

Supporting Information

Scalable, Sustainable and Catalyst Free Continuous Flow Ozonolysis of Fatty Acids

R. S. Atapalkar^{a,b,†}, Paresh. R. Athawale^{b,c,†}, D. Srinivasa Reddy^{b,c*} and A. A. Kulkarni^{a,b*}

a. Chem. Eng. & Proc. Dev. Div., CSIR-National Chemical Laboratory, Pune - 411008, India.

b. Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India

c. Div. of Org. Chem., CSIR-National Chemical Laboratory, Pune – 411008, India.

*E-mail: aa.kulkarni@ncl.res.in (AAK)

ds.reddy@ncl.res.in (DSR)

Table of Contents

Content	Page No
General information	S3
Continuous flow synthesis of AA and PA from OA.....	S3
Continuous flow synthesis of AA and PA from elaidic acid.....	S4
Continuous flow synthesis of AA and 3-Hydroxy nonanoic acid from ricinoleic acid	S4
Continuous flow synthesis of adipic acid and dodecanoic acid from petroselinic acid.....	S5
Continuous flow synthesis of tridecanedioic acid and PA from erucic acid.....	S5
Continues flow large scale synthesis of AA and PA from OA.....	S6
Yield Calculation.....	S7
Images of Synthesized products.....	S8
Observations of continuous flow catalyst free ozonolysis of various fatty acids.....	S9
¹ H and ¹³ C NMR spectra of synthesized acids.....	S10-S15

General Information

All the reagents and solvents (commercial grade) were used as received. All the reactions were carried out in a SS316 stainless steel (Pinch tube) reactor. All the reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 coated 0.25 mm plates, detected by UV. Flash chromatography was performed with the indicated solvents on silica gel (particle size 0.064–0.210 mm). Yields reported are for isolated, spectroscopically pure compounds. ^1H and ^{13}C NMR spectra were recorded on a Bruker 200 MHz instrument with TMS as the internal standard. Chemical shifts are given in ppm (δ), referenced to tetramethylsilane (TMS) for ^1H NMR and the ^{13}C resonances of CDCl_3 (= 77.0 ppm) for ^{13}C NMR as internal standards and $\text{DMSO-}d_6$ (= 40.0 ppm) for ^{13}C NMR. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiples, b=broad, respectively) coupling constant (J , Hz), and integration.

1. Continuous flow synthesis of Azelaic acid (AA) and Pelargonic acid (PA) from oleic acid (OA):

1 g oleic acid was dissolved in acetone: water mixture (47.5 mL: 2.5 mL). The oleic acid solution and ozone (O_2/O_3) were pumped at the flow rate of 1 mL/min and 500 mL/min respectively, in a flow reactor (volume = 20mL, inner diameter = 2mm, length 5m) at 0 °C. The sample obtained from outlet was analysed and isolated yield was obtained 89% azelaic acid and 74% pelargonic acid. (Yield calculated with respect to starting material (oleic acid) purity 99%). After completion of the reaction, known work up procedure was followed to obtain mixture of azelaic acid and pelargonic acid. Azelaic acid and pelargonic acid were separated by column chromatography.

NMR Data for Azelaic acid: ^1H NMR (200 MHz, $\text{DMSO-}d_6$) δ = 11.97 (s, 2 H), 2.10 - 2.34 (m, 4 H), 1.50 (t, J = 6.4 Hz, 4 H), 1.27 (br. s, 6 H); ^{13}C NMR (50 MHz, $\text{DMSO-}d_6$) δ = 174.8, 34.0, 28.8, 24.8.

NMR Data for Pelargonic acid: ^1H NMR (400 MHz, CDCl_3) δ ppm 0.72 - 0.87 (m, 3 H) 1.11 - 1.34 (m, 10 H) 1.56 (quin, J = 7.38 Hz, 2 H) 2.27 (t, J = 7.57 Hz, 2 H) ^{13}C NMR (100 MHz, CDCl_3) δ ppm 14.04, 22.5, 22.62, 24.67, 29.06, 29.19, 31.79, 34.12, 180.42.

2. Continuous flow synthesis of Azelaic acid and Pelargonic acid from elaidic acid:

1 g elaidic acid was dissolved in acetone: water mixture (47.5 mL: 2.5 mL). The elaidic acid solution and ozone (O₂/O₃) were pumped at the flow rate of 1 mL/min and 500 mL/min respectively, in a flow reactor (volume = 20 mL, inner diameter = 2 mm, length 5m) at 0 °C. The sample obtained from outlet was analyzed and isolated yield was obtained 87% for azelaic acid and 76% for Pelargonic acid. (Yield calculated with respect to starting material (elaidic acid) purity 97%). After completion of the reaction, work up procedure was followed to obtain mixture of azelaic acid and pelargonic acid. Azelaic acid and pelargonic acid were separated by column chromatography.

Data for Azelaic Acid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.25 (s, 6 H) 1.41 - 1.54 (m, 4 H) 2.19 (t, *J*=7.38 Hz, 4 H) 11.96 (s, 2 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 24.90, 28.87, 34.09, 174.95.

Data for Pelargonic acid: ¹H NMR (400 MHz, CDCl₃) δ ppm 0.75 - 1.01 (m, 3 H) 1.21 - 1.38 (m, 10 H) 1.58 - 1.68 (m, 2 H) 2.35 (t, *J*=7.50 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 14.06, 22.62, 24.67, 29.06, 29.08, 29.19, 31.79, 34.09, 180.30.

3. Continuous flow synthesis of Azelaic acid and 3-Hydroxy nonanoic acid from recinoleic acid:

1 g recinoleic acid was dissolved in acetone: water mixture (47.5 mL: 2.5 mL). The recinoleic acid solution and ozone (O₂/O₃) were pumped at the flow rate of 1 mL/min and 500 mL/min respectively, in a flow reactor (volume = 20 mL, inner diameter = 2 mm, length 5m) at 0 °C. The sample obtained from outlet was analysed and isolated yield was obtained 86% for azelaic acid and 70% for 3-Hydroxy pelargonic Acid. (Yield calculated with respect to starting material (recinoleic acid) purity 80%). After completion of the reaction, work up procedure was followed to obtain mixture of azelaic acid and 3-hydroxy pelargonic acid. Azelaic acid and 3-hydroxy pelargonic acid were separated and by column chromatography.

NMR Data for Azelaic acid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.25 (s, 6 H) 1.48 (t, *J*=6.75 Hz, 4 H) 2.18 (t, *J*=7.38 Hz, 4 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 24.92, 28.88, 28.91, 34.12, 174.96.

NMR data for 3-hydroxy nonanoic acid: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.80 - 0.91 (m, 3 H) 1.19 - 1.41 (m, 10 H) 2.15 - 2.32 (m, 2 H) 3.78 (dd, *J* = 7.19, 4.69 Hz, 1 H)

4.59 (br. s., 1 H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 14.42, 22.53, 25.49, 29.19, 31.76, 37.40, 67.54, 173.52.

4. Continuous flow synthesis of adipic acid and dodecanoic acid from petroselinic acid:

1 g petroselinic acid was dissolved in acetone: water mixture (47.5 mL: 2.5 mL). The petroselinic acid solution and ozone (O_2/O_3) were pumped at the flow rate of 1 mL/min and 500 mL/min respectively, in a flow reactor (volume = 20 mL, inner diameter = 2mm, length 5m) at 0 °C. The sample obtained from outlet was analysed and isolated yield was obtained 72% for adipic acid and 76% for dodecanoic acid. (Yield calculated with respect to starting material (petroselinic acid) purity 95 %). After completion of the reaction, work up procedure was followed to obtain mixture of adipic acid and dodecanoic acid. Adipic acid and dodecanoic acid were separated by column chromatography.

NMR Data for Adipic acid: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 1.37 - 1.61 (m, 4 H) 2.19 (br. s., 4 H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 24.63, 34.10, 175.00.

NMR Data for Dodecanoic acid: ^1H NMR (400 MHz, CDCl_3) δ ppm 0.76 - 0.85 (m, 3 H) 1.06 - 1.33 (m, 16 H) 1.47 - 1.62 (m, 2 H) 2.27 (t, $J = 7.57$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 14.09, 22.67, 25.25, 29.06, 29.24, 29.32, 29.42, 29.54, 29.59, 31.90, 34.05, 179.96.

5. Continuous flow synthesis of tridecanedioic acid and Pelargonic acid from erucic acid:

1 g erucic acid was dissolved in acetone: water mixture (47.5 mL: 2.5 mL). The erucic acid solution and ozone (O_2/O_3) were pumped at the flow rate of 1 mL/min and 500 mL/min respectively, in a flow reactor (volume = 20 mL, inner diameter = 2 mm, length 5m) at 0 °C. The sample obtained from outlet was analysed and isolated yield was obtained 88% for tridecanedioic acid and 74% for pelargonic acid. (Yield calculated with respect to starting material (erucic acid) purity 85 %). After completion of the reaction, work up procedure was followed to obtain mixture of tridecanedioic acid and pelargonic acid. Tridecanedioic acid and pelargonic acid were separated by column chromatography.

NMR Data for Tridecenedioic acid: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 1.24 (s, 14 H) 1.48 (t, $J=6.82$ Hz, 4 H) 2.18 (t, $J=7.32$ Hz, 4 H) 11.96 (br. s., 2 H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ ppm 23.89, 27.94, 28.13, 28.29, 33.06, 173.89.

NMR Data for Pelargonic acid: ^1H NMR (400 MHz, CDCl_3) δ ppm 0.77 - 0.95 (m, 3 H) 1.22 - 1.35 (m, 10 H) 1.61 (d, $J = 7.38$ Hz, 2 H) 2.33 (t, $J=7.50$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 14.03, 22.60, 24.65, 29.03, 29.06, 29.67, 31.77, 34.09, 180.29.

6. Continues flow gram scale synthesis of Azelaic acid and Pelargonic acid from oleic acid:

We further scaled up the reaction to verify the efficiency of this method using the above protocol. For this purpose we designed a slightly bigger reactor of 40 mL volume under optimized condition to produce 20 g/h of azelaic acid with 86% isolated yield along with 78% of pelargonic acid. We carried out the experiments at the optimized condition for over 10 hours. The results are among the best ever synthesis of azelaic acid by ozonolysis of oleic acid.

Procedure for large scale synthesis Azelaic acid:

200g oleic acid was dissolved in acetone: water mixture (1900 ml: 100 ml). The oleic acid solution and ozone (O_2/O_3) are pumped at the flow rate of 5.7 mL/min and 500 mL/min respectively, in a flow reactor (volume = 40mL, inner diameter = 2mm, length 10m) at 0 °C. The sample obtained from outlet was analysed and isolated yield was obtained 86% azelaic acid and 78% pelargonic acid. (Yield calculated with respect to starting material (oleic acid) purity 99%). After completion of the reaction, work up procedure was followed to obtain mixture of azelaic acid and pelargonic acid. Azelaic acid and pelargonic acid were separated by column chromatography. The product was analysed by NMR spectroscopy. Product obtained from scale up experiment as shown in **figure 1 and 2**.

Yield Calculation formula for AA:

Theoretical yield of AA= Molecular weight AA/ molecular weight of OA X Quantity of OA

$$= 188.22/282.47 \times 1\text{g}$$

$$= 0.66 \text{ g AA}$$

Practical yield of AA= 0.587 g of AA

% yield of AA = Practical yield of AA / theoretical yield of AA X 100

$$\% \text{ yield of AA} = 0.587/0.66 \times 100$$

$$= 88.9\% \text{ of AA}$$

Yield Calculation formula for PA:

Theoretical yield of PA= Molecular weight PA/ molecular weight of OA X Quantity of OA

$$= 158.23/282.47 \times 1\text{g}$$

$$= 0.56 \text{ g PA}$$

Practical yield of NA = 0.415 g of PA

% yield of PA = Practical yield of PA / theoretical yield of PA X 100

$$\% \text{ yield of PA} = 0.415 / 0.56 \times 100$$

$$= 74\% \text{ of PA}$$

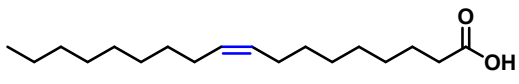
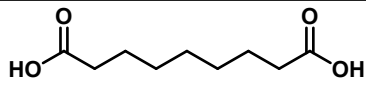
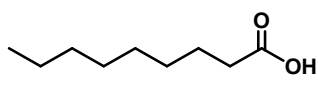
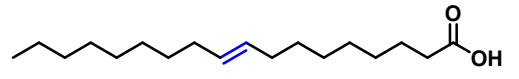
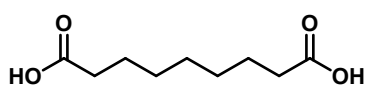
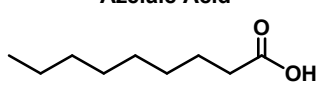
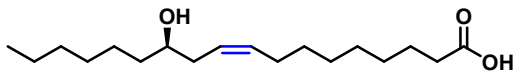
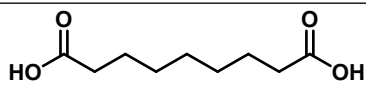
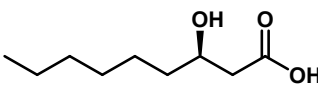
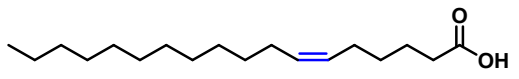
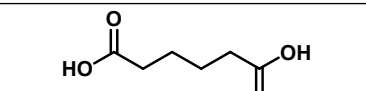
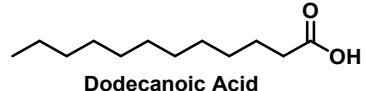
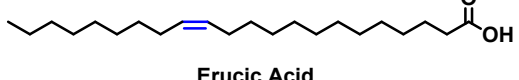
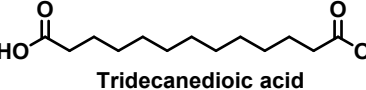
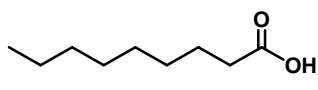


Figure 1: Azelaic Acid obtained from large scale experiment



Figure 2: Pelargonic acid obtained from large scale experiment

Table1: Observations of continuous flow catalyst free ozonolysis of various fatty acids

Sr. No.	Substrates	Products	Isolated Yield (%)
1.	 <p>Oleic acid</p>	 <p>Azelaic Acid</p>  <p>Pelargonic Acid</p>	89 74
2.	 <p>Elaidic Acid</p>	 <p>Azelaic Acid</p>  <p>Pelargonic Acid</p>	87 76
3.	 <p>Recinoleic acid</p>	 <p>Azelaic Acid</p>  <p>3- Hydroxy Nonanoic Acid</p>	86 70
4.	 <p>Petroselinic acid</p>	 <p>Adipic acid</p>  <p>Dodecanoic Acid</p>	72 76
5.	 <p>Erucic Acid</p>	 <p>Tridecanedioic acid</p>  <p>Pelargonic Acid</p>	88 74

¹H and ¹³C NMR spectral data of above examples:

