, respectively. With all the catalysts, formation of the α,β-dihydroxy acid (2,3-dihydroxybutanoic acid) was low due to the near neutral pH employed during reaction.

![Graph showing molar distribution obtained after the reaction of crotonic acid (0.255 mol L⁻¹) epoxidation at pH 6.4 and 65 °C and atmospheric pressure after 0.5 hours using 50 mg of catalysts and 230 µL of H₂O₂ at 10 vol. %.

| Compound | Feed [mol L⁻¹] | Product [mol L⁻¹] | Conversion [%] | Yield [%] |
|----------|----------------|-------------------|----------------|----------|
| Crotonic Acid | 0.14 | 0  | 100 | 0 |
| 2,3-dihydroxybutanoic acid | 0.21 | 0 | 100 | 0 |
| 3-methyloxirane-2-carboxylic acid | 0.036 | 0.036 | 100 | 0 |
| | 0 | 0.14 | 0 | 100 |
| | 0 | 0.19 | 0 | – |

After reaction, the crotonic acid and 3-methyloxirane-2-carboxylic acid were quantitatively hydrogenated towards butanoic acid and 3-hydroxy-butanoic acid, respectively. In contrast, the α,β-dihydroxy acid (2,3-dihydroxybutanoic acid) remained unreacted after the reaction. Notably, the chemo-selectivity of the hydrogenation of 3-methyloxirane-2-carboxylic acid towards 3-hydroxy-butanoic acid was 100%.

In summary, the utilization of tandem oxidation, epoxidation, followed by enoxy-ring activation by either hydrolysis or hydrogenation offers a flexible platform for the production of specialty chemical building blocks from biomass-derived ethanol derivatives. This strategy allows for the selective conversion of bio-ethanol to crotonic acid, 3-hydroxy butanoic acid, and 2,3-dihydroxyacid at high carbon yields (62, 21, and 29 %, respectively).

We have successfully demonstrated that using an intermediate step of epoxidation of the unsaturated acid it is possible to selectively produce β-hydroxy acids and α,β-dihydroxy acids, which are otherwise inaccessible via direct oxidation of the aldol-adduct. We envision that the heterogeneous catalytic cascade approach that we have developed...
here can serve as a basis for the production of numerous high-value chemical building blocks from bio-ethanol. Furthermore, tuning the aldol condensation process to increase the yield towards C₆ and C₈ aldehydes could enable the production of long-chain hydro-acids for the production of long-chain PHAs with enhanced mechanical properties.

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Conflict of interest

The authors declare no conflict of interest.

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