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ORIGINAL ARTICLE

Heterogeneous Catalytic Esterification of ω-Sulfhydryl Fatty Acids: Avoidance of Thioethers, Thioesters, and Disulfides

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Abstract Two mesoporous silicas functionalized with propylsulfonic (SBA-15-PSA) and arenesulfonic (SBA-15-ASA) acid groups, and a highly acidic, functionalized styrene divinylbenzene copolymer ion exchange resin (Amberlyst-15) were examined for their ability to catalyze the ethanolic esterification of the ω-sulfhydryl fatty acid, 11-mercaptoundecanoic acid (MUA), without catalyzing unwanted side reactions at the sulfhydryl group. All three solid acid catalysts catalyzed the MUA esterification in excess ethanol. The activation energy for the catalytic esterifications were determined from 50 to 75 °C, resulting in apparent E_a of 54, 71, and 59 kJ/mol for SBA-15-PSA, SBA-15-ASA, and Amberlyst-15, respectively. GC–MS analysis determined that all three catalysts produced near quantitative conversion of MUA to its ethyl ester with very little reactivity towards the sulfhydryl group. This was a marked improvement over the esterifications catalyzed by sulfuric and *p*-toluenesulfonic acids which produced thioethers and disulfide side products. The MUA ethyl ester synthesis was demonstrated on a gram scale at 70 °C catalyzed by Amberlyst-15, and the desired product was isolated in 80% yield at >95% purity with a minimum of purification.

Keywords Esterification · Fatty acid ethyl esters · FAEE · Solid acid catalysts · Sulfhydryl fatty acids · Thiol fatty acids

Introduction

Long chain alkanethiols, thioethers, and disulfides have been demonstrated as important and useful compounds in the materials sciences. Aliphatic long chain *n*-alkanethiol carboxylic acids are used for constructing well-ordered self-assembled monolayers on gold surfaces [1, 2]. The spontaneous electrostatic Au–S interaction is robust, leaving the carboxylic group free for covalent or electrostatic binding to proteins or other organic moieties [3]. These integrated molecular systems have been studied as the basis of myriad electrochemical sensors [3, 4].

Biologically, sulfur containing fatty acids such as lipoic acid have been investigated for their ability to augment the sulfhydryl groups of membrane proteins associated with Ca^{2+} channels, to lower blood pressure and normalize associated biochemical and histopathological changes in spontaneously hypertensive rats [5]. Thiol and disulfide containing fatty acids possess antioxidant capacity, which when used for the pretreatment of crush injuries of rat sciatic nerve confirmed the possible usefulness of sulfur containing fatty acids for humans with peripheral nerve injuries [6]. Additionally, in a very limited clinical study, disulfide fatty acids were shown to have pharmacokinetics effects in subjects with severe kidney damage and end-stage renal disease [7]. Thiol and dithiol fatty acids are also vital cofactors for some mitochondrial enzymes and act as micronutrients with varied pharmacologic and antioxidant properties, improving glycemic control, polyneuropathies associated with

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diabetes mellitus, and effectively mitigates toxicities associated with heavy metal poisoning [8].

Physiologically, thiol and disulfide fatty acids have been shown to directly terminate free radicals, chelate transition metal ions (e.g. iron and copper), increase cytosolic glutathione and vitamin C levels and prevent toxicities associated with their loss [8, 9]. From these numerous examples, it is obvious that thiol and disulfide containing fatty acids and essential components in the diverse areas of material and biological science research, and developing routes to new thiol fatty acids and derivatives is an important aspect of that research.

Our interest in thiol fatty acids lies in their antioxidative, free radical scavenging, and metal ion scavenging capabilities as applied to cosmeceutical and skin care formulations. The retail market is filled with products containing the disulfide-containing free fatty acid, lipoic acid. These products are promoted for the disulfide-containing fatty acid's beneficial effects towards wrinkle prevention, acne, and rosacea, all claims of which are empirical and not clinically proven. Regardless, the skin care industry is starved for additional, naturally derived thiol fatty acids and derivatives. Mercapto fatty acid esters are useful intermediates en route to thiol containing structured lipids and are more efficient substrates than their corresponding acids when used in nonaqueous, enzymatic transesterification processes. Most ω-sulfhydryl fatty acid esters are not commercially available and literature methods to the mercapto acid esters describe the catalysis with strong acids, which catalyze reactions at the ω-sulfhydryl group, resulting in low yields and unwanted side products [10]. Herein, we report the selective esterification of the ω-thiol fatty acid, 11-mercaptoundecanoic acid (MUA), with ethanol catalyzed by milder, solid acid catalysts. The solid acid catalysts were examined for their capacity to catalyze the esterification of MUA with ethanol while limiting the unwanted catalytic activity towards the sulfhydryl group.

Materials and Methods

Materials

11-Mercaptoundecanoic acid (MUA) was purchased from Sigma–Aldrich (Milwaukee, WI) and stored in a desiccator. Ethanol (200 proof) was purchased from Decon Laboratories, Inc. (King of Prussia, PA) and used fresh. Amberlyst-15 ion exchange resin, *p*-toluenesulfonic acid (*p*-TSA), tetraethylorthosilica (TEOS), mercaptopropyltrimethoxysilane (MPTMS), aminopropyltrimethoxysilane (APTMS), and the surfactant Pluronic P123 were purchased from Sigma–Aldrich and used as received. 2-(4-Chlorosulfonyl)ethyltrimethoxysilane (CSPTMS) solution (50 wt%, 1.76 M) in dichloromethane was purchased from Gelest (Morrisville, PA). All other solvents were purchased from Sigma–Aldrich and used as received.

Preparation of Solid Catalysts

Propylsulfonic Acid-Functionalized Mesoporous Silica (SBA-15-PSA)

SBA-15-PSA was prepared by co-condensation following the literature methods of Mbaraka et al. [11] TEOS (12.6 ml, 56.8 mmol, 227 mM), MPTMS (1.6 ml, 8.6 mmol, 34 mM) and H_2O_2 (140 mmol, 560 mM) were added to 250 ml of 3 wt% Pluronic P123 solution in 2 N HCl. The solution was stirred at 50 °C at 300 rpm for 18 h. The solution was then heated to 100 °C and held static for 24 h. The resultant white precipitate was collected by filtration, suspended in warm (45 °C) water, and collected by filtration; the warm water wash was repeated three times. The precipitate was finally suspended in ethanol and collected by filtration. The white solid was then dried in vacuo at 60 °C.

Phenylsulfonic Acid-Functionalized Mesoporous Silica (SBA-15-ASA)

SBA-15-ASA was prepared by co-condensation following the literature methods of Mbaraka et al. [11] TEOS (18.7 ml, 84.5 mmol) was added dropwise at room temperature to 300 ml of a 3 wt% Pluronic P123 solution in 2 N HCl. The solution was stirred at room temperature for 90 min, then CSPTMS (5.3 ml, 9.3 mmol, 31.1 mM) was added dropwise over 15 min. The solution was stirred at room temperature for 20 h, then heated to 75 °C while static for 24 h. The resultant white precipitate was collected by filtration and washed with warm water and ethanol as described above. The white solid was then dried in vacuo at 60 °C.

Synthesis of Ethyl 11-Mercaptoundecanoate, **1**

MUA Esterification with Excess Ethanol: Kinetic Studies

A 10-ml, 2-necked round bottom flask fitted with a reflux condenser was charged with MUA (100 mg, 0.46 mmol) and a four-paddle stir bar. The MUA was dissolved in ethanol (4 ml, 68.50 mmol) with hexadecane (20 µl, 68.41 µmol) added as an internal standard. Catalyst was added after the solution was heated to a prescribed temperature, 50, 55, 60, 65, 70, and 75 °C. The catalysts examined were Amberlyst-15 (5 mg), *p*-TSA (5 mg), SBA-15-PSA (50 mg), SBA-15-ASA (25 mg), and HMS-pNH_2 (50 mg). Reaction samples (100 µl) were withdrawn

at prescribed time points and diluted to 1 ml with acetone for GC–MS analysis.

MUA Esterification with Excess Ethanol: Larger Scale

A 300-ml Parr bomb reactor fitted with a mechanical stirrer was charged with MUA (3.76 g, 0.017 mol), ethanol (150 ml, 2.57 mol), Amberlyst-15 (1.00 g) and 3 Å molecular sieves (1.5 g). The bomb was evacuated and recharged with 100 psi nitrogen. The mixture was heated to 70 °C and stirred for 24 h. The resultant solution was filtered through a 20-ml, medium glass frit and the filtrate dried with magnesium sulfate (1.0 g). The magnesium sulfate was removed by filtration, and excess ethanol was removed from the filtrate via rotoevaporation, resulting in a yellow oil. The oil was dried in vacuo at 40 °C overnight and stored at 4 °C. Yield: 3.41 g (80.6% based on MUA) at >95% purity by GC/MS and ^{1}H NMR. EI MS (70 eV) 246 (M^{-}). ^{1}H NMR (d_6-acetone, 500 MHz, peak assignments referenced in Fig. 2): δ 4.08 (q, 2.00 H, H_2-a), 2.52 (q, 1.68 H, H_2-11), 2.28 (t, 2.08 H, H_2-2), 1.70 (m, 1.02 H, -SH), 1.61 (m, 4.34 H, H_2-3,10), 1.41 (m, 2.20 H, H_2-4), 1.32 (s, 10.35 H, H_2-5–9), 1.22 (t, 3.31 H, H_3-b). ^{13}C NMR (d_6-acetone, 126 MHz): δ 172.67 (s, C1), 59.49 (s, Ca), 34.00 (s, C2), 33.75 (s, C10), 30.00–28.00 (ms, C4–9), 24.80 (s, C3), 23.96 (s, C11), 13.73 (Cb).

GC/MS Analysis

GC–MS analyses were performed using an Agilent 6,890 N gas chromatograph with a 5,973 network mass selective detector using a 1.5 ml/min He flow, split ratio of 25:1, 70 eV ionization energy in the negative ion mode. Separation of products was accomplished on a Supelco Petrocol DH 50.2 column (50 m × 0.2 mm diam. × 0.2 μm film thickness). The injector was kept 300 °C and the oven programmed for 3 min at 100 °C followed by ramping to 320 °C at a rate of 20 °C/min.

The response factor of **1** (RF_1) was determined as the ratio of peak areas of equal molar concentrations of **1** (A_1) and internal standard (A_{IS}) as determined by GC/MS (Eq. 1).

$$RF_{\mathbf{1}} = A_{\mathbf{1}}/A_{IS} = 1.116. \quad (1)$$

The concentration of MUA and **1** (C_{MUA} and C_1) obtained from GC/MS analysis of the kinetic study time points were determined using the peak area of the internal standard at time zero, t_0, and time, t (A_{IS-t0} and A_{IS-t}, respectively) as follows (Eqs. 2, 3).

$$C_{MUA} = (A_{IS-t0}/A_{IS-t}) \times (A_{MUA-t}/A_{MUA-t0}) \times 460\ \mu mol. \quad (2)$$

$$C_{\mathbf{1}} = (A_{\mathbf{1}}/A_{IS-t}) \times 68\ \mu mol \times 1.116. \quad (3)$$

^{1}H and ^{13}C NMR

NMR spectra were obtained on a Bruker Avance 500 spectrometer (500 MHz ^{1}H/125.77 MHz ^{13}C) using a 5 mm BBI probe. All samples were dissolved in d_6-acetone and all spectra were acquired at 27 °C. Chemical shifts are reported as ppm from tetramethylsilane calculated from the lock signal ($\Xi_D = 15.350609\%$).

Solid Catalyst Surface Analysis

Textural properties of the solid catalysts were calculated from nitrogen isotherms collected at −196 °C using a Quantachrome (Boynton Beach, FL) Autosorb-1 surface analyzer. Samples were degassed at 120 °C prior to analysis. Surface area calculations were conducted via the multipoint BET method at $0.05 < P/P_0 < 0.25$ and pores sizes calculated using the BJH method on the adsorption branch of the isotherms.

Results and Discussion

Acid Catalyzed Esterification of MUA

From introductory chemistry it is known that the nucleophilic acyl substitution of carboxylic acids with alcohols proceeds via a two step mechanism [12]. The first step involves the attack of the alcohol's electron-rich oxygen atom on the electron-deficient carbonyl carbon, forming a tetrahedral intermediate with a delocalized charged transition state. The nucleophilic attack on the carbonyl carbon is enhanced by the electron withdrawal of the mobile π electrons from the carbonyl carbon to the more electronegative carbonyl oxygen. The second step involves the loss of the carboxylic acid's −OH leaving group, resulting in the esterified carbonyl group and water. The rate of the second step is influenced by the basicity of the leaving group. If the nucleophilic acyl substitution is acid catalyzed, a proton initially attaches to the carbonyl oxygen, making the carbonyl carbon even more susceptible to nucleophilic attack (Fig. 1). In this case the more electronegative carbonyl oxygen accepts the π electrons from the carbonyl carbon without having to accept a negative charge, allowing for a lower energy tetrahedral intermediate. The second step involves the loss of a proton from the carbonyl oxygen intermediate and the addition of a proton to the carboxylic acid's −OH group to form water.

The esterification of free fatty acids with short chain alcohols proceeds via this two step mechanism. Typically, strong acids such as HCl or H_2SO_4 are used to catalyze the free fatty acid esterifications [13]. However, if the fatty

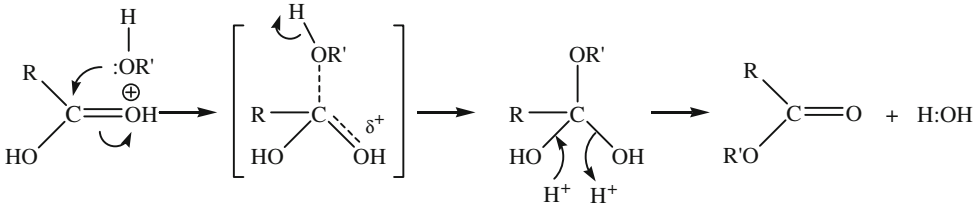

Fig. 1 Carboxylic acid esterification with an alcohol via acid catalyzed nucleophilic acyl substitution. Adapted from Morrison and Boyd, p. 862 [12]

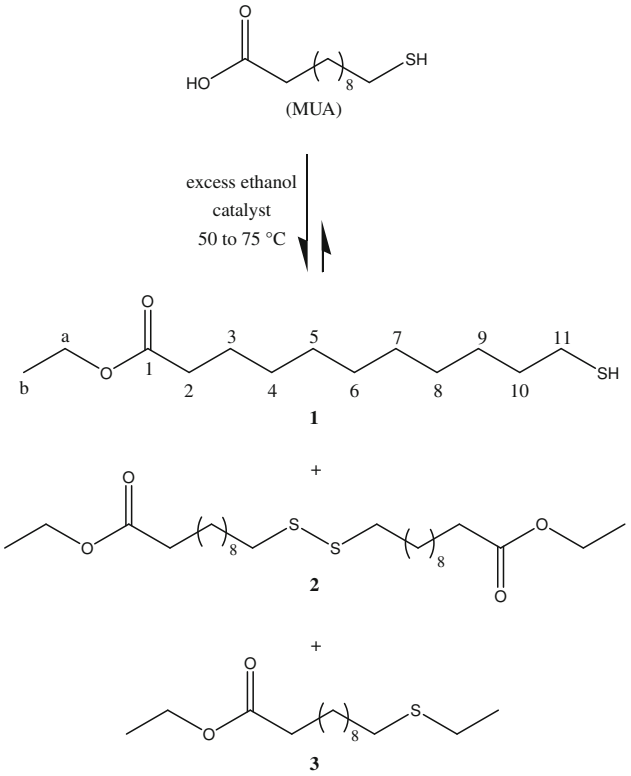

Fig. 2 Catalytic esterification of MUA with excess ethanol. Carbon labels for **1** provide reference for the NMR data reported in the "Materials and Methods" section

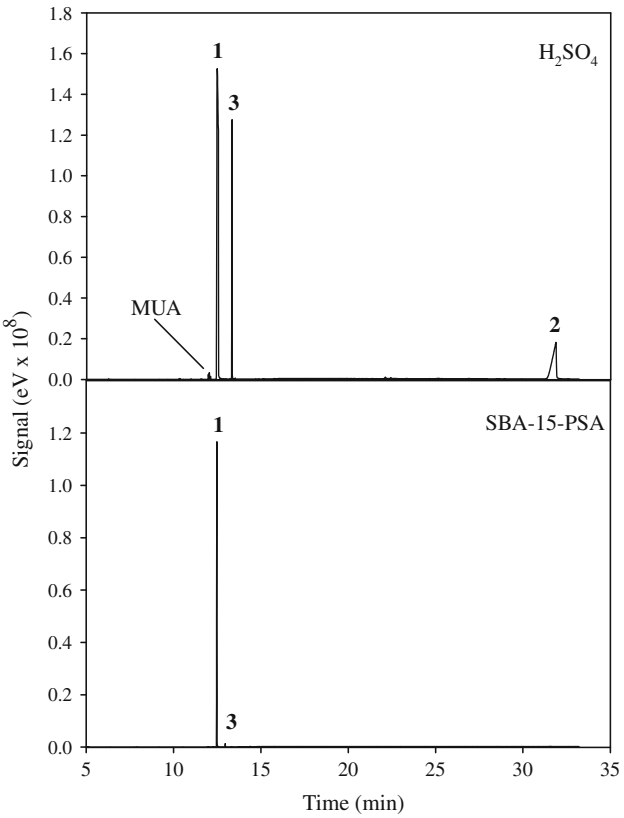

Fig. 3 Gas chromatograms from the GC–MS analysis of the H_2SO_4 and SBA-15-PSA catalyzed esterifications of MUA with excess ethanol at 75 °C for 24 h. The peak numbers and acronym correspond to the compounds defined in Fig. 2

acid contains a secondary reactive group the strong acid can catalyze unwanted side reactions. For example, the literature teaches that the esterification of long chain ω-sulfhydryl fatty acids is accomplished with H_2SO_4 in excess alcohol. While the same acid catalyzed reaction of the corresponding long chain fatty acid results in near quantitative yield of the ester, the ω-sulfhydryl fatty acid results in ester yields of approximately 60% [10]. The unwanted side products identified when the H_2SO_4 catalyzed esterification was attempted for this study are shown in Fig. 2. In addition to catalyzing the esterification of MUA to the desired ethyl 11-mercaptoundecanoate, **1**, the strong acid also catalyzed the oxidation of the sulfhydryl groups to form ethyl 11-mercaptoundecanoate disulfide dimer, **2**, and ethyl 11-mercaptoundecanoate ethyl thioether, **3**. The coproducts, identified by GC–MS, accounted for up to 75% of the MUA conversion (53% of **2**, 22% of **3**), depending on the reaction temperature and time (Fig. 3). Even under optimized conditions (55 °C, 12 h) the H_2SO_4 catalyzed esterification produced only 55% conversion of MUA to **1** as determined by GC–MS. The esterification was attempted with *p*-TSA with similar results. It was preferable to find an acid catalyst that quantitatively esterified the MUA carboxylic acid while remaining unreactive towards the MUA sulfhydryl group.

Solid Acid Catalyzed Esterification of MUA

An alternative to using strong protic acids (e.g. H_2SO_4, *p*-TSA) to catalyze the esterification of the bifunctional MUA was the use of milder, heterogenous, solid acid

Table 1 Physical and chemical properties of acid catalysts used for the esterification of MUA in excess ethanol

Catalyst	SA_{BET} (m^2/g)	MPD_{BJH} (nm)	Acid loading (mequiv/g)	pK_a	E_a (kJ/mol)
SBA-15-PSA	704	50	0.3	~1.4[a]	54
SBA-15-ASA	482	99	0.6	~1.3[a]	71
Amberlyst-15	–	NA	4.0	<1.0[b]	59
p-TSA	NA	NA	NA	−2.8[c]	–
H_2SO_4	NA	NA	NA	−3.0[c]	–

Catalyst acronyms are defined in the "Materials and Methods" section, SA_{BET} surface area, MPD_{BJH} mean pore diameter, mequiv/g milliequivalents per gram, *pKa* acid dissociation constant, E_a apparent activation energy, *NA* not applicable, – not determined

[a] Mbaraka and Shanks 2006 [16]

[b] Sankey 1995 [18]

[c] Serjeant and Dempsey 1979 [19]

catalysts. Solid acid catalysts have been widely reported in the literature to facilitate the transesterification of triacylglycerols and the esterification of fatty acids with short chain alcohols [14, 15]. Mesoporous silica functionalized with arene and propylsulfonic acid groups (SBA-15-ASA and SBA-15-PSA, respectively) possess acid dissociation constants (pK_a) 1.5 units higher than those of H_2SO_4 and *p*-TSA (Table 1). It should be noted that the pK_a values of the sulfonic acid functionalized SBA-15 reported by Mbaraka and Shanks [16] were determined in methanol, and are presumed to be fractionally lower than those determined in water. Additionally, the pK_a values are the average determined over a range of molar ratios of synthesis precursors. The relative pK_a values varied less than 0.1 units over this range. Nevertheless, the relative pK_a values of SBA-15-PSA and SBA-15-ASA are significantly higher than the stronger H_2SO_4 and *p*-TSA. While it was certain that these milder acids would catalyze the esterification of MUA with ethanol, it was unclear if the solid acid catalysts would be unreactive towards the MUA sulfhydryl group.

Kinetics of Solid Acid Catalyzed Esterification of MUA

The functionalized mesoporous silicas, SBA-15-PSA and SBA-15-ASA, were examined to determine which would best catalyze the esterification of MUA in excess ethanol. The catalytic reactivity of the functionalized silicas where compared to the highly acidic ion exchange resin, Amberlyst-15. Because the esterifications were conducted in excess ethanol, the reaction was assumed to be pseudo-first order and thus governed by the elementary rate law (4), were [MUA] was the concentration of the limiting reactant, MUA, and k (with units s^{-1}) was the rate constant.

$$-d[\mathrm{MUA}]/dt = k[\mathrm{MUA}]. \quad (4)$$

Integrating (4) resulted in (5), where t was time (s). The rate constant k was determined experimentally as the slope of the linear plot of ln[MUA] versus t.

$$\ln[\mathrm{MUA}] = -kt + \ln[\mathrm{MUA}]_0. \quad (5)$$

Determining k over a series of temperatures, the Arrhenius relationship (6) was used to determine the apparent activation energy, E_a, where R is the gas constant, T was the temperature, and A was the pre-exponential factor. The activation energy was determined experimentally as the slope of the liner plot of ln(k) versus 1/T.

$$E_a = -RT\ln(k/A) \rightarrow \ln(k) = -E_a/RT + \ln(A). \quad (6)$$

The rate constants of the MUA esterifications in excess ethanol were determined for the three solid acid catalysts, SBA-15-PSA, SBA-15-ASA, and Amberlyst-15, over the temperature range of 50 to 75 °C. The amount of catalyst used was adjusted based on the disparity of their respective acid loadings (Table 1) to normalize the milliequivalents of acid used throughout the experiments. All three solid acid catalysts produced the desired product, **1**, and produced little of the unwanted side products (discussed below). The apparent E_a for the solid acid catalysts were determined from the Arrhenius plots shown in Fig. 4. It was expected from the pK_a of the catalysts that SBA-15-PSA would result in the highest apparent E_a, however, it performed as well as the more acidic Amberlyst. SBA-15-ASA resulted in an apparent E_a approximately 1.3 times higher than the other two catalysts. This was contradictory to previous studies that showed that SBA-15-ASA was more catalytically active than SBA-15-PSA in the esterification of palmitic acid in methanol [16]. Regardless, the rate constants and apparent E_a values determined in this study compare relatively well with those of other fatty acid esterifications with solid acid catalysts, [16–18] and the thesis of this study was to not necessarily optimize the rate of esterification, but to maximize the esterification of MUA with regard to limiting the catalytic activity towards the sulfhydryl group.

Acid Catalyst Reactivity Towards the MUA Sulfhydryl Group

As discussed above, sulfuric acid catalyzed esterification of MUA in excess ethanol resulted in side products, **2** and **3** (Fig. 2). After 120 min at 75 °C, H_2SO_4 had converted ~99% of the MUA, but produced 53% **2** and 23% **3** as determined by GC–MS (Fig. 3). *p*-TSA, which has a higher pK_a (Table 1), quantitatively converted MUA to **1** in 5 h at 70 °C, but produced 16% **2** and 8% **3**. The three solid acid catalysts, all with higher pK_a than *p*-TSA, were examined

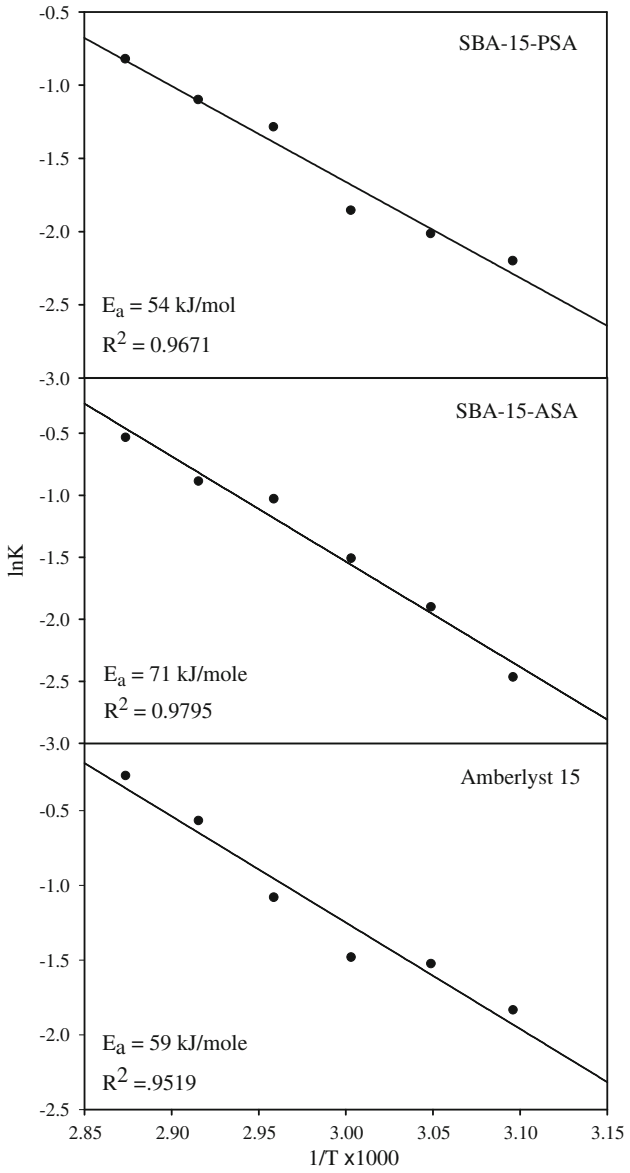

Fig. 4 Arrhenius plots for the solid acid catalyzed esterification of MUA in excess ethanol

for their catalytic activity to esterify MUA and their propensity to catalyze side reactions at the MUA sulfhydryl group. After 4 h at 75 °C, SBA-15-PSA had converted 75% of MUA to **1** without the formation of side products. After 24 h, the conversion to **1** was complete and no side products were evident as determined by GC–MS (Fig. 3). On a 24 h timescale SBA-15-ASA and Amberlyst-15 also achieved quantitative conversion of MUA to **1** without the formation of side products. While the three solid acid catalysts tested may have exhibited small differences with regard to their apparent E_a for esterifying MUA with ethanol, there was no measurable difference in their ability to catalyze the quantitative conversion of **1** without forming the side products **2** and **3**. Thus, all three solid acid catalysts proved to be viable candidates for the gram scale synthesis and isolation of **1**.

Gram Scale Synthesis and Isolation of **1**

Because catalytic conversions to a product as monitored analytically does not always correspond to the isolated yield of the product when done on a practical lab scale, Amberlyst-15 was used to esterify MUA in excess ethanol on a gram scale. As in the small scale kinetic reactions, Amberlyst-15 converted MUA to **1** with a minimum formation of side products when used on a gram scale. The yellow oil, **1**, was recovered with a minimum of purification in 81% yield (3.41 g), a 20% improvement over the synthesis reported in the literature using H_2SO_4 [10]. The isolated **1** was found to be ~95% pure as determined by GC–MS and ^{1}H NMR. It was likely that some of **1** was lost to unidentified degradation products during the isolation and drying procedures. For subsequent studies which will incorporate **1** into structured lipids, a purity of 95% will suffice; therefore, no further purification was attempted. However, for integrated molecular systems and electrochemical sensor applications **1** can be isolated at higher purities via recrystallization [10].

Conclusions

The solid acid catalysts, SBA-15-PSA, SBA-15-ASA, and Amberlyst-15, quantitatively esterified MUA in excess ethanol to the corresponding ethyl ester, **1**, with little or no catalytic activity towards the MUA sulfhydryl group. This was significantly superior to literature methods that employed stronger acid catalysts (i.e. H_2SO_4 and *p*-TSA), which resulted in unwanted thioether and disulfide side products due to the stronger acids' propensity to catalyzed reactions at the sulfhydryl group. The solid acid catalysts were shown to offer a practical route to gram scale quantities of high purity ω-sulfhydryl fatty acid esters, which are desired as intermediates for structured lipid and integrated electrochemical molecular systems.

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