

From tetroses to methionine hydroxy analogues through Sn (IV) Lewis acid catalysis using methanethiol as sulphur feedstock

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ABSTRACT

Methionine hydroxy analogues (MHAs) form part of a million tonne scale commodity market of compounds useful in livestock nutrition. The chemocatalytic synthesis of MHAs from carbohydrates is an important albeit understudied transformation *en route* to a sustainable and circular economy. Here we report our first results for the conversion of tetroses to MHAs in the presence of methanethiol (MeSH) and SnCl₄·5H₂O. Our study allowed to corroborate the major reaction pathways involved in this Lewis acid-catalysed transformation. It was also found that the ratio between MeSH and MeOH, the pressure of inert gas, and the water content strongly affect the reaction performance. When these parameters were combined the yield and selectivity towards MHAs increased to the highest reported value of 38 % in one hour reactions at 413 K. Our findings have the potential to unlock the sustainable synthesis of MHAs from renewable feedstock such as tetroses and other carbohydrates.

1. Introduction

Replacing non-renewables by biomass-derived carbohydrates as feedstock for the synthesis of bulk and fine chemicals is of paramount importance to reach a sustainable future [1,2]. Vast efforts have been made to convert carbohydrates to chemicals and materials that replace those obtained from non-renewable sources such as oil and coal [2,3]. The production of the racemic mixture of D- and L-methionine (DL-Met) and of 2-hydroxy-4-(methylthio)butyric acid (HMTBA), a methionine hydroxy analogue (MHA), is key to achieve both the “zero hunger” and the “responsible consumption and production” sustainable development goals of the United Nations, [1] since these compounds are used to supplement animal feed to achieve optimal development and protein yields in livestock for human consumption [4] while minimizing livestock waste [5,6].

In 2018, close to 1.6 million tonnes of DL-Met and HMTBA [7,8] were produced by chemical synthesis [9,10]. These chemical methods rely heavily on non-renewable feedstock from the oil industry, such as propylene or acrolein, [8,11–14] and involves hazardous byproducts such as cyanide, making these processes less sustainable than desired.

Wilke reviewed in 2014 the industrial production of methionine and HMTBA, describing the methods available, their potential and challenges [8]. Wilke highlighted other industrially relevant methods to synthesize methionine, the L-isomer, by fermentation or enzymatic processes that also depend on precursors obtained by chemical synthesis. These methods are relatively more sustainable and involve less hazardous byproducts but they produce lower yields and concentrations of methionine in solution, making them more expensive. Attempts to produce methionine from carbohydrates using genetically modified bacteria and yeast typically have yields well below 30 % [8], leaving these processes far behind the current chemical methods with yields of up to 95 % or 85 %, calculated on acrolein or propylene, respectively [10,15].

Research on the chemocatalytic conversion of carbohydrates to platform molecules that can be converted to HMTBA or other MHAs could improve the sustainability of MHAs synthesis. The conversion of carbohydrates to 2-hydroxy-γ-butyrolactone (2-HBL) and methyl vinyl glycolate (MVG) in yields of up to 70 % and 50 %, respectively, have been achieved in recent years, mainly by homogeneous and heterogeneous Sn catalysts [16–20]. On the other hand, it has long been

Abbreviations: DL-Met, racemic mixture of D- and L-methionine; ERO, erythrose; ERU, erythrulose; 2-HBL, 2-hydroxy-gama-butyrolactone; HMTBA, 2-hydroxy-4-(methylthio)butyric acid; MHA, methionine hydroxy analogue; MVG, methyl vinyl glycolate.

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known that 2-HBL and MVG can be efficiently converted to MHAs [21, 22].

It is undeniable that research on the direct chemocatalytic conversion of carbohydrates to MHAs has been very scarcely explored [23]. Recently we reported the main reaction pathways involved in the conversion of erythrose to sulphides of alpha hydroxy thioesters and esters (SAH(T)Es) in the presence of butanethiol and Lewis acid catalysts [24]. These SAH(T)Es are HMTBA analogues, where the alkyl chain bounded to the sulphur atom is a butyl instead of a methyl group. We found there that the formation of thioacetals was the main limiting factor for the reaction's selectivity towards SAH(T)Es. Addition of KOH, water or polar protic solvents contributed to decrease the formation of thioacetals and increase selectivity towards SAH(T)Es. Yield and selectivity towards SAH(T)Es of 23 % were obtained in a reaction catalyzed by $\text{SnCl}_4 \cdot 5 \text{H}_2\text{O}$ in a butanethiol/methanol mixture at 353 K during 6 h.

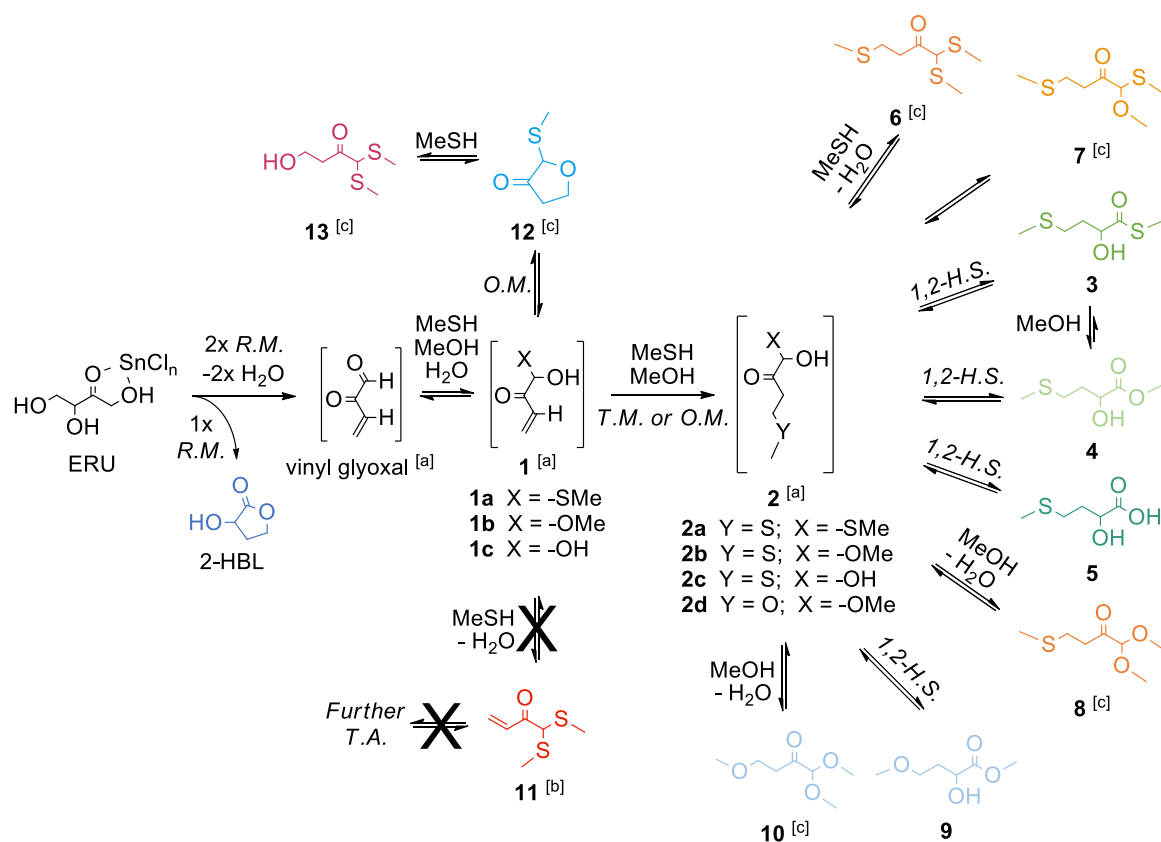
Here we describe the conversion of tetroses to industrially relevant MHAs in the presence of methanethiol (MeSH) and $\text{SnCl}_4 \cdot 5 \text{H}_2\text{O}$. Our results show that the ratio between MeSH and MeOH, the pressure of inert gas, and the presence of small amounts of water in the reaction mixture affected the selectivity towards MHAs and other sulphides of interest. The combination of these parameters allowed to increase the yield and selectivity towards MHAs to the highest reported value of 38 % in one hour reactions at 413 K. Additionally, product isolation, characterization through mass spectrometry and NMR spectroscopy (see Figs S1-S20, S22-S25), quantification through GC-FID and HPLC and rationalization based on our previous work in SAH(T)Es synthesis allowed to corroborate the reaction pathways of the system as presented in Scheme 1. As opposed to butanethiol, we found that MeSH does not form the very detrimental thioacetals of vinyl glyoxal previously identified in the synthesis of SAH(T)Es, hence the improved selectivity

towards MHAs can be attributed in part to the lower nucleophilicity of MeSH with respect to butanethiol. On the other hand, the higher vapor pressure of MeSH, when compared to butanethiol, strongly affected the gas-liquid equilibrium of the sulphur source in the system and introduced a new reaction variable that did not show an effect in our previous work with butanethiol, namely the pressure of inert gas. Reactions with MeSH showed improved selectivity towards the sulphides of interest when working at high pressure under nitrogen atmosphere, allowing a higher yield of MHAs when combined with an adequate balance between MeSH and methanol (MeOH) and the addition of small amounts of water. These results offer a roadmap for future improvements to the sustainable chemocatalytic synthesis of MHAs from tetrose sugars that can be obtained from more readily available carbohydrates such as glucose (through its retro-aldolization [25] or aldolization of glycolaldehyde [26,27] prepared by retro-aldolization or pyrolysis of glucose [28,29]).

2. Experimental methods

2.1. Chemical reactions

Reactions were carried out in a 50 mL Parr ® reactor with a glass liner. In a standard experiment the reactor is loaded with a tetrose substrate (7.5 mmol, e.g. 1.06 g of L-(+)-erythrose, 85 % from Sigma-Aldrich), $\text{SnCl}_4 \cdot 5 \text{H}_2\text{O}$ (268.5 mg equivalent to 0.75 mmol of Sn(IV), 98 % from Honeywell Fluka), methanol (11.88 g, 99.8 % from Acros Organics) and naphthalene (30.0 mg, 99 % from Acros Organics) that is added as internal standard. The reactor is closed, purged three times with N_2 gas and cooled to 258 K prior to the addition of MeSH (e.g. 368.2 mg in gas phase at a pressure of 0.5 bar-g, 98 % from Sigma-



Scheme 1. Reaction pathways for the catalytic conversion of tetroses to methionine hydroxy analogues in MeSH/MeOH mixtures. [a] Intermediate not detected. [b] Compound not detected. [c] Product identified by GC-MS fragmentation pattern and ^{13}C and ^1H spectrometry in reaction mixtures. X is either -SMe, -OMe or -OH. Y is a sulphur or oxygen atom. R.M. = retro-Michael reaction. T.M. = Thiol-Michael reaction. O.M. = Oxa-Michael reaction. T.A. = thioketalization reaction. 1,2-H.S. = 1,2-hydride shift.

Aldrich) through a mass flow controller. The reactor is pressurized to 40 bar-g with N₂ and finally it is heated to 413 K for 60 min with mechanical stirring at 800 rpm. The reaction is stopped by putting the reactor in an ice-water bath for 15 min. Finally, the reactor is depressurized, flushed three times with nitrogen gas, opened and the reaction mixture is taken for analysis.

All water used in the experiments and analysis was Milli Q® water, unless otherwise specified.

2.2. Product characterization

Reaction products were characterized by GC-MS and NMR analysis of either crude reaction mixtures or compounds isolated therefrom through flash chromatography (see Figs. S1-S24). Isolated compounds were used to make calibration curves for their quantification by GC-FID and HPLC.

2.2.1. GC-MS analysis

GC-MS was carried out in a gas chromatographer (Agilent 6890) provided with a HP-5 ms column (30 m x 0.25 mm; film thickness = 0.25 μm) and a single quadrupole mass spectrometer detector (Agilent 5973 N MSD) with electron ionization. The carrier gas was Helium (flow rate = 0.7 mL·min⁻¹). Samples were injected by means of a split/splitless injector at 523 K using a split ratio of 1/20. The temperature profile of the GC oven was as follows: 333 K_ hold:1 min; ramp to 433 K_ rate: 3 K·min⁻¹; ramp to 533 K_ rate: 10 K·min⁻¹; 533 K_ hold: 10 min. The mass spectrometer used a ion source temperature of 503 K, an ionization energy of 70 eV, a mass scan range of m/e of 30–550 amu, an electron multiplier voltage of 900 V, and a solvent delay of 2.1 min.

2.2.2. NMR analysis

Pure compounds were also characterized through ¹³C, DEPT 90, DEPT 135, ¹H-¹³C HSQC and ¹H NMR spectrometry using a Bruker Avance III HD 400 spectrometer, provided with a Bruker Ascend™ 400 magnet and a 5 mm PABBO BB/19 F-1 H/D probe with z-gradients and ATM device. The compounds were solubilized in 0.6 mL of either CD₃CN or DMSO-d₆ prior to analysis. Spectra were acquired at 298 K.

2.3. Compound quantification

2.3.1. GC-FID analysis

Reaction products were quantified by GC-FID analysis of reaction mixtures in an Agilent 6890 gas chromatographer equipped with a HP-5 column (30 m x 0.32 mm; film thickness = 0.25 μm) and a flame ionization detector (FID). The carrier gas was N₂. The conditions for the carrier gas, sample injection as well as the temperature profile in the GC oven were the same applied in GC-MS. The temperature of the FID was 543 K.

2.3.2. HPLC analysis

Tetrose conversion was quantified by HPLC analysis using an Agilent 1200 series liquid chromatographer provided with a Metacarb 67 H column along with a refractive index detector. The samples were analysed at 308 K, eluting with an aqueous solution of H₂SO₄ (5 mM) at a flow rate of 0.5 mL·min⁻¹.

Quantification of 5 and 2-HBL was carried out by reverse phase HPLC analysis in a Waters Alliance e2695 HPLC provided with a C-18 column (Shim-pack GIS (G), 250 × 4.6 mm; 5 μm particle size) coupled with a UV/Vis detector (λ = 210 nm). Column temperature was set at 313 K prior analysis. Samples were analysed in gradient mode, employing both a mixture of acetonitrile, water and H₃PO₄ (5:94.6:0.4, solution A) and a mixture of acetonitrile and water (95:5, solution B) as mobile phase at a flow rate of 1 mL·min⁻¹. Profile of the mobile phase: 0 min (100 % solution A), hold for 6 min; 16 min (32 % A, 68 % B); 17 min (5 % A, 95 % B), hold for 8 min; 28 min (100 % A), hold for 8 min

2.4. Determination of conversion and yield

Tetrose conversion was determined as shown in Eq. (1).

$$Conv_{Tet}(mol\%) = ([Tet]_I - [Tet]_F) \cdot \left(\frac{100}{[Tet]_I} \right) \quad (1)$$

with [Tet]_I and [Tet]_F as the molar concentration of the carbohydrate before and after reaction, respectively.

Product yield was determined as shown in Eq. (2).

$$Y_P(mol\%) = n \cdot [P] \cdot \left(\frac{100}{z \cdot [Tet]_I} \right) \quad (2)$$

with [P] as the molar concentration of a product P, and with “n” and “z” as the stoichiometric coefficients for the tetrose and P, respectively, in the reaction that converts said tetrose to P.

3. Results and discussion

Replacing butanethiol, a liquid under standard conditions, by the more volatile MeSH increased the complexity of our reaction setup, which now requires low temperature feeding of the sulphur source to guarantee its condensation in order to achieve its reliable incorporation in the reaction mixture. As these thiols present at least different physical properties, we first studied the effect of MeSH content in the conversion of tetroses (erythrulose (ERU) or erythrose (ERO)) to MHAs in the presence of SnCl₄·5H₂O and MeOH at 413 K during one hour. The reactions were performed under a N₂ pressure of 40 bar since, as it will be discussed later, high N₂ pressures led to a higher selectivity toward our sulphides of interest. Both tetroses showed similar results as shown in

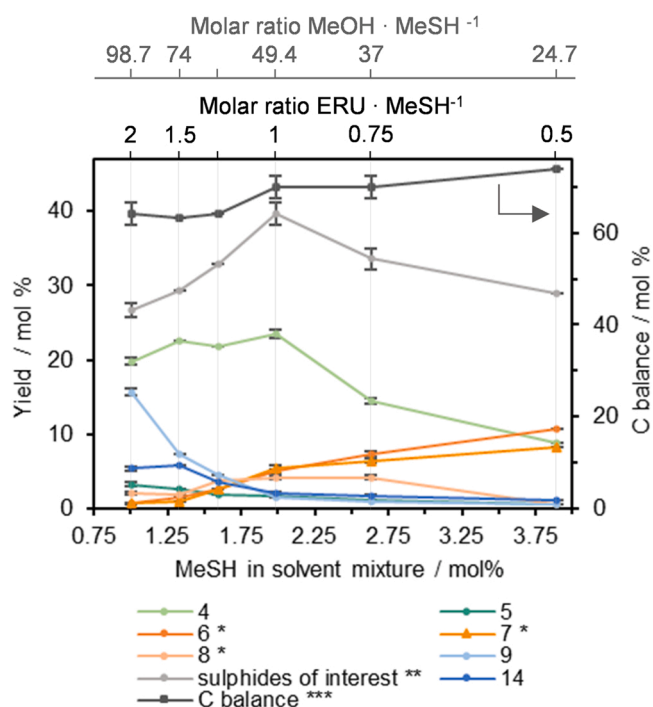


Fig. 1. Effect of MeSH content on the conversion of ERU to alpha-hydroxy methionine analogues in the presence of MeOH and SnCl₄·5 H₂O at 413 K for one hour under a N₂ pressure of 40 bar. Molar ratio ERU to Sn of 10. ERU reached full conversion in all reactions. * Yield calculated by GC-FID using the ECN method. ** sulphides of interest is the sum of yields of compounds 3 to 8. *** The carbon balance takes into account the yield of all identified species that were detected by GC-FID and HPLC. Error bars (standard error of the mean for a triplicate experiment) included for reactions with MeSH contents of 1, 2 and 2.6 mol. % in the solvent mixture.

Fig S21. For ERU, the results of Fig. 1 show that the highest yield of 23 % for the MHA 4 was obtained in the presence of 2 mol. % of MeSH in the solvent mixture (at molar ratio MeOH to MeSH of 49). The yield of other sulphides that can be converted to MHAs, namely the dimethylthio acetal 6, the monomethylthio acetal 7 and the dimethyl acetal 8, was around 5 % each. Under these conditions, the yield of MHAs was 25 % while the yield of all sulphides of interests, *i.e.* including 4, HMTBA (namely compound 5 in Scheme 1), 6, 7 and 8, was 40 %.

¹³C NMR spectroscopy measurements of this reaction showed that the sulphides of interest reported here correspond to the main products of the reaction pathways in Scheme 1 (Figs S22-S24) assuming that all reaction products remain in the liquid phase as no precipitation or pressure increase due to the formation of volatile products in the gas phase were observed. These measurements also proved that all other products presented in Scheme 1 and the missing 30 % of the carbon balance corresponded to minor products with concentrations below the detection limit of qualitative ¹³C NMR spectroscopy.

The MHA 3 was found in traces in the reaction mixture as an evidence to its high conversion towards 4 at high temperature (413 K). This is in agreement with additional experiments that demonstrated that the thioester 3 is a kinetically preferred product that is converted to its thermodynamically favored ester 4 in case of long time reactions or high temperatures (Fig S25). These results are consistent with the literature reporting the thermodynamic preference of esters over thioesters in acyl transfer reactions with thiols and alcohols [30].

At MeSH loadings higher than 2 mol. % in the solvent mixture (molar ratio MeOH to MeSH lower than 49), the intermediate vinyl glyoxal was preferably converted to its hemithioacetal 1a. After thiol-Michael addition on 1a, the excess of thiol led to the conversion of the Michael adduct 2a to larger amounts of the thio- and mono- acetals 6 and 7 and smaller amounts of 4. The formation of 12 and 13 supports the prevalence of this reaction pathway at high thiol contents. Our results demonstrate that the conversion of tetroses in the presence of MeSH differs from that with BuSH [24]. For the reactions with MeSH we did not evidence the formation of thioacetals of vinyl glyoxal (such as 11), which led to the higher selectivity of the reaction towards MHAs (see Figs S22–S24, particularly Fig S23 c showing that the proton signals do not have the multiplicity of the vinylic protons in thioacetals of vinyl glyoxal).

Conversely, at MeSH loadings lower than 2 mol. % in the solvent mixture (molar ratio MeOH to MeSH higher than 49), the excess of MeOH effectively competed with MeSH for addition to the aldehyde carbonyl in vinyl glyoxal to preferably yield its hemiacetal 1b. The latter can later undergo thiol or oxa-Michael addition reactions with MeSH or MeOH, respectively. After thiol-Michael addition on the hemiacetal 1b, the formed Michael adduct 2b was mainly converted to 4 since the excess of MeOH prevented its thioacetalization. Under these conditions, most of the MeSH is available for the desired thiol-Michael reaction, which explains why the yield of 4 did not decrease drastically upon halving the MeSH content from 2 to 1 mol. % in the solvent mixture. The oxa-Michael addition of MeOH to the hemiacetal 1b, that led to the formation of 9, is expected to occur in the late stage of the reaction when the medium was depleted of thiol, as it was previously demonstrated through *in situ* ¹³C NMR experiments in the BuSH system [24].

When compared with our previous results with BuSH, where the highest yield of SAH(T)Es was obtained at a molar ratio MeOH to BuSH of around 100 [24], it turns out that the presence of the more volatile MeSH strongly affected the gas-liquid equilibrium of the sulphur source in the system, which now requires double the molar amount of thiol to reach the highest yield of sulphides of interest. Furthermore, the improved selectivity towards MHAs and other sulphides of interest that was obtained with MeSH is attributed to its expected lower nucleophilicity (based on its lower pK_a [31] and the smaller alkyl chain that makes it a poorer electron donating group than BuSH). We consider that the addition of a weaker nucleophile (MeSH or the weaker MeOH) to the aldehyde carbonyl in vinyl glyoxal preserves better the electrophilicity

of the terminal carbon in the enone 1, making it a notable electrophile for the desired thiol-Michael addition.

We also found that the pressure of inert nitrogen gas used in the reactions involving MeSH affected the yield of products, as shown in Fig. 2, an effect that was not observed when working with BuSH. For the reactions with MeSH, higher nitrogen pressures produced a similar effect as increasing the thiol loading in the reaction mixture, thus leading to higher yields of thioacetals (such as 6) and lower yields of acetals (such as 8) and 9. The effect of nitrogen pressure on the formation of the MHAs 3 to 5 was minimal in the range tested. As a consequence, higher nitrogen pressures produced a higher selectivity toward the sum of sulphides of interest, offering an approach to increase the yield of MHAs when combined with the addition of small amounts of water to the reaction mixture, as it will be shown later.

At a first glance these results could suggest an increase of thiol content in the liquid phase with higher pressures of nitrogen gas, meaning an improved incorporation of sulphur in the reaction. However, Raoult's law predicts an increase of MeSH in the liquid phase of less than 0.003 mol. % as a consequence of decreasing its partial pressure by dissolution of higher amounts of nitrogen gas in methanol at 40 and 60 bar (see Table S1) [32]. Therefore, this minor increase of molar fraction of MeSH in the liquid phase cannot fully explain our results. We also considered the idea that these results could arise from a better removal of residual oxygen (from air) when the reaction is carried out at high nitrogen pressures, then preventing the oxidation of MeSH. However, we found that the yield of oxidized sulfur products (dimethyl disulphide and dimethyl sulphide) was low and comparable at the different pressures tested.

These results could also be attributed to other properties of the system that are affected by pressure such as the activation volume, which in turn can affect the reaction rate, equilibrium constant and selectivity, among others [33]. For instance, reactions with negative activation volumes have a faster reaction rate at higher pressures. Negative activation volume are typical in, but not limited to, addition reactions [34]. Although our reaction cascade is very complex and the activation volume of each reaction step (and that of the overall transformation) cannot be established by simple means, the reaction pathways of Scheme 1 show that additions to the carbonyl (of vinyl glyoxal) and Michael additions to the enone of 1 could involve negative activation volumes, so

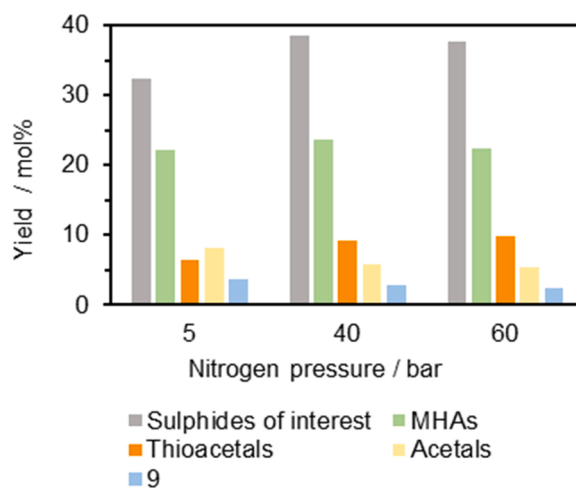
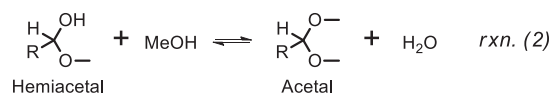
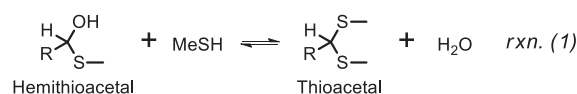


Fig. 2. Effect of nitrogen gas pressure in the conversion of ERU to alpha-hydroxy methionine analogues in the presence of MeOH and SnCl₄·5H₂O at 413 K for one hour. Molar ratios ERU to Sn of 10 and MeOH to MeSH of 49. ERU reached full conversion in all reactions. Sulphides of interest is the sum of yields of compounds 3–8. MHAs is the sum of yields of compounds 3, 4 and 5. Thioacetals is the sum of yields of compounds 6, 7 and minor thioacetal byproducts. Acetals is the sum of yields of compounds 8, 10 and minor acetal byproducts.

that these reactions could be accelerated by the increase of pressure on the system. Interestingly, these reactions are crucial for the formation of the thioacetals that evidenced the (very modest) increase in selectivity in our experiments at higher nitrogen gas pressures. However, it is clear that testing this hypothesis will demand further investigation from both the theoretical and experimental point of view. Among the future work is performing experiments in a piston-cylinder reactor, where pressures above 100 bar can be easily reached, to evaluate the benefits of high pressure in the conversion of carbohydrates to MHAs and its sulphur efficiency (a parameter we could not establish for our system due to the configuration of the experimental setup and its safety requirements involving reactor venting and flushing with nitrogen after reaction).

Finally, we studied the effects of water content in the reaction. Specifically, this variable was assessed in the reaction using 2 mol. % of MeSH in the solvent mixture and a nitrogen pressure of 40 bar. Fig. 3 shows that increasing the water content from 3 mol. % (from water present in ERU substrate and catalyst) to 16 mol. % increased the yield of **4** and **5** from 23 % to 35 % and from 1 % to 3 %, respectively, for a total yield of MHAs of 38 %.

The results show that the addition of small amounts of water increased the selectivity towards **4** by hindering the (thio)acetalization reactions that form **6**, **7** and **8**. The Le Chatelier's principle that applies to the reversible (thio)acetalization reactions, as depicted in Scheme 1 and reactions (1) and (2), indicates that the presence of water since the beginning of the reaction can hinder the conversion of freshly formed hemi(thio)acetals (Michael adducts **2a** and **2b** in Scheme 1) to their corresponding (thio)acetals (**6**, **7** and **8**). As a consequence, said Michael adducts will be available for conversion to MHAs through a Lewis acid catalyzed 1,2-hydrate shift [35].



The addition of water to the system is a successful strategy to minimize the formation of thioacetals as long as the hemithioacetals are consumed, as fast as possible, to form MHAs. Otherwise, thioacetals will be formed despite the presence of water, given the well-known large formation constants of thioacetals, and their low rate of hydrolysis (at least when catalyzed by Brønsted acidity).[36,37] Conversely, the hydrolysis of acetals is rather easier to achieve due their typically smaller formation constant and their higher rate of hydrolysis (e.g. the rate constants for hydronium catalyzed hydrolysis of the ethyl thioacetal and ethyl acetal of benzaldehyde to the aldehyde form are $k_{\text{benzal-thioacetal}} = 3.5 \times 10^{-4} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ vs $k_{\text{benzal-acetal}} = 160 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$, where the hydrolysis of the (thio)acetal to the hemi(thio)acetal is normally the rate determining step of the process) [38,39].

We also observed that the presence of small amounts of water increased the selectivity towards **5**, although at a modest extend. In this case, water may slightly hinder the formation of the hemithioacetal **1a** and hinder more effectively the formation of the hemiacetal **1b**, while promoting the formation of the hydrate of vinyl glyoxal **1c**, which would be later converted to **5**. The competition between water and MeSH for addition to the aldehyde carbonyl in vinyl glyoxal is expected to favor the addition of the thiol. On the one hand, thiols are typically better nucleophiles than water, so that the addition of MeSH to the aldehyde carbonyl in vinyl glyoxal is kinetically preferred. On the other hand, the equilibrium constants for the addition of thiols to aldehyde carbonyl to form hemithioacetals (K_{hemithio}) are typically larger than the equilibrium constants for the addition of water to form hydrates (K_{hydrate}), so that the addition of MeSH to the aldehyde carbonyl is also thermodynamically preferred (e.g. the equilibrium constants for addition of ethanethiol and water to acetaldehyde are $K_{\text{hemithio-EtSH}} = 36 \text{ M}^{-1}$ vs $K_{\text{hydrate-water}} = 0.85 \text{ M}^{-1}$) [40]. These considerations explain the modest increase in selectivity towards **5** that is caused by the presence of water. Under these considerations a large formation of the MHA **3** would be expected, however only traces of **3** are found in the reaction mixture as **3** is converted to **4** at the temperature of the reaction (as previously mentioned).

Water contents above 16 mol. % of the solvent mixture resulted in lower yields of compounds requiring Lewis acidity for their formation such as MHAs and **9**. These results indicate that high water contents decreased the Lewis acidity of the catalyst by hydrolysis and likely lead to inactive $\text{Sn}(\text{OH})_x$ and SnO_x species and Brønsted acidity (HCl). In a system with reduced Lewis acidity, Brønsted acidity could become more dominant and catalyze the conversion of a larger proportion of the substrate to by-products involving retro-Michael [19], hemi(thio)acetalization [40], and (thio)acetalization [41,42] reactions (despite the presence of water hindering the formation of the latter). Our experiments at high water contents produced larger amounts of by-products involving said reactions, such as **12**, **13** and other minor by-products with a C₁ to C₄ backbone such as the monothioacetal of formaldehyde methoxy-(methylthio) methane, acetals and thioacetals of glycolaldehyde, acetal of methyl pyruvate, methyl lactate, methyl-3-(methylthio)propanoate and 3,3-dimethoxy-2-butanone (not shown). The formation of these species in important amounts confirms that the excess of water caused the loss of Lewis acidity in the catalyst.

These results suggest that controlling the Brønsted acidity in the system could improve the reactions selectivity toward the formation of MHAs. Furthermore, additional work will be required to establish the identity and reaction pathways of some of the minor reaction products

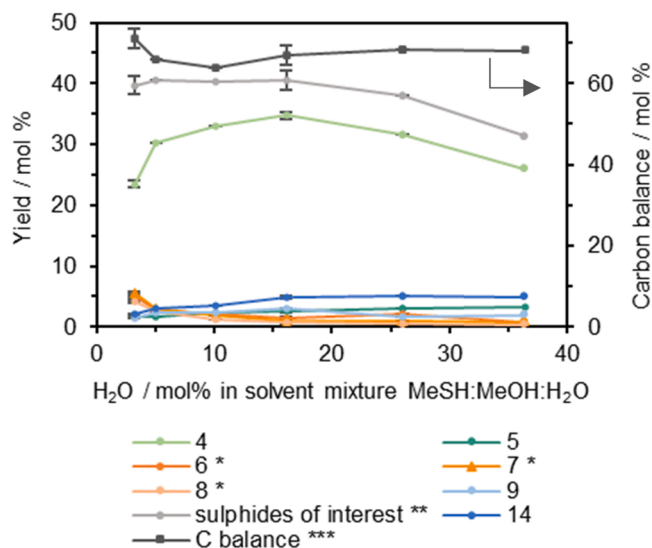


Fig. 3. Effect of water content on the conversion of ERU to alpha-hydroxy methionine analogues in the presence of MeSH, MeOH and $\text{SnCl}_4 \cdot 5 \text{H}_2\text{O}$ at 413 K for one hour under a N_2 pressure of 40 bar. Molar ratios ERU to Sn of 10 and MeOH to MeSH of 49. ERU reached full conversion in all reactions. * Yield calculated by GC-FID using the ECN method. ** Sulphides of interest is the sum of yields of compounds **3–8**. *** The carbon balance takes into account the yield of all identified species that were detected by GC-FID and HPLC. Error bars (standard error of the mean for a triplicate experiment) included for reactions with water contents of 3.2 and 16.1 mol. % in the solvent mixture.

that account for up to 30 % of the carbon balance of the reaction.

4. Conclusions

In conclusion, our studies of the conversion of tetroses to methionine hydroxy analogues (MHAs), one of the main amino acid-like feed additives, in the presence of MeSH, MeOH and SnCl₄·5H₂O corroborated the major reaction pathways involved in this Lewis acid catalyzed transformation. These reaction pathways allowed to rationalize the effects of varying certain reaction parameters such as the thiol and water content. Our results showed that both an adequate balance between MeSH and MeOH and the addition of small amounts of water to the reaction increased the selectivity towards MHAs by minimizing the unfavorable thioacetalization side-reactions. Furthermore, an increase in selectivity towards certain sulphides of interest with thioacetal functionality was found when working at high pressures of inert nitrogen gas. This finding offered a way to increase the yield of MHAs when combined with the strategies intended for minimizing thioacetalization reactions. Using a molar ratio MeOH to MeSH of 49, 40 bar of pressure of nitrogen gas, and a water content of 16 mol. % in the solvent mixture, the yield of MHAs increased to a maximum of 38 % in one hour reactions at 413 K. In contrast with the synthesis of SAH(T)Es with butanethiol, we found that in the presence of MeSH no thioacetal of vinyl glyoxal was formed, so that the improved selectivity towards MHAs can be attributed in part to the lower nucleophilicity of MeSH with respect to butanethiol. Our results suggest that the selectivity towards MHAs could be also improved in a system with controlled Brønsted acidity (which is generated by catalyst hydrolysis). Evidence of increased thiol concentration in the liquid phase of the reaction by working at high pressure of nitrogen, suggest that the synthesis of MHAs could benefit from high pressure synthesis in piston-cylinder reactors. Finally, our results exposed one of the main hurdles of the catalytic conversion of tetroses, namely the formation of a large number of minor by-products with a very low yield that renders their identification challenging. The findings of this study have the potential to unlock the sustainable synthesis of MHAs from renewable feedstock such as C₄ carbohydrates, that can be obtained from abundant carbohydrates such as glucose.

CRedit authorship contribution statement

S. Calderon-Ardila: Conceptualization, Investigation, Formal analysis, Methodology, Writing - original draft. **F. Rammal:** Data curation, Formal analysis, Writing - original draft. **E. Peeters:** Data curation, Formal analysis, Methodology, Writing - review & editing. **J. Van Waeyenberg:** Formal analysis, Validation, Writing - review & editing. **O. Péruch:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **D. Morvan:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **V. Bellière-Baca:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **M. Dusselier:** Conceptualization, Methodology, Supervision, Writing - review & editing. **B. F. Sels:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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