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Medium-dependent regioselectivity of electrochemical bromination of methyl levulinate†

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An electrochemical method for the bromination of renewable methyl levulinate using ammonium bromide is reported. Regioselectivity depended on the solvent used: the formation of 5-bromolevulinate was favored in methanol and 3-bromolevulinate in a MeCN : H_2O mixture. To explain the observed change, different bromination mechanisms were proposed.

Introduction

There is a clear and urgent need for the more sustainable production of energy carriers, food, and materials.[1] In recent years, a significant number of environmentally friendly processes based on the utilization of renewable raw materials to replace fossil-based feedstocks has been described.[2–4] As such, biomass has been identified as an interesting alternative to produce fuels and chemicals.[5] Biobased chemicals are also already functionalized, so their use as building blocks may require fewer synthetic steps compared to starting from fossil-based feedstocks.[6]

Levulinic acid (LA)[7] has been identified as one of the most promising value-added platform chemicals that can be derived from biomass.[8] Already currently, it had a global market size of $80 million in 2022, which is expected to grow at a compound annual growth rate (CAGR) of 8.2% from 2021 to 2030.[9] LA and its esters can be produced using high-temperature acid hydrolysis or alcoholysis of carbohydrates such as glucose and sucrose but can also from cellulose present in wood and agricultural waste.[10,11]

Sustainability spotlight

Establishing the sustainable production of chemicals from renewable feedstocks is an important step towards achieving a circular economy. Bromo-derivatives of biomass-derived levulinic acid and its esters (3- and 5-bromolevulinates) serve as precursors for the production of biologically active compounds used in various market segments. Traditionally, these structures are synthesized by reaction with bromine – a hazardous and volatile chemical. In this work, we developed a method for electrochemical bromination of methyl levulinate using non-toxic ammonium bromide as a bromine source. This allowed to generate and convert bromine *in situ*, thereby reducing reliance on hazardous reagents. Implementing the developed green chemistry practices allows to minimize environmental harm in chemical manufacturing aligning with UN SDG 12 (Responsible Consumption and Production).

Having both keto- and carboxylic functional groups, LA and its esters can be transformed into many chemicals relevant for different bulk and fine chemical markets.[12,13] For example, alkyl levulinates find their application as green solvents and fuel additives,[14] while LA is a starting material for γ-valerolactone (GVL) also used as green solvent and fuel additive,[15,16] bioplastics,[17,18] as well as succinic acid (used in the cosmetics and pharmaceutical industry).[19,20] In addition, bromo-derivatives of levulinic acid (3- and 5-bromolevulinates) are of particular interest. These structures serve as versatile building blocks for the production of various biologically active compounds. For example, 5-bromolevulinic acid and its esters are the starting material for the synthesis of 5-aminolevulinic acid,[10,21] which exhibits anti-cancer-,[22–24] anti-bacterial activity,[25] and is active as a herbicide.[26] On the other hand, 3-bromolevulinic acid and its esters serve as precursors for the synthesis of heterocyclic compounds (thiazoles,[27,28] pyridazines,[29] pyridines,[30,31] *etc.*), which can be further used for the preparation of biologically active compounds (Scheme 1).

3-Bromolevulinate **2** and 5-bromolevulinate **3** are traditionally synthesized *via* bromination of levulinic acid or its esters with molecular bromine (Scheme 2).[32] Typically, a mixture of products **2** and **3** is formed in this reaction, after which the

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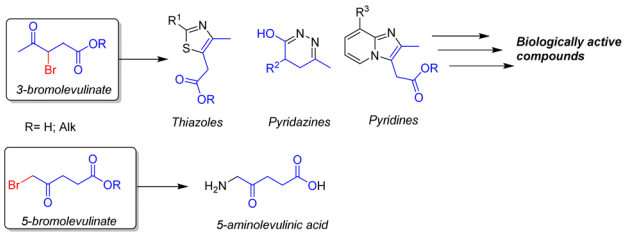


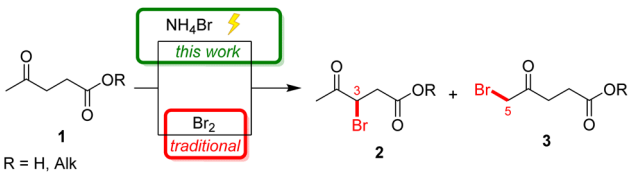
Scheme 1 Application of 3- and 5-bromolevulinates.

individual isomers are separated by distillation.[33] The regioselectivity of bromination depends heavily on the reaction conditions: performing this reaction in acidic aqueous media or in ionic liquids favors the formation of the 3-brominated product **2** in a ratio of up to 1 : 6, while employing MeOH or $CHCl_3$ as a solvent leads to 5-bromolevulinate **3** as the major product in a ratio of up to 3 : 1.[29,32]

Although the use of molecular bromine in organic synthesis is common, due to its hazardous nature, it should be prevented or minimized.[34] Indeed, from the perspective of green chemistry, developing more environmentally friendly and safer alternatives remains an important goal.[35]

Currently, due to its safety, controllability, and possibility to drive chemical reactions by renewable electricity, electrosynthesis is becoming a powerful alternative tool for organic synthesis.[36–38] For example, it allows electrochemical halogenations by facile electrochemical oxidation of halide anions, as an alternative to methods using hazardous and volatile bromine or chlorine. Utilization of the non-toxic and inexpensive inorganic halides as halogen precursors, especially in combination with green electricity, is becoming a greener alternative not only to using halogens, but also to expensive and/or toxic halogenating agents used in conventional halogenation reactions, *e.g.*, *N*BS (*N*-bromosuccinimide) or $SOCl_2$.[39,40] For LA or its esters, electrochemical bromination has, to our knowledge, not been reported yet, however.

Here, a convenient method for electrochemical bromination of methyl levulinate using non-toxic bromide salt as a bromine precursor to obtain 3- and 5-bromolevulinates as products will be presented. After preliminary optimization with respect to the type of Br-salt, temperature, substrate concentration, and current, the influence of solvent and addition of acid on substrate conversion and regioselectivity was studied. As bromo derivatives of levulinic acid are generally used as precursors in the form of esters,[21,41,42] in this work, instead of LA, methyl levulinate (ML) was chosen as a model substrate, also allowing to avoid possible electrochemical side reactions with the unprotected carboxylic group of the free acid.[43] The experiments were performed using Pt electrodes, as this electrode material was earlier reported to be used for electrochemical bromination of ketones.[44,45] ICP-OES analysis of the reaction mixtures after electrolysis confirmed that no platinum leaching took place (additional information available from the ESI†), nevertheless, the use of non-CRM can be considered for future studies.



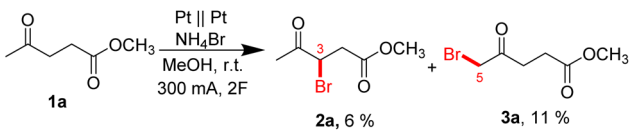
Scheme 2 Bromination methods for levulinic acid and its esters.

Results and discussion

First, preliminary studies were performed on the role of the nature of Br-salt, temperature, the concentration of ML, and current in methanol in an undivided cell. All the experimental details, as well as the characterization of the resulting reaction mixtures, are reported in the ESI (see Tables S1–S4 and Schemes S1–S4† for preliminary optimization). In all these experiments, the solutions turned slightly yellow from the beginning of the electrolysis which indicated the successful formation of bromine. However, since the intensity of the color (checked visually) did not increase, its concentration did not build up indicating that the bromine was further converted to products. Upon completion of electrolysis and after stirring at room temperature overnight, the reaction mixtures turned clear and colorless, indicating full consumption of electrochemically generated bromine. In these experiments, only 3-bromolevulinate methyl ester **2** and 5-bromolevulinate methyl ester **3** were found as products, while the formation of 2-bromolevulinate and 3,5-dibromolevulinate was never observed. Having carried out the preliminary optimization, studies were continued using the following conditions: NH_4Br as bromine salt (15 mmol), 4 mmol (0.26 M) ML, 300 mA current (2F passed = 2573 s electrolysis time) and room temperature (Scheme 3). Under these conditions, products **2a** and **3a** were obtained with yields of 6% and 11%, respectively, at a conversion of 19%.

Effect of acid

To increase reaction rate and selectivity, both strong and weak acids have been utilized in thermochemical bromination reactions.[34] For example, acetic acid is often used as it stabilizes the intermediates and/or activates the bromine molecule.[46] Among the others, such application of acetic acid as a solvent or an additive is also known for the thermochemical bromination of ketones and electrochemical bromination of arenes.[47–50] On the other hand, strong acids are also commonly used for the thermochemical bromination of ketones as they are known to favor the bromination into the internal α-position,[51] also for levulinic acid.[29,52] This is explained by the fact that strong acids favor the formation of enol forms, more reactive towards bromination.[53]



Scheme 3 Optimal conditions for the electrochemical bromination of methyl levulinate after preliminary optimization.

To investigate whether acid addition would also benefit electrochemical bromination of methyl levulinate, the reaction was performed with acetic acid (CH_3COOH), formic acid (HCOOH), and sulfuric acid (H_2SO_4) using MeOH as a solvent. In Table 1, the results on the influence of the type of acid and its concentration are compiled.

In the absence of acid (Entry 1), 3- and 5-bromolevulinates **2a** and **3a**, with yields of 6% and 11%, respectively, were formed at 19% conversion (best performance obtained during preliminary optimization, given here for comparison). Acetic acid addition proved detrimental for ML bromination, as in 0.25 M acetic acid (Entry 2), the conversion was slightly lower (14%) compared to the experiment without acid, while products **2a** and **3a** were not observed. In the presence of 0.25 M formic acid (Entry 3), product **3a** was formed with a yield of 8% at a conversion of 18%. Therefore, it can be concluded that the addition of these carboxylic acids was not beneficial for the electrochemical bromination of ML. In contrast, when using 0.25 M sulfuric acid (Entry 4), the conversion increased to 85%, yielding 16% for **2a** and 52% for **3a**. Moreover, in the presence of sulfuric acid, the electrochemically generated bromine was consumed immediately, as no coloration of the reaction mixture was observed. Although strong acidic media are known to favor bromination of the internal (in this case, C-3) alpha position,[52] here, the product of C-5 bromination **3a** was the major one formed (16% *vs.* 52% at 85% conversion).

After establishing that the addition of H_2SO_4 significantly improved bromination performance while maintaining good selectivity, the influence of the concentration of sulfuric acid was investigated. Decreasing its concentration to 0.1 M (Entry 5) resulted in a significant drop in both conversion and yield. Also, immediately after the start of electrolysis, the reaction mixture turned slightly yellow, meaning that bromine was no longer consumed immediately after generation, just like in a reaction without acid (Entry 1). When the acid concentration was increased to 0.5 M (Entry 6), ML conversion increased to 92% and yields of products **2a** and **3a** increased to 24 and 66%, respectively. Further increase in acid concentration to 0.75 M (Entry 7) showed a small decrease in products' yield at a small increase in the conversion. Selectivity dropped further upon further increase of acid concentration to 1 M (Entry 8), with yields of **2a** and **3a** to 15% and 39%, respectively, at 96% conversion. In the experiments where the total yield was significantly lower than conversion, the substrate and/or products were found to degrade under the electrochemical conditions (Entries 2, 3 and 8), individual products of these side reactions were not isolated. Thus, an 0.5 M sulfuric acid concentration proved most productive for **3a** with faradaic efficiency of 90% at average cell voltage of 5 V (Entry 6).

Table 1 Effect of acid on bromination of methyl levulinate[a]

Entry	Solvent	Acid, (M)	Conversion **1a**, %	Yield **2a**, %	Yield **3a**, %
1	MeOH	—	19	6	11
2	MeOH	AcOH (0.25 M)	14	0	0
3	MeOH	HCO_2H (0.25 M)	18	0	8
4	MeOH	H_2SO_4 (0.25 M)	85	16	52
5	MeOH	H_2SO_4 (0.1 M)	56	9	22
6	MeOH	H_2SO_4 (0.5 M)	92	24	66
7	MeOH	H_2SO_4 (0.75 M)	96	23	64
8	MeOH	H_2SO_4 (1 M)	96	15	39

[a] Reaction conditions: 0.54 g (4 mmol) **1a**, 1.47 g (15 mmol) NH_4Br, 12 ml MeOH, acid. 2F charge passed using Pt electrodes at rt (2573 s electrolysis time). The crude products were analyzed by ^1H NMR using 1,4-dinitrobenzene as internal standard with typical error of 3%.

Effect of solvent

Previously, it has been reported that performing the thermochemical bromination reaction in aqueous acidic media can favor the internal α-bromination with molecular bromine.[29,54] Moreover, many studies on the electrochemical bromination are carried out in an aqueous–organic solvent mixtures,[44,55] as the addition of water improves the conductivity and allows the dissolution of electrolytes. To further explore the dependence of regioselectivity on the reaction conditions, the effect of the addition of water was studied next.

Interestingly, in MeOH : H_2O (1 : 4 v/v) in the presence of 0.3 M sulfuric acid (Table 2, Entry 1), we now obtained 3-bromolevulinate **2a** as the major product and 5-bromolevulinate **3a** as the minor product with yields of 17% and 10%, respectively at 80% conversion. Even though the total product yield was only 27%, in this case, the selectivity has shifted towards the C-3 brominated product **2a** in contrast to the reaction performed solely in MeOH (Table 1, Entry 4 *vs.* Table 2, Entry 1) albeit at a slightly different acid concentration. When the reaction was performed in MeCN : H_2O (1 : 4 v/v) in the presence of 0.3 M sulfuric acid, a solvent mixture previously used for electrochemical bromination of ketones,[44] selectivity towards the C-3-brominated product further increased, with product yields for **2a** and **3a** being 30% and 11%, respectively, at 43% conversion (Table 2, Entry 2 *vs.* Table 2, Entry 1).

Having noted the significant improvement of reaction performance in the acidic MeCN : H_2O (1 : 4 v/v) media, the role of acid concentration using a MeCN : H_2O mixture as a solvent was studied next. An increase in acid concentration to 1 M (Table 2, Entry 3) resulted in the increase of conversion to 81% while the high selectivity towards the product of C-3

Table 2 Bromination of methyl levulinate in aqueous media[a]

Entry	Solvent	Acid, (M)	Conversion **1a**, %	Yield **2a**, %	Yield **3a**, %
1	MeOH–H_2O	H_2SO_4 (0.3 M)	82	17	10
2	MeCN–H_2O	H_2SO_4 (0.3 M)	43	30	11
3	MeCN–H_2O	H_2SO_4 (1 M)	81	59	20
4	MeCN–H_2O	H_2SO_4 (2 M)	96	12	2
5	MeCN–H_2O	—	Trace	0	0
6	H_2O	H_2SO_4 (0.3 M)	90	Trace	Trace

[a] Reaction conditions: 0.54 g (4 mmol) **1a**, 9.6 g (98 mmol) NH_4Br, organic solvent : water (4 + 16 ml), *X* ml H_2SO_4. 2F charge passed using Pt electrodes at rt (2573 s electrolysis time). The crude products were analyzed by ^1H NMR using 1,4-dinitrobenzene as internal standard with typical error of 3%.

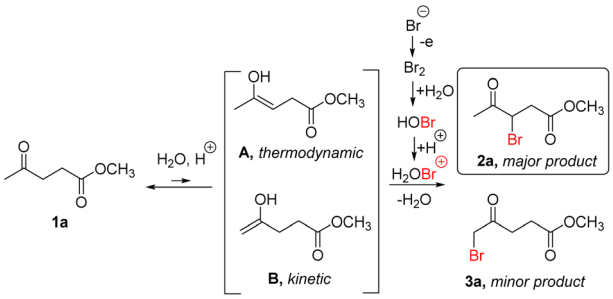
bromination was maintained. In this experiment, the yields of products **2a** and **3a** increased further to 59% and 20%, respectively. When the acid concentration was further increased to 2 M (Table 2, Entry 4), the yield of products **2a** and **3a** significantly dropped while the conversion increased to 96%. Such an increase in conversion accompanied by the drop in the product yields can possibly be explained by the hydrolysis of the ester group of both substrate and products.

Control experiments in either MeCN : H_2O without acid or in purely aqueous acidic medium showed that in the absence of sulfuric acid, the desired products were not formed (Entry 5), while in the absence of MeCN the desired products were formed in trace amounts at a ML conversion of 90% (Entry 6), probably due to a faster hydrolysis of the ester group in purely aqueous conditions.[56] Thus, both sulfuric acid and MeCN were crucial to achieve successful C3-favored electrochemical bromination of methyl levulinate. Best performance was achieved using 1 M concentration of sulfuric acid (Entry 3), with faradaic efficiency of 79% at average cell voltage of 1.5 V. Under optimal conditions (for both MeCN : H_2O and methanol), the reaction on the counter electrode (cathode) was hydrogen evolution, from either acid or solvent (water and MeOH). Formation of ammonia was also detected in trace amounts, but only in the experiments which were performed without acid. In presence of the acid, the electrochemically generated ammonia dissolved in the solvent, where under acidic conditions it again formed the ammonium cation. Upon completion of electrolysis, the ammonium salt was concentrated in the aqueous phase during extraction. Existing technologies (for example, membrane concentration) allow efficient and sustainable recovery of these salts from such solutions,[57] with subsequent reuse allowing lower costs and also environmental impact.

Biobased solvents (EtOH, mTHF) were also tested in combination with water, however both of them demonstrated significantly lower performance compared to originally used MeCN : H_2O system (detailed information available from p. 8 in the ESI†). Although MeCN is not considered as a green solvent, in this studies it was used as a co-solvent with volumetric concentration of 20%. At the same time, existing techniques allow to efficiently recover it (also from high-salt wastewater) thereby minimizing environmental impact.[58,59]

Rationalizing the regioselectivity

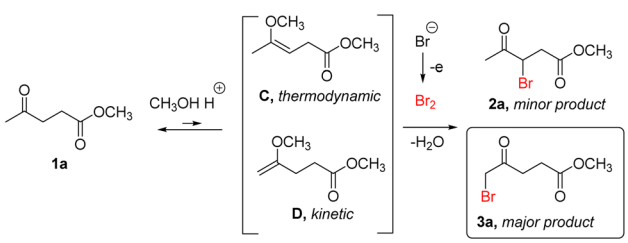
To explain the opposite trends in regioselectivity of electrochemical bromination using MeCN : H_2O and MeOH as solvents, mechanisms are proposed in Scheme 4 (for acidic MeCN : H_2O mixture) and in Scheme 5 (for acidic MeOH), based on our observations and literature data on (electrochemical) bromination of ketones under the same or similar reaction conditions. According to the proposed mechanism (Scheme 4), similar to electrochemical bromination of acetophenone,[44] hypobromous acid (HOBr) is formed *in situ* from electrochemically generated bromine under aqueous conditions.[60,61] Next, under acidic conditions, this intermediate undergoes protonation to form a more electrophilic H_2OBr^+ intermediate.[62,63] At the same time, acidic conditions can promote the enolization of



Scheme 4 Proposed mechanism for the electrochemical bromination of ML in MeCN : H_2O mixture.

carbonyl compounds to form more reactive enol species.[64] On the next step, H_2OBr^+ reacts with thermodynamic internal enol tautomer **A** of methyl levulinate,[65] resulting in the formation of the 3-bromo derivative **2a** as a major product due to the higher stability of internal enol **A**, as shown in Scheme 4 (thermodynamic stability of intermediates **A** and **B** was compared using DFT, see Table S5 in the ESI† for more information). This is in line with reported data for non-electrochemical bromination of levulinic acid with molecular bromine in purely aqueous acidic medium.[29]

On the other hand, that electrochemical LA bromination in methanol in the presence of sulfuric acid, yields the terminal 5-bromolevulinate **3a** as a major product, is not common for ketones under acidic conditions.[66] It has been observed, for thermochemical bromination of ketones in methanol without acid,[21,67] however, the bromination of the α-CH_3 group of ketones is usually performed solely in methanol without adding external acids.[68–70] It is likely that in methanol, in the presence of strong acid, the ML **1a** forms a mixture of enol ethers **C** and **D** (Scheme 5), as reported for various ketones.[64,71,72] Under such conditions (in acidic methanol without water), a pathway of bromination *via* enol ether was dominating over the others in the studies of kinetics and mechanism for bromination of acetone.[64] This indirectly suggests that ML can be brominated following the same pathway. Due to higher reactivity of enol ethers compared to corresponding enols,[73] the kinetic factor can dominate and determine their reactivity because their reaction occurs faster than the equilibration of enol forms, defining the regioselectivity of the reaction. In the case of bromination in acidic methanol,[74] unlike bromination in MeCN : H_2O discussed above, the position where bromination



Scheme 5 Proposed mechanism for the electrochemical bromination of ML in MeOH.

of enol ether occurs is determined by the form that reacts most rapidly with the bromine, *i.e.*, kinetically favored and sterically more accessible enol ether **D**, rather than the thermodynamically favored and sterically less accessible enol ether **C** (thermodynamic stability of enol ethers **C** and **D** was compared using DFT, see Table S6 in the ESI† for more information). This can explain the formation of the product of C-5 bromination **3a** as a major one. In such a case, the observed immediate bromine consumption in the media of acidic methanol can be explained by the bromination proceeding *via* more reactive enol ethers, which indirectly confirms such a pathway. Faster reaction of enol ether compared to corresponding enol was also confirmed by kinetic studies on bromination of acetophenone.[73] For bromination in methanol, in order to form the active enol ether, keto-group of the initial ketone first gets protonated, forming hemiketal and then enol ether.[64,73] Most likely, strength of the tested organic acids was not enough to achieve this protonation resulting in considerably lower performance compared to strong sulfuric acid. An overview of ^{1}H NMR spectra of crude products in acidic MeCN : H_2O mixture and in acidic MeOH is available from the ESI (Fig. S1 and S2).†

Conclusions

Overall, we reported herein an electrochemical method for bromination of renewable methyl levulinate, where commercially available and non-toxic ammonium bromide was used as a bromine source. Having studied the influence of the media on reaction regioselectivity, we demonstrate that in the media of acidic MeCN : H_2O mixture, the formation of C-3 bromolevulinate was favored. In contrast, performing the reaction in acidic methanol resulted in the formation of C-5 bromination product as a major. This can be possibly explained by different bromination pathways. According to the proposed mechanisms, both bromination reactions proceed through enolization. In an acidic MeCN : H_2O mixture, more thermodynamically stable internal enol underwent the bromination resulting in the formation of a C-3 brominated product, while on the other hand, in the acidic methanol mixture, a more reactive terminal enol ether was converted into the C-5 brominated product. Unlike enol, enol ether reacted faster with bromine, forming the kinetic product of C-5 bromination. In the optimized conditions, upon passing 2F charge, the bromination products were formed in approximately 3 : 1 and 1 : 3 ratio with the total yield of 81 and 90%, respectively. As these compounds have application in different fields and quantities, more selective (electrochemical) synthesis is important for favoring formation of the desired isomer with higher yield.

Data availability

The data supporting this article is available from the ESI.†

Author contributions

Dmitry A. Pirgach: investigation, conceptualization writing – original draft. Raghavendra Meena: software – DTF studies. Guanna Li: supervision. Fedor M. Miloserdov: writing – review & editing, supervision. Daan S. van Es: writing – review & editing, supervision. Pieter C. A. Bruijnincx: writing – review & editing, supervision. Johannes H. Bitter: writing – review & editing, project administrator, funding acquisition; supervision.

Conflicts of interest

There are no conflicts to declare.

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