Acid catalyzed condensation of levulinic acid with glyoxylic acid: Synthesis of 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione

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Abstract: The sulfuric acid catalyzed condensation of levulinic acid with glyoxylic acid at 80 °C, for 24 h under neat conditions gives 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione in 92% yield. Catalytic reduction of this unsaturated *bis*-lactone provides a facile route to produce polyester monomer 1-methyl-2,8-dioxabicyclo[3.3.0]octane-3,7-dione from renewable feedstocks.

Keywords: levulinic acid; glyoxylic acid; aldol condensation; polyester monomer; *bis*-lactone

The increasing concern over declining petroleum reserves and climate change has promoted current explorations for renewable resources based fuels as well as platform chemicals for chemical and polymer industries. Triglycerides, succinic acid, lactic acid, glycerol, 5-hydroxymethylfurfural, furfural, and 4-oxopentanoic acid or levulinic acid (LA, 1, figure 1) produced from plant based biomass are the forefront of this new generation of feedstocks^{1, 2, 3}. Levulinic acid is a key renewable feedstock chemical since this five carbon keto-acid can be produced from the most abundant biopolymer cellulose *via* a series of acid catalyzed reactions in water⁴. It was listed as one of the top 12 most promising value added chemicals from biomass by the Biomass Program of the US

Department of Energy in 2004 ⁵ and continues to rank highly in more recent reviews of most important biorefinery target products ⁶. The 2013 global LA consumption is around 2600 tons, and is expected to increase steadily in the near-future, specially due to the introduction of the Biofine process, which has been projected to lower LA costs to as low as 0.09–0.22 \$/kg ⁷. This versatile building block can be used in the synthesis of various organic chemicals such as levulinate esters, γ -valerolactone, acrylic acid, 1,4-pentanediol, β -acetylacrylic acid, α -angelica lactone, 2-methyl THF, δ -amino levulinic acid, etc. ^{7, 8}. Levulinic acid and its derivatives have been used as building blocks for the preparation of polymers ^{9, 10, 11, 12, 13, 14, 15}. In particular, 5-hydroxylevulinic acid synthesized by hydroxylation of levulinic acid has been used as a monomer for the preparation of *poly*(5-hydroxylevulinic acid) and biodegradable *poly*(5-hydroxylevulinic acid-*co*-L-lactic acid) ^{10, 11}. Direct condensations of levulinic acid, with another renewable resources based material glycerol is known to give ketal-ester oligomers ⁹. In addition, we have recently shown that NaOH catalyzed condensation reaction between levulinic acid and 5-hydroxymethylfurfural in water gives a mixture of aldol products: (*E*)-6-[5-(hydroxymethyl)furan-2-yl]-hex-4-oxo-5-enoic acid and (*E*)-3-[5-(hydroxymethyl)furan-2-yl]methylene-4-oxo-pentanoic acid in 82 % combined yield ¹⁶. A similar reaction between levulinic acid and furfural gives the linear polymer, *poly*[1-carboxymethyl-4-(furan-2-yl)-2-oxo-butane-1,4-diyl] in excellent yield ¹⁶. Our interest in upgrading renewable feedstocks to value added chemicals ^{17, 18} has led us to study the condensations of LA with glyoxylic acid (GA, 2, figure 1); and as far as we are aware condensations between these two carbonyl compounds are not reported in the literature. Most importantly glyoxylic acid is a relatively unexplored potential renewable feedstock that can be obtained by biomass degradation and fermentation techniques ^{19, 20}. In this communication we are reporting the acid catalyzed condensation of levulinic acid with glyoxylic acid producing 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (3) in excellent yield as shown in figure 1.

Figure 1. Acid catalyzed condensation of levulinic acid (**1**) with glyoxylic acid (**2**) producing 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**)

Initial attempts to increase the carbon number of levulinic acid by aldol condensation with glyoxylic acid using base catalysts (NaOH, Na₂CO₃) in ethanol and aqueous mediums failed to give any products under room temperature as well as under reflux conditions. The salts are formed in the base catalyzed reactions, and starting materials were recovered after acidification of the reaction mixtures. However, the reaction carried out under acidic conditions using concentrated sulfuric acid as the catalyst and neat conditions showed complete consumption of starting levulinic acid producing one isolable product. The results of a series of experiments testing various acid catalysts under different conditions, levulinic acid - glyoxylic acid mole ratios, and the yields of **3** produced are shown in table 1 (experimental procedure in SD). The optimum reaction conditions were found to be heating a mixture of LA and GA in 1:1.5 mole ratio for 24 h at 80 °C, with 20 mol % con. H₂SO₄ as the catalyst, as shown in table 1. The experiments carried out at 80 °C with only 10 mol % catalyst and shorter reaction times gave lower yields (entries 1 and 2) as well as longer reaction times resulted in excessive polymerizations, lowering the yield (entry 5). In addition we tested other strong acid catalysts: phosphoric and *p*-toluenesulfonic acids as well as the acidic ionic liquid: 1-(3-propylsulfonic)-3-methylimidazolium chloride [(HSO₃)³C₃C₁im][Cl]^{21, 22}; nevertheless these acids produced only lower yields of **3** (entries 6-8). Solid acids Amberlyst-15 (4.7 mmol H⁺/g) as well as sulfonated silica: SiO₂-SO₃H (0.726 mmol H⁺/g) were tested under similar acid loading as shown in entries 9 and 10. Amberlyst-15 gave a 90% yield, comparable to conc. H₂SO₄, whereas SiO₂-SO₃H gave a moderate 61 % yield. These solid acid catalysts are easier to recover for reuse and can be considered as environmentally benign catalysts for the aldol condensation.

Table 1. Reactant mole ratios, catalysts, reaction conditions and yields in the acid catalyzed condensation of levulinic acid (LA, **1**) with glyoxylic acid (GA, **2**) producing 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**)

Entry	LA:GA (mole : mole)	Catalyst (mole %)	Reaction conditions temperature, time	3 Yield (%)
1	1 : 1	H ₂ SO ₄ (10)	80 °C, 6 h	39
2	1 : 1.5	H ₂ SO ₄ (10)	80 °C, 6 h	55
3	1 : 1.5	H ₂ SO ₄ (20)	80 °C, 6 h	68
4	1 : 1.5	H ₂ SO ₄ (20)	80 °C, 24 h	92
5	1 : 1.5	H ₂ SO ₄ (20)	80 °C, 48 h	81
6	1 : 1.5	H ₃ PO ₄ (20)	80 °C, 24 h	32
7	1 : 1.5	<i>p</i> -TsOH (20)	80 °C, 24 h	78
8	1 : 1.5	[(HSO ₃) ³ C ₃ C ₁ im][Cl] (20)	80 °C, 24 h	37
9	1 : 1.5	Amberlyst -15 H ⁺ form (20)	80 °C, 24 h	90
10	1 : 1.5	SiO ₂ -SO ₃ H, (20)	80 °C, 24 h	61

The product was isolated by column chromatography on silica, eluting with 10% methanol in methylene chloride and was identified as 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**) by spectroscopic methods. High resolution mass spectrum of the product indicated the molecular formula of **3** as C₇H₆O₄. The ¹H NMR of **3** showed a CH₃ group singlet at 1.63 ppm and an olefinic peak at 6.12 ppm (d, d, *J* = 1.6, 1.6 Hz). In addition the two methylene protons were observed at 3.31 ppm (d, d, *J* = 1.6, 18.8 Hz) and 3.44 ppm (d, d, *J* = 1.6, 18.8 Hz) (SD). The ¹³C NMR spectrum of **3** showed seven peaks at 23.6, 32.0, 106.8, 118.7, 163.8, 170.5 and 172.7 ppm (SD). A comparison of the spectroscopic data with similar known compounds further confirmed the structure. For instance, C-1 of **3** showed the ¹³C NMR peak at 106.8 ppm, whereas the corresponding peak in the saturated analog 2,8-dioxo-1-methylbicyclo[3.3.0]octane-3,7-dione (**4** in figure 3) was observed at 113.1 ppm^{23, 24}. Additionally, C-4 and C-5 alkene carbons were observed at 118.7 and 167.7 ppm in ¹³C NMR spectrum of **3**; in comparison similar alkene carbon absorptions are reported at 115.8 and 166.7 ppm for the unsaturated γ -lactone 4-methylfuran-2(5H)-one²⁵. The FT-IR spectrum of **3** showed a broad peak at 1731 cm⁻¹ due to ester C=O groups and an absorption at 1652 cm⁻¹ for

the C=C in the α,β -unsaturated lactone system. The UV-Vis spectrum recorded in methanol showed a λ_{max} at 210 nm, further confirming the α,β -unsaturated γ -lactone structure in **3**²⁶.

Figure 2. Proposed reaction mechanism for the formation of 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**) in the H_2SO_4 catalyzed condensation of levulinic acid (**1**) with glyoxylic acid (**2**).

The formation of unsaturated *bis*-lactone 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**) in the acid catalyzed condensation of levulinic acid (LA, **1**) with glyoxylic acid (GA, **2**) can be explained using the mechanism shown in figure 2. Acid catalyzed aldol type condensation of LA with GA is the initial phase of the mechanism. Kumar et al. has studied a similar acid catalyzed condensation of glyoxylic acid with 2-pentanone and 4-methyl-2-pentanone using phosphoric acid as the catalyst at 75 °C²⁷. In these reactions they found that condensation occurs exclusively at C-1 of these ketones. Surprisingly in our experiments with levulinic acid we have not detected the condensation reaction at the less substituted carbon. In the next step protonation of the keto group leads to the first lactone ring formation. This step is followed by the second lactonization, and dehydration may lead to the stable product **3**.

Figure 3. Catalytic reduction of 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**) in neat and in methanol to give **4** and **5**.

Catalytic reduction of **3** under 1 atm. H_2 and neat conditions using 10% Pd-C catalyst gave the known saturated *bis*-lactone 2,8-dioxa-1-methylbicyclo[3.3.0]octane-3,7-dione (**4**) in 96% yield^{23, 24}; whereas the reduction in methanol under similar conditions gave the ring opened product 3-acetyl-dimethylglutarate (**5**) in quantitative yield as shown in figure 3 (experimental procedures in SD). The products **4**, **5** formed in reduction reactions were confirmed by comparison with published spectroscopic data^{23, 24, 28}. The symmetrical *bis*-lactone 2,8-dioxa-1-methylbicyclo[3.3.0]octane-3,7-dione (**4**) is a versatile monomer in polyester synthesis and currently this polymer precursor is prepared by reaction of tricarballic acid with acetic anhydride and pyridine in low yield^{23, 24}. The base catalyzed condensation of epoxides with *bis*-lactone **4** is an elegant method to produce polyesters^{23, 24}. Consequently, the presented route to monomer **4** *via* the 1-methyl-2,8-dioxabicyclo[3.3.0]oct-4-ene-3,7-dione (**3**) is an all renewable carbon based path to produce this useful feedstock.

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Supplementary data (SD)

Supplementary data associated with this article can be found at: xxx: xxx
Experimental procedures; characterization data of **3**

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