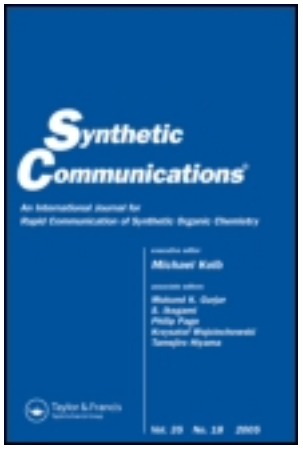

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Raney Nickel-Catalyzed Hydrogenation of Unsaturated Carboxylic Acids with Sodium Borohydride in Water

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RANEY NICKEL–CATALYZED HYDROGENATION OF UNSATURATED CARBOXYLIC ACIDS WITH SODIUM BOROHYDRIDE IN WATER

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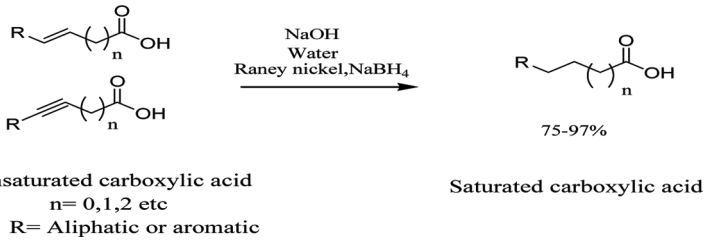
GRAPHICAL ABSTRACT



Abstract *A mild, selective, and green method for the reduction of unsaturated carboxylic acids with sodium borohydride–Raney nickel (W6) system in water is reported. This method is practical and safe and avoids use of organic solvents.*

Keywords Reduction; sodium borohydride; unsaturated carboxylic acids; water

INTRODUCTION

Reduction of olefin is an important transformation in organic chemistry and is very well reviewed in the literature.[1] The large number of protocols developed for this transformation indicates the importance and usefulness of this in organic chemistry.[1–3] Most of the common procedures for the reduction of olefins use molecular hydrogen along with metal catalysts such as Pd-C,[1] Pt-C,[4] Ni,[5] and several other noble metals.[1] Additionally, biochemical and enzymatic methods have also been employed for the reduction of olefins.[3b–3d] The utility of sodium borohydride for

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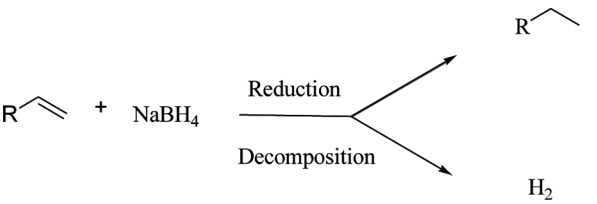
the reduction of olefins was discovered by Brown and coworkers in 1962.[6a] In this reduction, the in situ–generated hydrogen gas from sodium borohydride is consumed. Subsequently, there were several other reports on the modification of this approach for the reduction of olefins using sodium borohydride.[6b–6i] Many of these strategies use sodium borohydride in the presence of metals and their derivatives such as Pd, Rh, In, and $NiCl_2$ to bring about this reduction.[7b–7h]

Sodium borohydride, a very well-known metal hydride, have been extensively used in the organic transformation.[7a] This is known to be a safe, relatively stable hydride and is commercially available in powder form and aqueous alkaline solution in various concentrations below 30% w/w (Montgomery Chemicals, Conshohocken, PA, USA). Sodium borohydride is widely used for the reduction of carbonyl functional groups such as aldehyde, ketone, and ester.[7a] While a considerable amount of work has been reported to improve the utility of sodium borohydride–metal–catalyzed hydrogenation, one of the major disadvantages in these methods is the requirement for a large amount of sodium borohydride.[7,8] This is mainly because of competing decomposition of sodium borohydride (Scheme 1), thereby and a amount of hydrogen is wasted.

The recent reports on the use of $RuCl_3$-catalyzed sodium borohydride hydrogenation of mono- and disubstituted olefins in tetrahydrofuran (THF) and water[9] and sodium borohydride–Pd catalyst for reduction of alkenes and alkynes in isopropyl alcohol in the presence of acetic acid[10] is a slight improvement of the reaction conditions in these directions. Compared to the earlier reports, the sodium borohydride/Pd-C method appears to be more general and can be used for the reduction of alkenes and alkynes. Although this method works well in many solvents, including water, the general applicability of this procedure in the presence of other functional groups has not been demonstrated.

Sodium borohydride–nickel chloride is known to accomplish the reduction of olefins.[7] However, application of this method for reduction of unsaturated carboxylic acids did not give a clean product in our laboratory. While carrying out the reaction, we observed that the carboxylic acid reacted with sodium borohydride to form borate ester, which precipitates from the reaction medium, thereby blocking further reduction. This prompted us to develop an alternative reaction condition.

While a considerable amount of work has been carried out to use noble metal catalysts in combination with sodium borohydride for the reduction of olefins, surprisingly, there are no reports on the use of commercially available Raney nickel. Therefore, we decided to explore the reduction of unsaturated carboxylic acid by using commercially available Raney nickel (W6 grade) in water.



Scheme 1. Competing decomposition of sodium borohydride.

RESULTS AND DISCUSSION

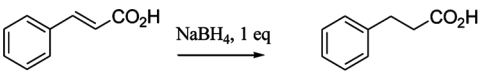
Development of new methodology in organic synthesis based on green chemistry is an important goal toward a sustainable future.[11a–f] In our continuing efforts to develop new methodologies in water, we were interested in developing an alternate practical method for the reduction of unsaturated carboxylic acids in water. We have selected sodium borohydride as hydrogen source and Raney nickel (W6 grade) as catalyst for all our experiments.

Our initial experiments to reduce cinnamic acid with sodium borohydride–Raney nickel in water did not yield any product (Table 1, entry 1). Attempts to change the solvents to methanol and tetrahydrofuran (THF) also gave poor yield (Table 1, entries 2 and 3). Even nickel chloride as catalyst did not furnish a reduced product in good yield (Table 1, entries 4 and 5).

While carrying out these reactions, we observed two main problems. The first one is the solubility issue of the substrates, and the second one is the rapid decomposition of sodium borohydride under the reaction condition. The solubility issue has been addressed by converting the substrates into their corresponding sodium salt in water. This would also address the unintended reactivity of sodium borohydride with the carboxylic group. Additionally, sodium borohydride is known to be more stable under a basic reaction condition.

When sodium salt of cinnamic acid **1** (Table 2, entry 1) was subjected to reduction in water in the presence of Raney nickel, the reduction proceeded to furnish phenylpropionic acid **1a** with good yield. During the reaction, we observed that the decomposition of sodium borohydride has been slowed considerably. Based on this result, it is evident that sodium borohydride is slowly liberating hydrogen gas in the presence of Raney nickel under basic conditions, which is consumed during hydrogenation. An attempted control experiment in the absence of Raney nickel did not give any reduced product. In the general optimized reaction conditions, the substrates are made soluble in water by converting them to corresponding sodium salt at room temperature. Then Raney nickel (W6) about 30–40% by weight is added, followed by sodium borohydride (normally a molar equivalent) at room temperature, and then the mixture is heated at 50–60 °C for 1 h. After the completion of the reaction as monitored by thin-layer chromatography (TLC), the crude

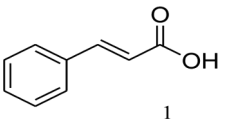
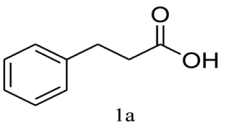
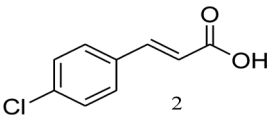
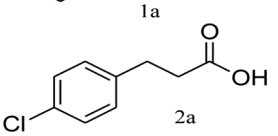
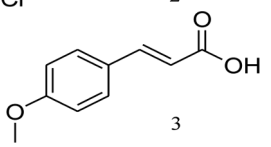
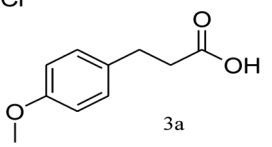
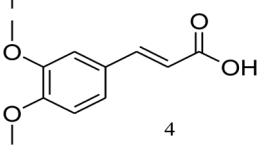
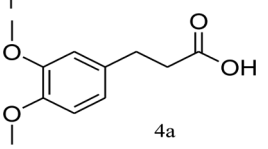
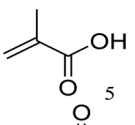
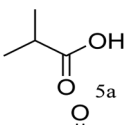
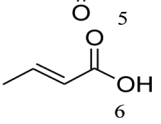
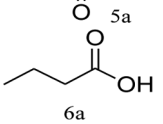
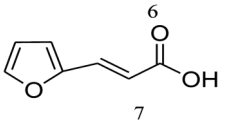
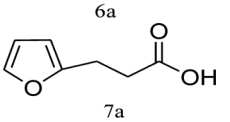
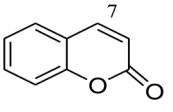
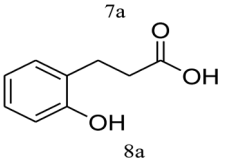
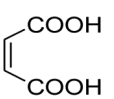
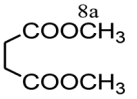
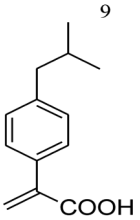
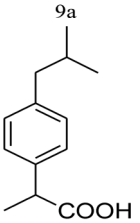
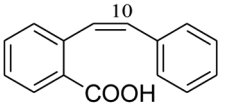
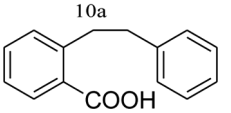
Table 1. Attempted reduction with sodium borohydride and Raney nickel



Cinnamic acid — Phenyl propionic acid

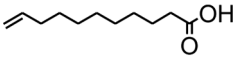
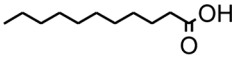
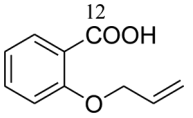
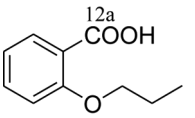
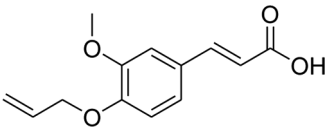
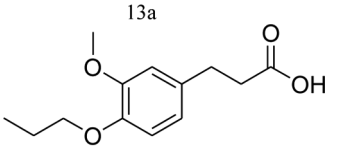
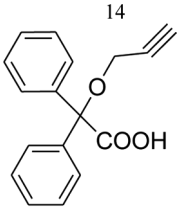
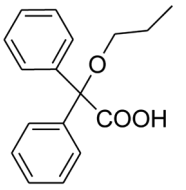
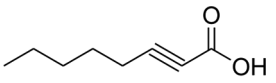
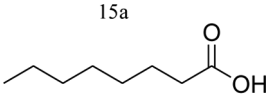
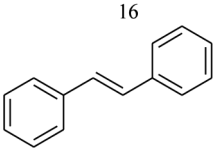
Entry	Solvent	Catalyst (30%wt)	Yield (%)
1	Water	Ra-Ni	0
2	Methanol	Ra-Ni	10
3	THF	Ra-N	22
4	Water	$NiCl_2$	0
5	Methanol	$NiCl_2$	15

Table 2. Raney nickel–catalyzed hydrogenation with alkaline aqueous borohydride

Entry	Substrate	Product	Yield[a] (%)
1	 1	 1a	89
2	 2	 2a	92
3	 3	 3a	90
4	 4	 4a	92
5	 5	 5a	90
6	 6	 6a	90
7	 7	 7a	75
8	 8	 8a	92
9	 9	 9a	86
10	 10	 10a	91
11	 11	 11a	89

(*Continued*)

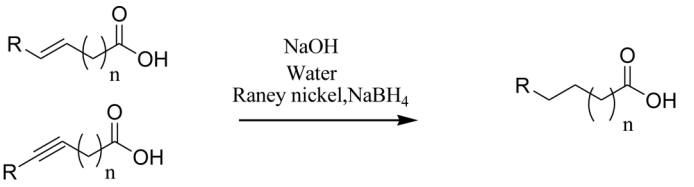
Table 2. Continued

Entry	Substrate	Product	Yield[a] (%)
12			97
13	 12	 12a	90
14	 13	 13a	85
15	 14	 14a	89
16	 15	 15a	92
17	 16	No reaction 16a	
18		No reaction	

[a]Isolated pure yield based on starting material.

product was neutralized with dilute acid and extracted with CH_2Cl_2 to furnish the product.

When cinnamic acid **1** (Table 2, Scheme 2) is subjected to reduction with sodium borohydride and Raney nickel, it is reduced to phenylpropionic acid **1a** with 89% yield. Similarly *p*-chlorocinnamic acid **2** and methoxy substituted cinnamic acids **3** and **4** are reduced to the corresponding phenylpropionic acids **2a**, **3a**, and **4a** with yields of 92%, 90%, and 92% respectively. It is interesting to note that the chloro group is not affected in the reaction. Simple unsaturated acids like α-methylacrylic acid **5** and β-methylacrylic acid **6** were reduced completely to their saturated acids **5a** and **6a** with good yield. This method has also been extended to sensitive substrates having furoic acid groups. β-Furylacrylic acid **7** is reduced to corresponding saturated acid **7a** with 75% yield. Other substrates such as coumarin **8** are



Scheme 2. Reduction of unsaturated acid.

reduced to the corresponding saturated hydroxy acid **8a** with good yield. This method has also been extended to maleic acid **9**. Because of the solubility of the succinic acid, it is isolated as corresponding methyl ester **9a** with 86% yield, and the same methodology has been extended to the synthesis of ibuprofen **10a** from the corresponding unsaturated acid **10**. Even *o*-styrylbenzoic acid **11** is reduced to 2-phenylethylbenzoic acid **11a** in good yield. Similarly, undecylenic acid **12**, having an isolated double bond, is completely reduced to saturated undecanoic acid **12a** with excellent yield (97%). Substrates having allylic ether groups **13** and **14** undergo clean reduction to corresponding saturated acids **13a** and **14a** with good yield. In substrate **14** it is interesting to note that both α,β-unsaturated and isolated double bonds are reduced completely with 85% yield. Substrate **14** required 2 equivalents of sodium borohydride for the complete reduction.

The generality of this method has also been extended to substrates having propargylic carboxylic acid. Substrate **15**, which is an intermediate in the synthesis of pargiverine and has an having isolated propargyl group, underwent clean reduction to the corresponding saturated acid **15a** with a good yield. Similarly simple aliphatic α,β-unsaturated 2-octynoicacid **16** (Scheme 2) is completely reduced to the corresponding saturated octanoic acid **16a** in very good yield. Alkyne system also required 2 equivalents of sodium borohydride for the complete reduction. This clearly indicates that this method works very well for isolated and α,β-unsaturated triple bonds. Simple substrates like stilbine **17** and α-methylstyrene **18** did not give any reduced product even after adding excess catalyst and sodium borohydride. This clearly indicates solubility of the substrates in water is essential for the successful reduction. This is in clear contrast to the recently published report where in the reduction works very well in water when sodium borohydride–palladium catalyst and insoluble substrates are used.[10] Substrate **11** has been scaled up to a kilo batch without any problems. We have successfully reused Raney nickel 10 times without any appreciable change in yield or activity for the reduction of substrate **11**.

It is interesting to note that in comparison to reported procedure in the literature for the reduction of olefins[6–8] using sodium borohydride, a large excess of sodium borohydride is not used in this reaction. A molar equivalent of sodium borohydride is sufficient to bring about the reduction. This is possibly because the reported procedures are done either at mild acidic or neutral pH conditions, and under these conditions decomposition of sodium borohydride is one of the main

side reactions with a large amount of hydrogen liberation. In contrast, the basic pH of the reaction medium has relatively reduced the decomposition of sodium borohydride.

CONCLUSION

In brief, we have developed a practical green method for the reduction of unsaturated carboxylic acids using a sodium borohydride–Raney nickel system in water. It is very essential that the substrates need to be dissolved in water by converting them into metal carboxylate salts for successful reduction. Further the method is environmentally friendly and economically viable to carry out on a large scale.

EXPERIMENTAL

All solvents and reagents were purchased from suppliers and used without further purification. Yields reported are for isolated yield unless otherwise stated. ^{1}H NMR (400, 300, and 200 MHz) and ^{13}C NMR (100, 75, and 50 MHz) spectra were recorded in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) at room temperature. The chemical shift is based on internal tetramethylsilane (TMS). Infrared (IR) spectra were recorded by a Shimadzu FTIR instrument. Analytical thin-layer chromatography (TLC) was performed on Merck silica-gel (60 GF_{254}) plates (0.25 mm) and components were visualized with ultraviolet light (254 nm wavelength) and iodine vapors. Melting points were determined on a Thermonic instrument and are uncorrected.

General Procedure for the Reaction of Conjugated Olefins: 3-Phenylpropanoic Acid (1a)[12a]

Raney nickel (0.30 g, W6 grade) was added to a stirred a solution of cinnamic acid (0.740 g, 5 mmol) in 0.52 M aqueous sodium hydroxide (10 mL). To this slurry, sodium borohydride (0.190 g, 5 mmol) is added in small portions at room temperature. After 30 min, the reaction mixture was stirred at 50–60 °C until the completion of the reaction (3 h, monitored by TLC), cooled to room temperature, and filtered to remove Raney nickel. The filtrate was acidified to pH 2 with dilute HCl and extracted with dichloromethane (2×40 mL). The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was removed completely to get the desired product. The product thus obtained is practically pure by NMR. Colorless solid. Mp 46–48 °C (lit.[12b] 46–47 °C). IR (KBr): 1704, 3250 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.68 (t, $J = 7.8$ Hz, 2H), 2.96 (t, $J = 7.8$ Hz, 2H), 7.22−7.26 (m, 5H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0, 36.0, 126.8, 128.7, 129.0, 140.6, 179.6.

General Procedure for the Reaction of Unconjugated Olefins: 2-(2-Phenylethyl)benzoic Acid (11a)[13a]

Raney nickel (30 g, W6 grade) was added to *o*-styrylbenzoic acid[4] (112 g, 0.5 mol) dissolved in aqueous sodium hydroxide solution (20.8 g, 0.52 mol in

600 mL) and stirred for 15 min. To this aqueous slurry, sodium borohydride (19 g, 0.5 mol) is added in small portions over a period of 20 min at room temperature and stirred until the frothing stopped. Then the reaction mixture was stirred at 50–60 °C until the completion of the reaction (monitored by TLC), cooled to room temperature, and filtered to remove Raney nickel. Filtrate was acidified to pH 2 with concentrated HCl and extracted with dichloromethane (3 × 400 mL). The combined organic layer was dried over anhydrous sodium sulfate; solvent was evaporated to get 2-(2-phenyl ethyl) benzoic acid as a white solid. Mp 130–132 °C (lit.[13b] 130 °C). IR (KBr): 1685, 3155 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.94 (t, $J = 8.0$ Hz, 2H), 3.35 (t, $J = 8.0$ Hz, 2H), 7.15–7.51 (m, 8H), 8.09 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6, 38.6, 126.4, 126.7, 128.6, 128.8, 129.0, 132.0, 132.3, 133.5, 142.4, 145.3, 173.9.

Selected Data

3-(4-Chlorophenyl)propanoic acid (2a).[12a] White solid. Mp 122–124 °C (lit.[12c] 119–121 °C). IR (KBr): 1695, 3207 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.49 (t, $J = 7.6$ Hz, 2H), 2.7 7(t, $J = 7.6$ Hz, 2H), 7.14–7.30 (m, 4H).

3-(4-Methoxyphenyl)propanoic acid (3a).[12a] White solid. Mp 98–100 °C (lit.[12b] 101–102 °C). IR (KBr): 1703, 3217 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (t, $J = 7.5$ Hz, 2H), 2.90 (t, $J = 7.5$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 9.0$ Hz, 2H).

3-(3,4-Dimethoxyphenyl)propanoic acid (4a).[15] Cream solid. Mp 96–98 °C (lit.[14] 96–97 °C). IR (KBr): 1701, 3205 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.66 (t, $J = 7.5$ Hz, 2H), 2.91 (t, $J = 7.5$ Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.71–6.81 (m, 3H).

2-Methylpropanoic acid (5a).[16] Colorless liquid. IR (neat): 1707, 3205 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.15–1.21 (m, 6H), 2.53–2.62 (m, 1H), 10.65 (s, 1H).

Butanoic acid (6a).[17] Brown liquid. IR (neat): 1711, 3191 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.9 7(t, $J = 7.2$ Hz, 3H), 1.62–1.71 (m, 2H), 2.34 (t, $J = 7.4$ Hz, Hz, 2H), 9.93 [s (broad), 1H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 18.5, 36.4, 180.8.

3-(2-Furyl)propanoic acid (7a).[18a] White solid. Mp 56–58 °C (lit.[18b] 56 °C). IR (KBr): 1701, 3213 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.49 (t, $J = 7.6$ Hz, 2H), 2.78 (t, $J = 7.6$ Hz, 2H), 6.04 (s, 1H), 6.29 (s, 1H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.8, 32.8, 106.0, 111.2, 142.2, 155.2, 174.3.

3-(2-Hydroxyphenyl)propanoic acid (8a).[19] Solid. Mp 84–86 °C (lit.[19] 83–85 °C). IR (KBr): 1686, 3389 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.76 (t, $J = 7.8$ Hz, 2H), 2.91 (t, $J = 7.8$ Hz, 2H), 6.81–6.89 (m, 2H), 7.11 (q, $J = 8.0$ Hz, 2H).

Dimethylbutandioic acid (9a).[20] Yellow liquid. IR (neat): 1711, 3191 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 51.8, 173.0.

2-(4-Isobutylphenyl)propanoic acid (10a).[21] White solid. Mp 74–76 °C (lit.[21] 75–77 °C). IR (KBr): 1706, 3189 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.9 (d, $J = 8.0$ Hz, 6H), 1.49 (d, $J = 8.0$ Hz, 2H), 1.83–1.86 (m, 1H), 2.45 (d, $J = 8.0$ Hz, Hz, 2H), 3.71 (q, $J = 8.0$ Hz 1H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 22.9, 30.7, 45.5, 127.8, 129.9, 137.4, 141.3, 182.0.

Undecanoic acid (12a).[22] Viscous liquid. IR (neat): 1702, 3205 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.87–2.33 (m, 21H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 25.1, 29.3, 29.5, 29.6, 31.9, 34.4, 35.3, 37.3, 180.0.

2-Propoxybenzoic acid (13a).[23] Yellow oil. IR (neat): 1703, 3215 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, $J = 7.5$ Hz, 3H), 1.90–2.01 (m, 2H), 4.22 (t, $J = 6.6$ Hz, 2H), 7.03–7.15 (m, 2H), 7.52–7.58 (m, 1H), 8.18 (dd, $J = 9.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2, 22.2, 71.6, 112.5, 121.9, 133.5, 134.9, 157.5, 165.4.

3-(3-Methoxy-4-propoxyphenyl)propanoic acid (14a).[24] Cream solid. Mp 66–68 °C. IR (KBr):1718, 3219 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, $J = 7.5$ Hz, 3H), 1.81–1.88 (m, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 2.89 (t, $J = 7.5$ Hz, 2H), 3.86 (s, 3H), 3.95 (t, $J = 6.6$ Hz 2H), 6.71–6.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.3, 22.4, 30.2, 35.8, 55.9, 70.6, 112.2, 113.3, 120.1, 132.8, 147.1, 149.4, 179.0.

2,2-Diphenyl-2-propoxyethanoic acid (15a).[25] White solid. Mp 118–120 °C (lit.[25] 120–121 °C). IR (KBr):1706, 3155 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, $J = 7.5$ Hz, 3H), 1.55 (q, $J = 6.6$ Hz, 2H), 3.05 (t, $J = 6.9$ Hz, 2H), 7.19–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 23.0, 67.0, 86.5, 127.6, 127.9, 128.2, 128.6, 139.3, 175.1.

Octanoic acid (16a).[26] Yellow oil. IR (neat): 1709, 3201 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.5$ Hz, 3H), 1.26 (s, 8H), 1.63 (t, $J = 7.5$ Hz, 2H), 2.35 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 24.7, 29.0, 29.1, 31.7, 34.3, 180.3.

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