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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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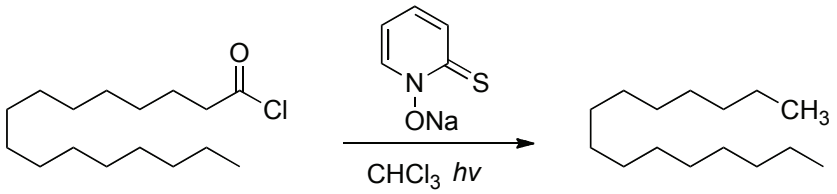
Reductive Radical Decarboxylation of Aliphatic Carboxylic Acids



Submitted by Eun Jung Ko,[1] Craig M. Williams,[1] G. Paul Savage,[2] and John Tsanaktsidis.[2]
Checked by Samantha R. Levine, Aaron Bedermann, and John L. Wood.

1. Procedure

An oven-dried (Note 1) 500-mL four-necked, round-bottomed flask (Note 2) is equipped with a 3-cm Teflon-coated oval stir bar, a 125-mL pressure-equalizing addition funnel sealed with a septum, a thermometer, a septum, and a reflux condenser fitted with a gas inlet adapter and connected to a dual manifold (Note 3). The reaction vessel is charged with chloroform (120 mL) (Note 4), 1-hydroxypyridine-2(1*H*)-thione, sodium salt (5.90 g, 39.6 mmol, 1.2 equiv) (Note 5) and 4-*N,N*-dimethylaminopyridine (0.040 g, 0.33 mmol, 0.01 equiv) to give an off-white suspension. The addition funnel is charged with palmitoyl chloride (10 mL, 9.06 g, 33.0 mmol, 1.0 equiv) followed by chloroform (60 mL), and the entire apparatus is blanketed with a slight positive pressure of nitrogen to maintain an inert atmosphere throughout the course of the reaction (Note 6).

The reaction vessel is heated to reflux over 25 min (silicon oil bath, external bath temperature 80 °C, internal temperature 57 °C) and the palmitoyl chloride solution is then added drop-wise over 85 min with concomitant irradiation from a tungsten lamp (120V, 150W) (Note 7). The reaction mixture remains a suspension, which gradually turns yellow upon the addition of palmitoyl chloride. Visible evolution of carbon dioxide is observed by 30 min. After an additional 25 min of stirring an orange suspension is observed (Note 8). Heating and irradiation is then discontinued and the resulting orange/brown suspension is allowed to cool to an internal temperature of 25 °C and transferred to a 500-mL separatory funnel containing 1M HCl (100 mL) and CH_2Cl_2 (100 mL). The aqueous

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phase is separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers are washed with saturated NaCl solution (100 mL), dried over 5.9 g of $MgSO_4$, filtered through a 350 mL medium porosity sintered glass funnel, and concentrated by rotary evaporation (bath temperature increased from 25 to 35 °C, 250 mmHg) and then at 3 mmHg to afford a yellow-brown oil.

The neat product is charged on a plug (6 x 10 cm) of 150 g of silica gel (Note 9) and eluted with 1 L of petroleum ether 35 – 60 °C directly into a 2-L round-bottomed flask (Note 10). This solution is concentrated by rotary evaporation (bath temperature increased from 25 to 30 °C, pressure reduced from 400 to 250 mmHg) and then at 3 mmHg to afford 6.29 g (90%) (Note 11) of pentadecane as a clear, colorless oil (Note 12).

2. Notes

1. The submitters used an oven set to 180 °C, assembled the apparatus while still hot, and allowed it to cool to ambient temperature (23 °C) under vacuum (0.9 mmHg). The checkers used an oven set to 180 °C, allowed the apparatus to cool to ambient temperature (20 °C) in a dessicator containing Drierite, assembled it, and evacuated and backfilled the system three times with nitrogen.

2. The submitters used a 500-mL two-necked round-bottomed flask, the checkers chose to use a four-necked flask to facilitate TLC and internal reaction temperature monitoring.

3. Depiction of the experimental set-up, including the position of the light source, is illustrated in **Figure 1**.

4. The submitters obtained 4-*N*,*N*-dimethylaminopyridine (99%) and palmitoyl chloride (98%) from Sigma-Aldrich, Inc. which were used as received. Chloroform (99.8%) was purchased from ChemSupply Co., Inc. and distilled from P_2O_5 prior to use. The checkers obtained 4-*N*,*N*-dimethylaminopyridine (99%) from Acros Organics and palmitoyl chloride (98%) from MP Biomedicals, LLC., both of which were used as received. Chloroform (99.8%) was purchased from Mallinckrodt Chemicals, Inc., and was washed with water, dried over K_2CO_3, and distilled from Na_2SO_4 prior to use.

5. The submitters purchased 1-hydroxypyridine-2(1*H*)-thione, sodium salt as a 40 % solution in water from Merck. The water was removed under reduced pressure (40 °C, 20 mmHg) and the resulting yellow solid

was recrystallized from ethanol to give a white powder. The checkers purchased 1-hydroxypyridine-2(1*H*)-thione, sodium salt as a 40 % solution in water from Alfa Aesar. The water was removed under reduced pressure (30 °C, 3 mmHg) and the resulting yellow solid was dissolved in ethanol and triturated with hexanes to give an off-white powder.

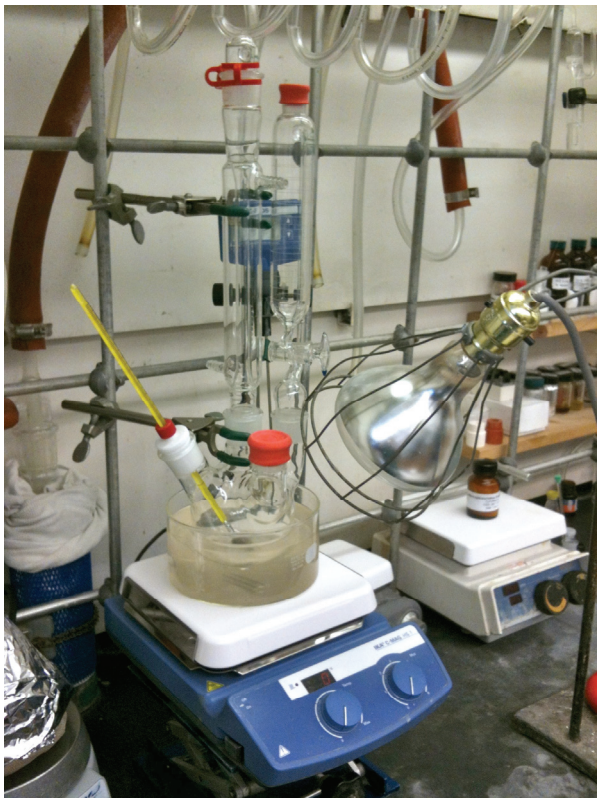


Figure 1. Experimental set-up used in the reaction

6. The submitters used argon to maintain an inert atmosphere.

7. The submitters performed the addition over 40 min (1.5 mL/min) with concomitant irradiation from a tungsten lamp (240V, 500W). The reaction mixture turned bright yellow upon addition of the palmitoyl chloride, with the color fading as the evolution of carbon dioxide was observed. After 1 h the bright yellow coloration faded to an orange/brown color.

8. The progress of the reaction was monitored by TLC analysis on silica gel with 15% EtOAc-hexanes as the eluent and visualization with *p*-anisaldehyde. The acid chloride starting material has R_f = 0.53 (white), the alkane product is not observable by TLC.

9. The submitters obtained silica gel (particle size 0.040 – 0.063 mm) 230-400 ASTM mesh from Advanced Molecular Technologies. The

checkers obtained silica gel (particle size 0.04 – 0.063 mm) 230-400 mesh from Silicycle.

10. The submitters diluted the brown residue with CH_2Cl_2 (10 mL), which was charged on plug (9 cm Ø) of 250 g of silica gel, eluting with petroleum ether 40 – 60 °C (1500 mL) which was obtained from Merck and purified by distillation prior to use. After removal of the solvent by rotary evaporation (40 °C, 300 mmHg) a yellow oil was obtained. This oil was further purified by bulb-to-bulb distillation using a Büchi Glass Oven B-580 Kugelrohr at 93 °C (0.9 mmHg) whose receiving bulb was cooled with dry ice to yield 5.7 g (81%) of pentadecane as a colorless oil.

11. When the reaction was carried out on a 27.9 mmol scale the checkers obtained a yield of 83%.

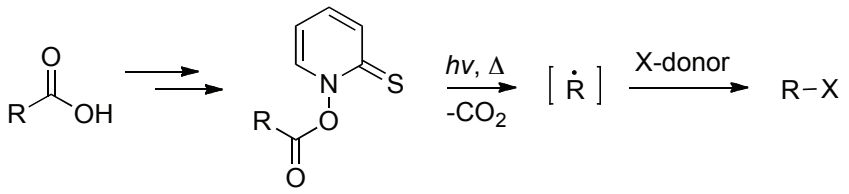
12. The product exhibits the following properties: ν_{max}/cm^{-1} (neat) 2956, 2923, 2853; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (26H, br s), 0.88 (6H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 32.1, 29.9, 29.8, 29.5, 22.9, 14.3; *m/z* GC/MS 212; Anal. calcd. for $C_{15}H_{32}$: C, 84.82; H, 15.18; found: C, 84.70; H, 14.91.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

The Barton decarboxylation is a radical reaction in which a carboxylic acid is first converted to a thiohydroxamate ester, which upon heating (optionally in the presence of a radical initiator or light) undergoes homolytic cleavage, followed by loss of carbon dioxide (Scheme 1). The resulting aliphatic radicals can then be trapped by a variety of reagents leading to new functionality. Using this reaction it is possible to remove the carboxylic acid group from aliphatic carboxylic acids and replace it with other functional groups.[3]

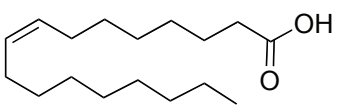
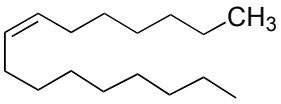
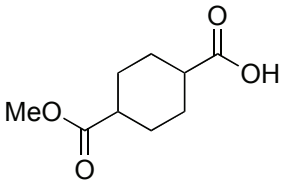
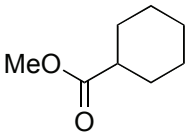
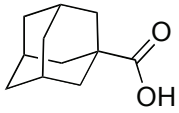
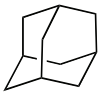
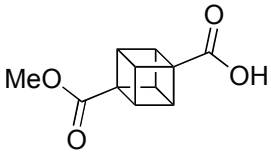
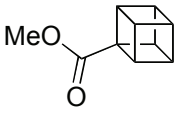
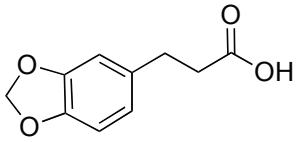
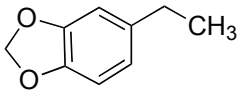
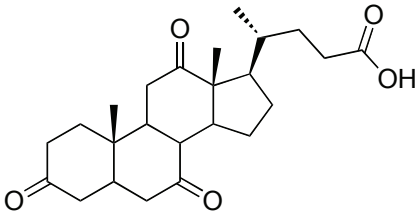
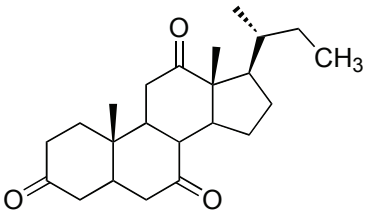


Scheme 1. Barton radical decarboxylation reaction.

The intermediate thiohydroxamate ester can be obtained by reacting an acid chloride and the sodium salt of 1-hydroxypyridine-2(1*H*)-thione (5) as in this report, or directly from the carboxylic acid using *N,N*'-dicyclohexylcarbodiimide (DCC) and similar coupling methods.[4] We found that the acid chloride method was generally more reliable. The acid chlorides can be prepared by the action of oxalyl chloride or thionyl chloride on the carboxylic acid.[5]

Reductive decarboxylation (**Scheme 1**, X = H) is an important subset of the Barton procedure, which ultimately results in replacing the carboxylic acid function with a hydrogen atom.[6] Under this protocol, reductive decarboxylation is accomplished by mild photochemical decomposition of the corresponding thiohydroxamate ester, in the presence of a suitable hydrogen donor (H-donor), originally tributyltin hydride or tert-butylthiol. We recently discovered that it is more convenient, safer, and less expensive to use chloroform as both solvent and H-donor in these reactions.[7] Aromatic carboxylic acids do not undergo this reaction. The procedure described herein is applicable to aliphatic carboxylic acids with the best results generally from primary and secondary acids (**Table 1**). The reductive decarboxylation product of especially hindered tertiary carboxylic acids using this method may sometimes be contaminated with the corresponding alkyl chloride, which arises by competing chlorine atom transfer from chloroform. In these cases, the addition of a stronger H-donor, such as tert-butyl thiol, is recommended.

Table 1. Examples of Barton reductive decarboxylations

Carboxylic acid	Product	Yield %
		66
		77
		69[a]
		82
		77
		68

[a] 2:1 mixture of adamantane:1-chloroadamantane

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3. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

4. Barton, D. H. R.; Samadi, M. *Tetrahedron* **1992**, *48*, 7083–7090.
5. Allen, C. F. H.; Byers Jr., J. R.; Humphlett W. J. *Org. Synth.* **1957**, *37*, 66; Coll. Vol. 4, p.739 (**1963**).
6. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun*. **1983**, 939–941.
7. Ko, E. J.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. *Org. Lett.* **2011**, *13*, 1944–1947.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

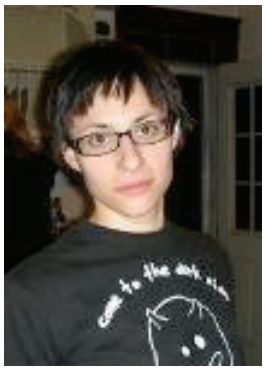
1-Hydroxypyridine-2(1*H*)-thione, sodium salt: 2(1*H*)-Pyridinethione, 1-hydroxy-, sodium salt; (3811-73-2)
4-*N,N*-Dimethylaminopyridine: 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3)
Palmitoyl chloride: Hexadecanoyl chloride; (112-67-4)

G. Paul Savage received his PhD under the direction of Dr R. F. Evans at the University of Queensland in 1988, and this was followed by a two-year postdoctoral position with Professor Alan R. Katritzky FRS at the University of Florida. He returned to Australia to take up a research scientist position with CSIRO, Australia's premier government research organization. He was promoted to Program Manager and completed an MBA in 2005 from the Chifley Business School, La Trobe University. His research interests include heterocyclic chemistry, dipolar cycloaddition reactions, synthesis methodology, and medicinal chemistry.

Dr Tsanaktsidis obtained his BSc (Hons) in 1983 at Flinders University and his PhD in 1988 under the supervision of Dr. Ern Della. Following postdoctoral appointments at the University of Chicago with Professor Philip Eaton, and at the Australian National University with Professor Athel Beckwith, he joined the faculty at the School of Chemistry, at the University of Melbourne in 1991. Dr Tsanaktsidis accepted an offer to join the Commonwealth Scientific and Industrial Research Organization (CSIRO) in 1995. His career achievements were recognized in 2006 through a Distinguished Alumni Award from The Flinders University of South Australia.

Eun Jung Ko was born in 1983 in Rome, Italy. She received her MSci degree in chemistry in 2006 from Imperial College London. In 2010 she was awarded her PhD from The University of Leeds, where she worked on the total synthesis of okaramine B under the supervision of Prof. Stephen P. Marsden. She is currently working as a postdoctoral fellow at the University of Queensland, under the guidance of Dr Craig M. Williams on the development of methodologies for the functionalisation of strained hydrocarbons.

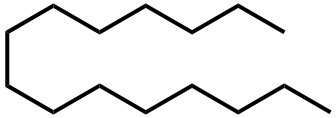
Craig M. Williams received his BSc (Hons) and PhD (1997) degrees from Flinders University (Supervisor Prof. Rolf H. Prager). He worked as an Alexander von Humboldt Postdoctoral Fellow with Prof. Armin de Meijere at the Georg-August-Universität (1999) and then took up a postdoctoral fellowship at the Australian National University with Prof. Lewis N. Mander. He has held an academic position at The University of Queensland since 2000 and during this time has won a number of awards including a Thieme Chemistry Journals Award in 2007. His research focus is on constructing complex natural products and associated synthetic methodology.



Samantha R. Levine was born in Hackensack New Jersey in 1985. In 2008 she received her B. S. in chemistry from The California Institute of Technology, where she did undergraduate research in the laboratory of Professor Brian M. Stoltz. Samantha is pursuing her graduate studies in the research group of Professor John L. Wood.

Aaron Bedermann was born in Madison, Wisconsin. He received his BS in Chemistry from the University of Wisconsin, where he performed undergraduate research under the supervision of Professor Richard Hsung. He is currently pursuing graduate research at Colorado State University under the guidance of Professor John L. Wood.

^{1}H-NMR, 400 MHz
$CDCl_3$



^{13}C-NMR, 100 MHz
$CDCl_3$