Synthesis of $\alpha$-Hydroxy Fatty Acids from Fatty Acids by Intermediate $\alpha$-Chlorination with TCCA under Solvent-Free Conditions: A Way to Valorization of Waste Fat Biomasses

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ABSTRACT: Within food wastes, including edible and inedible parts, fat biomasses represent a significant portion, often uneconomically used or improperly disposed causing pollution issues. Interesting perspectives for their management and valorization could be opened by conversion of fatty acids (FAs), which are their main constituents, into $\alpha$-hydroxy FAs ($\alpha$-HFAs), fine chemicals of great, but largely untapped potential, possibly due to current poor availability. Here, a simple and efficient procedure is reported to $\alpha$-chlorinate FAs with trichloroisocyanuric acid (TCCA), a green halogenating agent, under solvent-free conditions and to directly convert the resultant $\alpha$-chloro FAs, without previous purification, into $\alpha$-HFAs. The procedure was applied to stearic, palmitic, and myristic acid and, with analogous success, to their mixture, ad hoc created to simulate a FAs mixture obtainable from a fat biomass.

INTRODUCTION

Through the food supply chain, from initial agricultural production down to final household consumption, food waste amounted to 1300 million tonnes annually in 2011, including edible parts and inedible parts, namely components associated with a food that are not intended to be consumed by humans.1 In 2019, the report of Food Waste Index estimated that food waste from households, retail establishments, and the food service industry was 931 million tonnes each year.2

Among the substances found in food wastes and in inedible parts associated with food production, fatty acids (FAs) can represent significant or high weight percentages.3,4 That is the case, for instance, of peels and seeds of some fruits, of waste cooking oils, and of animal fats that include the grease of shared fleeces. In particular, this last waste biomass, annually amounting, just in EU, to more than 200 thousand tons of low-quality shorn wool, equivalent to 30 thousand tons of wool grease, is an example of inevitable byproduct, in this instance of the farming of sheep reared only for food.5 It is the peculiar and fine characteristic of wool grease, namely, the high content of $\alpha$-hydroxy FAs ($\alpha$-HFAs) besides FAs6,7 that suggested to us that conversion of FAs into $\alpha$-HFAs could contribute to maximize the value of biomasses, rich in FAs, and to make their management profitable and sustainable. In fact, $\alpha$-HFAs are high-value fine chemicals and, unlike short chain $\alpha$-hydroxy acids, such as lactic acid, their potential is far from being fully exploited, possibly due to limited commercial availability. Indeed, the $\alpha$-carbon of FAs has rarely been targeted for chemical/biological hydroxylation. Thanks to their physical, chemical, and biological features, $\alpha$-HFAs are used in the field of cosmetics for their surfactant and antimicrobial properties, but they could be applied also in the (bio-)remediation field for their surfactant and chelating ability and in the production of biodegradable polymers.8−12 Recently, they have been reported as the useful precursors of noncanonical long-chain $\alpha$-amino acids, which are of increasing interest and demand in many fields.13

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Apart from the biocatalytic hydroxylations, the simplest way to convert a carboxylic acid into the corresponding α-hydroxyacid by chemical synthesis is to α-halogenate it and then to substitute halogen with hydroxyl. However, the traditional Hell–Volhard–Zelinsky α-halogenation of carboxylic acids with molecular halogens is not environmentally friendly, and its scaling up raises many problems because halogens are hazardous, corrosive, and toxic. Byproduced hydrogen halide requires special attention for waste disposal and banned or not recommended solvents are necessarily used as reaction media.

Here, conversely, we describe an efficient and green two-step conversion of FAs into α-HFAs by α-chlorination, followed by the substitution of chloride by hydroxyl, which uses, in the α-chlorination step, an inexpensive, safe, environmentally benign, and atom-economic organohalogen like trichloroisocyanuric acid (TCCA, 1) (Figure 1). The procedure was applied to single FAs first and then to their mixture, ad hoc created to simulate a FAs mixture obtainable from wool grease and, typically, also from other waste fat biomasses.

## RESULTS AND DISCUSSION

### TCCA as a Chlorinating Agent.

A large variety of reagents for the chlorination of organic substrates can be found in the literature. Among these, 1 stands out for many fine qualities. It is inexpensive, innocuous, environmentally benign, and stable. With respect to atom economy, TCCA is better than other chlorinating agents, such as Na-chlorosuccinimide, N-chlorosaccharin, chloramine-T, or 1-chlorobenzo triazole, as it is capable of transferring three chlorine atoms, corresponding to 45.5% of its mass. Furthermore, the byproduct of chlorination is cyanuric acid (2), which can be reused by conversion into more TCCA through a green process using NaCl and oxone. Importantly, 1 is soluble in many organic solvents, whereas 2, the chlorination byproduct, is highly insoluble. Alternatively, the water-soluble sodium dichloroisocyanurate (NaDCC, 3) can be used in biphasic water/organic solvent systems. Such a difference in the solubility profile between 1 and 2 allows chlorination to be driven to completion in suitably selected solvents and it facilitates the quantitative removal of 2 in the reaction work-up by simple filtration. 1 or 3 efficiently chlorinates the nitrogen of primary and secondary amines and amides, yielding intermediates whose dehydrohalogenation gives access to synthetically useful unsaturated derivatives, such as nitriles, imines, enamines, azo-compounds, isocyanates, and α,β-unsaturated α-amino esters. C-Halogenation of alkenes, alkyl aromatic hydrocarbons, and carbonyl compounds is the other important chapter of the applications of 1 as a halogenating reagent in organic synthesis. In the development of new green technologies, the potential of 1 as a halogenating agent relies not only on its intrinsic environmental benignity but also on its suitability for newly conceived more efficient and sustainable procedures. Recent examples are the amplification of the electrophilicity of TCCA chloride by visible-light catalysis to chlorinate electron-deficient amines and heteroarenes under mild conditions, solvent-free chlorination of aromatics and carbonyl compounds in the solid state by ball milling, and conversion of methane into chloromethane by mechanochemical activation. Based on these literature premises and on our experience with 1 use, we planned the α-chlorination of FAs with 1 under solvent-free conditions, at temperatures slightly higher than their melting points.

### α-Chlorination of FAs.

Three saturated long-chain FAs were chosen as substrates because the main exponents, besides α-HFAs, of carboxylic acids in wool wax are as follows: octadecanoic (stearic) acid (4), hexadecanoic (palmitic) acid (5), and tetradecanoic (myristic) acid (6). To our knowledge, the only example of FAs α-chlorination is that of 4 by treatment with Cl2 at 150 °C for about 1 h in the presence of chlorosulfonic acid (3 mol %) as a catalyst and 7,7,8,8-tetracyanoquinodimethane (TCNQ, 0.5 mol %) as a free radical inhibitor. According to this procedure, α-chlorostearic acid (4a) was isolated with 88% yield by crystallization from acetonitrile. Although not exemplified, the same reaction was run with all of the even-chain saturated acids between C6 and C16 by the same researchers claiming essentially identical results. As explained above, our approach was to avoid the use of chlorine by replacing it with much more acceptable 1 under solvent-free conditions. Slightly exceeding 1 (1.4 equiv) and catalytic PCl3 (0.1 equiv), to generate, according to the generally accepted mechanism of the Hell–Volhard–Zelinsky α-halogenation of carboxylic acids, the necessary initial small amount of the acid chloride in enolic form, were used in all the experiments while varying time and temperature. Typically, the FA (35 mmol) was heated to melt (80 °C) under stirring and nitrogen in a flask wrapped with foil to exclude light. 1 h after adding catalytic PCl3 (1.2 mmol), 1 (16.3 mmol) was added portion-wise over 30 min while heating was continued. The screening of temperatures ranging between 80 and 100 °C and of times ranging between 3 and 24 h indicated 80 °C and 24 h as the best reaction conditions to be applied. At the end, ethyl acetate was added to the reaction mixture at room temperature to precipitate cyanuric acid, which was removed by filtration. The filtrate was washed with aqueous sodium metabisulphite, to
As a consequence of the successive treatment of crude halogenated FAs with aqueous KOH under reflux could provide the corresponding α-HFAs, isolable pure by simple precipitation from the acidified reaction medium and successive trituration in a suitable solvent. 

The robustness of the whole two-step procedure was demonstrated by its successful application to the equimolar mixture of the three FAs, which were converted into the corresponding α-HFAs with a near unaltered molar ratio.

The process, designed to valorize the saturated FAs of wool wax and to indirectly make the waste wool management more sustainable, provides appealing opportunities for converting other FAs and FA mixtures, recoverable from lipid-based waste biomasses, into valuable fine chemicals of great potential, such as α-HFAs.

### Experimental Section

Materials and Methods. Stearic acid, palmitic acid, myristic acid, linoleic acid, and phosphorus trichloride were purchased from Sigma and used without further purification. 1H-NMR and 13C-NMR spectra were recorded in CDCl₃, DMSO-d₆, and CD₃OD at 300 and 75 MHz, respectively, with a Varian Mercury 300 spectrometer and elaborated with Mnova software. Chemical shifts are reported in ppm relative to a residual solvent as internal standard.

GC/MS analyses were performed on a Varian-Agilent 3900 gas chromatograph Trace GC with a FID and autosampler AS2000 (Thermo Fisher). Before the analysis, the sample (5 mg) was derivatized, as methyl ester, using a 500 μL of HCl 3 M solution in MeOH and left in the oven at 55 °C overnight. Hexane (1.2 mL) was then used as an extraction solvent, and 1 mL was transferred into a 2 mL vial and analyzed.

Chromatographic separation was carried out on a DB-5 MS UI fused silica capillary column (30 m, 0.25 mm I.D., 0.25 μm film thickness, Agilent). The GC-FID system was operated under the following conditions: injection temperature 280 °C (split mode 30:1); the initial column temperature was 180 °C and was subsequently increased to 280 °C at a rate of 5 °C/min. Helium was used as the carrier gas at a flow rate of 1.0 mL/min. The FID was operated at 300 °C.

GC/MS analyses were performed on a Varian-Agilent 3900 gas chromatograph with an ion trap mass selective detector Saturn 2100T (Varian-Agilent) and autosampler CP8400. Chromatographic separation was carried out on a HP-1 MS UI fused silica capillary column (12 m x 0.18 mm i.d., film thickness 0.18 μm, Agilent). The GC/MS system was operated under the following conditions: injection temperature 250 °C (split mode 50:1); interface transfer line 300 °C; and the initial column temperature 150 °C, which was subsequently increased to 250 °C at a rate of 5 °C/min. Helium was used as the carrier gas at a flow rate of 0.9 mL/min. MS analysis was performed in a SCAN MODE (35/650 m/z) operated in a chemical ionization mode with methanol as a reactant gas and an emission current of 10 μA. The injection volume was 1 μL with a solvent delay of 2 min.

High resolution electrospray mass spectra were acquired with Q-TOF Synapt G2 Si (WATERS). The percent of conversion, selectivity, and the identity of the compounds were determined using GC/FID, GC/MS, and high-resolution mass spectrometry (HRMS) analysis.
Synthesis of 2-Chloro Stearic Acid (7). Obtained as a white solid crude (10.83 g, 97.0% of theoretical amount): mp 62.2 °C, RF (dichloromethane/methanol 9:1) = 0.55, 19 ¹H NMR (300 MHz, DMSO-°d6): δ 4.42 (dd, J = 7.7, 5.9 Hz, 1H), 2.01–1.68 (m, 2H), 1.27 (s, 24H), 0.83 (t, J = 6.6 Hz, 3H). ¹3C NMR (75 MHz, CDCl₃): δ 175.53, 70.07, 34.73, 31.90, 29.66, 29.65, 29.63, 29.61, 29.46, 29.34, 29.27, 28.79, 25.86, 22.67, 14.09. GC–MS: [M + H]° = 333.5, GC-FID: Rᵣ = 12.65 min, conversion = 100%, purity = 91.7%.

Synthesis of 2-Chloro Palmitic Acid (8). Obtained as a white solid crude (9.81 g, 96.4% of theoretical amount): mp 55.7 °C, RF (dichloromethane/methanol 98:2) = 0.6, ¹H NMR (300 MHz, DMSO-d₆): δ 4.42 (dd, J = 7.7, 5.9 Hz, 1H), 2.01–1.68 (m, 2H), 1.27 (s, 24H), 0.83 (t, J = 6.6 Hz, 3H). ¹3C NMR (75 MHz, CDCl₃): δ 175.53, 70.07, 34.73, 31.90, 29.66, 29.65, 29.63, 29.61, 29.46, 29.34, 29.27, 28.79, 25.86, 22.67, 14.09. GC–MS: [M + H]° = 305.5, GC-FID: Rᵣ = 9.53 min, conversion = 100%, purity = 89.0%.

Synthesis of 2-Chloro Myristic Acid (9). Obtained as a white solid crude (8.84 g, 96.1% of the theoretical amount): mp 43.7 °C, RF (dichloromethane/methanol 98:2) = 0.4, ¹H NMR (300 MHz, DMSO-d₆): δ 4.42 (dd, J = 7.7, 5.9 Hz, 1H), 1.99–1.67 (m, 2H), 1.49–1.13 (m, 20H), 0.84 (t, J = 6.7 Hz, 2H). ¹3C NMR (75 MHz, CDCl₃): δ 175.54, 70.05, 34.73, 31.89, 29.61, 29.56, 29.52, 29.49, 29.45, 29.32, 29.27, 29.24, 28.79, 25.86, 22.67, 14.09. GC–MS: [M + H]° = 277.3, GC-FID: Rᵣ = 6.728 min, conversion = 100%, purity = 84.6%.

Synthesis of 2-Chloro Stearic Acid, 2-Chloro Palmitic Acid, and 2-Chloro Myristic Acid Mixture. Obtained as a white solid crude (9.33 g, 91.7% of the theoretical amount) from 35 mmol of an equimolar mixture of 4, 5, and 6 according to the general procedure adopted for the single FAs: mp 40.9 °C, GC-FID: Rᵣ = 6.717 min, 9.537 min, 12.622 min, conversion = 100%, purity = 85.5%.

General Procedure for the Conversion of α-chloro FAs into α-HFAs. In a round-bottom flask, KOH (140 mmol, 7.85 g) and water (200 mL) were stirred at 80 °C for 30 min. The crude 2-chloro FA resultant from the chlorination step was added to the KOH water solution, and the mixture was refluxed for 24 h. Then, the mixture was cooled down at room temperature and the pH was adjusted to 1 using HCl 1 M. A white solid precipitated. The mixture was filtered, and the solid was recovered. After purification by trituration with acetonitrile, in a 1:3 ratio, the desired α-HFA was obtained as a white solid.

Synthesis of 2-Hydroxy Stearic Acid (10). Obtained as a white solid in 68% yield: mp 90.8 °C, RF (dichloromethane/methanol 9:1) = 0.62, ¹H NMR (300 MHz, DMSO-d₆): δ 3.88 (dd, J = 7.6, 4.5 Hz, 1H), 3.38 (bs, 1H, exchange with D₂O), 1.64–1.37 (m, 2H), 1.25 (s, 28H), 0.83 (t, J = 6.7 Hz, 3H).

¹3C NMR (75 MHz, CD3OD): δ 176.62, 70.03, 34.00, 31.64, 29.35, 29.33, 29.26, 29.21, 29.05, 24.70, 22.31, 13.01. ESI negative HRMS: calcd for C16H31O3[M – H]°, m/z 295.2586; found, 295.2585, GC-FID: Rᵣ = 12.142 min, purity = 99.8%.

Synthesis of 2-Hydroxy Palmitic Acid (11). Obtained as a white solid in 64% yield: mp 85.7 °C, RF (dichloromethane/methanol 9:1) = 0.53, ¹H NMR (300 MHz, DMSO-d₆): δ 3.88 (dd, J = 7.6, 4.6 Hz, 1H), 3.30 (bs, 1H, exchange with D₂O), 1.85–1.45 (m, 2H), 1.22 (s, 24H), 0.85 (t, J = 6.7 Hz, 3H). ¹3C NMR (75 MHz, CDCl₃): δ 176.59, 70.02, 34.00, 31.65, 29.36, 29.34, 29.26, 29.20, 29.05, 24.70, 22.30, 13.01. ESI negative HRMS: calcd for C14H27O3[M – H]°, m/z, 271.2273; found, 271.2272. GC-FID: Rᵣ = 9.062 min, purity = 99.4%.

Synthesis of 2-Hydroxy Myristic Acid (12). Obtained as a white solid in 66% yield: mp 83.5 °C, RF (dichloromethane/methanol 9:1) = 0.46, ¹H NMR (300 MHz, DMSO-d₆): δ 3.88 (dd, J = 7.6, 4.6 Hz, 1H), 1.66–1.42 (m, 2H), 1.25 (s, 20H), 0.83 (m, 3H). ¹3C NMR (75 MHz, CDCl₃): δ 177.11, 70.23, 34.15, 31.71, 29.45, 29.42, 29.37, 29.31, 29.17, 29.13, 24.81, 22.37, 13.15 ESI negative HRMS: calcd for C12H25O3[M – H]°, m/z, 243.1960; found, 243.1958, GC-FID: Rᵣ = 6.297 min, purity = 99.0%

Synthesis of 2-Hydroxy Stearic Acid, 2-Hydroxy Palmitic Acid, and 2-Hydroxy Myristic Acid Mixture. It was obtained as a white solid in 74.2% yield from the mixture of crude α-chloro FAs, which was in turn obtained from 35 mmol of equimolar mixture of 4, 5, and 6, according to the procedure adopted for the hydroxylation of single crude α-chloro FAs: mp 69.3 °C, GC-FID: Rᵣ = 6.295 min, 9.050 min, 12.120 min, purity = 100%.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04640.

1H NMR, ¹3C NMR spectrums, GC-FID, GC–MS, and HRMS analyses (PDF)

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ABBREVIATIONS

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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ABBREVIATIONS

FA, fatty acid; α-HFA, alpha-hydroxy fatty acid; TCCA, trichloroisocyanuric acid.

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