Organic Process Research & Development **2009**, *13*, 581–583

A Simple and Efficient Large-Scale Synthesis of Metal Salts of Medium-Chain Fatty Acids

Boulos Zacharie,* Abdallah Ezzitouni, Jean-Simon Duceppe, and Christopher Penney

ProMetic BioSciences Inc., 500 Boulevard Cartier Ouest, Bureau 150, Laval, Québec, Canada H7V 5B7

Abstract:

A simple, inexpensive, one-step general procedure was developed for the preparation of medium-chain fatty acid (MCFA) metal salts. This approach offers the advantage of a practical route and is superior to literature methods. Also, it overcomes many of the limitations previously reported for the preparation of fatty acid salts. The potential utility of this method is illustrated by the production of pilot-scale quantities of high-purity (>99.9%) sodium decanoate.

Introduction

Medium-chain fatty acids (MCFAs), such as hexanoic, octanoic, decanoic, and dodecanoic acid and their metal salts are known to be nontoxic compounds with numerous commercial applications.[1−7] They are major components of seed and coconut oil and are used in the food, perfume, and pharmaceutical industries.

MCFA metal salts are generally produced on a commercial scale by either the fusion method[8] (double decomposition), the precipitation method,[9] or other less common methods.[10] However, they all possess drawbacks and are often fraught with technical difficulties. This limits the potential for scale-up of these procedures.

The literature methods do not differentiate between the preparation of medium- and long-chain fatty acids. In fact, MCFAs have properties which are different from the usual fatty acids.[11] This includes the solubility of the acid, lipophilicity, acid strength as reflected by the dissociation constant of the carboxyl group, the surfactant aggregation, and the molecular association of the resulting salt. These characteristics must be taken into consideration when scaling up the synthesis of MCFA metal salts. Herein we report a simple, efficient, and high-yield general one-step procedure for the synthesis of water-soluble or insoluble MCFA metal salts from water-insoluble MCFAs.

Results and Discussion

Kilogram quantities of high-purity MCFA salts were required for our therapeutic program. One approach was the treatment of the acids with strong base. It was reported[12] that sodium hydroxide (5% in excess) reacted with long-chain fatty acids such as stearic acid to form the corresponding sodium salt. This procedure was followed for the preparation of sodium decanoate. In our hands, this reaction tended to be problematic with regard to product yield (43%) and purity (<90%). For example, the use of water in the workup to remove excess of sodium hydroxide also solubilized a portion of the sodium decanoate salt and consequently reduced the yield. However, this is not the case with sodium stearate which is not soluble[13] in water and can be obtained in respectable yield. Solubility in water is one of many differences that distinguish long-chain fatty acid salts from MCFA salts. Sodium decanoate obtained by this procedure was contaminated with a residual amount of sodium hydroxide which explained the low purity of the MCFA salt. The next step was to find other bases. For example, the use of aluminum alkoxides[14] was reported in the literature for the preparation of aluminum salts of long-chain fatty acids. No examples were reported for the preparation of MCFA salts. Again, this may be due to the differences in the physical properties of these fatty acid salts. Accordingly, a variety of alternative synthetic strategies were evaluated with a view to scale-up for manufacture.

Development Scale Production, 1 to 500 g. Sodium decanoate was chosen as a representative example of an MCFA metal salt. The first step was to select the appropriate base to react with the acid and a suitable solvent. It was reported that

* Author for correspondence. E-mail: b.zacharie@prometic.com.

(1) (a) Motlekar, N. A.; Srivenugopal, K. S.; Wachtel, M. S.; Youan, B.-B. *J. Drug Target* **2005**, *13*, 573. (b) Burton, A. F.; McLean, D. U.S. Patent 5,175,190, 1992; *Chem. Abstr.* **1993**, *118*, 132158x.

(2) (a) Donovan, M. D.; Flynn, G. L.; Amidon, G. L. *Pharm. Res.* **1990**, *7*, 808. (b) Chao, A. C.; Nguyen, J. V.; Broughall, M.; Griffin, A.; Fix, J. A.; Daddona, P. E. *Int. J. Pharm.* **1999**, *191*, 15. (c) Raoof, A. A.; Ramtoola, Z.; McKenna, B.; Yu, R. Z.; Hardee, G.; Geary, R. S. *Eur. J. Pharm. Sci.* **2002**, *17*, 131.

(3) Lindmark, T.; Söderholm, J. D.; Olaison, G.; Alván, G.; Ocklind, G.; Artursson, P. *Pharm. Res.* **1997**, *14*, 930.

(4) Klimentová, J.; Kosák, P.; Vávrová, K.; Holas, T.; Hrabálek, *Bioorg. Med. Chem.* **2006**, *14*, 7681, and references cited therein.

(5) Nair, M. K.; Joy, J.; Vasudevan, P.; Hinckley, L.; Hoagland, T. A.; Venkitanarayanan, K. S. *J. Dairy Sci.* **2005**, *88* (10), 3488.

(6) Hoffman, K. L.; Han, I. Y.; Dawson, P. L. *J. Food Prot.* **2001**, *64* (6), 885.

(7) MCFAs and especially the salts of decanoic and octanoic acid are able to induce hematopoiesis; see: (a) Christopher, P.; Gagnon, L.; Laurin, P.; Zacharie, B. WO 2004/069237, 2004; *Chem. Abstr.* **2004**, *141*, 185103. (b) Duceppe, J.-S.; Ezzitouni, A.; Penney, C.; Zacharie, B. WO 2005/012217 A2, 2005; *Chem. Abstr.* **2005**, *142*, 197581.

(8) Borzelli, R. D.; Cunder, J. U.S. Patent 4,307,027, 1981; *Chem. Abstr.* **1982**, *96*, 87447e.

(9) Davis, G. M.; Township, C. U.S. Patent 2,945,051, 1960; *Chem. Abstr.* **1960**, *54*, 106447.

(10) Ohuchida, S.; Kishimoto, K.; Tateishi, N.; Ohno, H. U.S. Patent 7,176,240, 2002; *Chem. Abstr.* **2003**, *122*, 160096.

(11) (a) Sneth, G. N.; Subrahmanyam, V. V. R. *J. Indian Chem. Soc.* **1982**, *59*, 860. (b) Burton, A. F.; Mclean, D. U.S. Patent 5,175,190, 1992; *Chem. Abstr.* **1993**, *118*, 132158x. (c) Vold, M. J.; Macomber, M.; Vold, R. D. *J. Am. Chem. Soc.* **1941**, *63*, 168. (d) Morigati, K.; Walde, P.; Misran, M.; Robinson, B. H. *Colloids Surf., A* **2003**, *213*, 37.

(12) Pan, H.; Lou, A.; Pan, G. CN Patent 1,052,846, 1991; *Chem. Abstr.* **1992**, *116*, 105632.

(13) McBain, J. W.; Sierichs, W. C. *J. Am. Oil Chem. Soc.* **1948**, *25*, 221.

(14) IG Farbenindustrie. DE Patent 569946, 1933; *Chem. Abstr.* **1933**, *27*, 41360.

10.1021/op900038v CCC: $40.75
Published on Web 04/08/2009

Table 1. **Scale-up of sodium decanoate (production batch size)[a]**

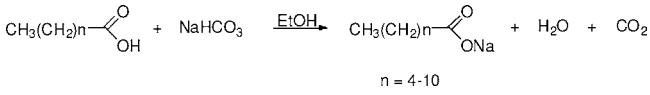
			final product test				
				solubility (appearance)			
entry (batch)	number of batches	batch size	purity LC−MS >99.5%	in water 100 mg/mL to be clear	in MeOH 60 mg/mL to be clear	sodium content 11.3−11.6% expected	melting point 249 ± 2 °C
1	2	500 g	fail	clear	not clear[b]	12.5	fail
2	2	500 g	fail	cloudy[c]	clear	ND	fail
3	6	500 g	pass	clear	clear	11.4−11.5	pass
4	20	2.5 kg	pass	clear	clear	11.3−11.6	pass
5	4	8.5 kg	pass	clear	clear	11.4−11.5	pass

[a] In all cases the final product was a white amorphous powder. [b] Presence of trace sodium bicarbonate in the final product. [c] Presence of trace decanoic acid in the final product.

a mixture of sodium carbonate/sodium bicarbonate was used for the industrial preparation of the sodium salts of long-chain fatty acids (C14 to C22) as intermediates to the calcium salts.[15] In this case, the sodium salt was subsequently reacted with calcium oxide to give the corresponding calcium salt. This method is not suitable for scale-up because it is limited to the ratio and purity of the bicarbonate/carbonate mixture (recycled from another industrial process) which can only generate a calcium salt with a maximum purity of 85%.

A simple solution was to use sodium bicarbonate exclusively. This solved purity concerns and is cheap and readily available. Our process strategy was the treatment of a slight excess of decanoic acid (10%) with sodium bicarbonate in a solvent that could precipitate the corresponding salt from the reaction mixture in high yield and purity. A variety of reaction solvents were investigated including water, acetone, and toluene/water, but ultimately we found the best choice to be ethanol. Thus, the use of 95% ethanol prevented foaming, produced high solubility of the acid in ethanol, and rapidly precipitated the sodium salt from the reaction medium. The reaction temperature was also optimized. The reaction was refluxed for 12 h and then cooled to 45 °C at a rate of 1 °C/min. This rate helped to obtain a precipitate which could be easily filtered; otherwise rapid cooling of the reaction mixture produced a heavy, waxy solid contaminated with the corresponding acid. This impure solid was very difficult to manipulate or filter from the reaction. These above efforts resulted in the simplified general synthesis illustrated in Scheme 1.

Scheme 1



This procedure served to produce 17 batches of 1−50-g sodium decanoate at yields of 80−85% and ∼99% purity. However, three batches (2 × 1 g, 1 × 20 g) from this route still did not give satisfactory purity, causing concern for the robustness of this process. This was due to contamination of the final product with decanoic acid in excess in the reaction mixture. In order to remove any residual acid, different wash solvents were investigated. Decanoic acid was typically present in 10% excess in order to eliminate any unreacted sodium bicarbonate which would otherwise be difficult to remove during the workup. While 95% ethanol was the best wash solvent, the resulting solid mass was dense and led to a slow filtration rate. Ultimately, we discovered the best overall solvent was the use of *tert*-butyl methyl ether. This allowed the decanoic acid metal salts to be isolated in >90% yield and 99.9% purity. This optimized procedure was successfully repeated at 2 × 100 g and 1 × 300 g scale and then scaled up to 500 g (Table 1). Our acceptance criteria for the final product included specifications such as visual appearance, melting point, purity, solubility, and sodium content. Using the above procedure, 10 × 500 g batches of sodium decanoate were prepared. The first four batches of 500 g did not pass the product specification due to the presence of traces of bicarbonate (Table 1, entry 1) or decanoic acid (Table 1, entry 2). It was hypothesized that batch failure on this scale was due to the rate of cooling of the reaction mixture (1 °C/min). On smaller scale, up to 300 g, this procedure was suitable. Slowing the rate of cooling from 1 °C/min to 5 °C/h did lead to satisfactory results for the larger batches (Table 1, entries 3−5). Thus, this final process modification led to our optimized process to produce sodium decanoate.

Large-Scale Production, 2.5−8.5 kg. This procedure was used for kilogram scale. However, the quantity of ethanol was reduced by 80% from the optimized procedure used on small scale to solve the problem of low throughput. The rate of cooling (5 °C/h) was kept constant, and *tert*-butyl methyl ether was added at the end of the reaction to maintain in solution any excess of decanoic acid and ensure a rapid rate of filtration. Table 1 demonstrates that all batches at 2.5 kg passed the specifications (Table 1, entry 4). Overall, 20 × 2.5 kg batches of sodium decanoate were synthesized by this route in >90% yield and 99.9% purity. For the pilot-plant scale, the synthesis was outsourced, and the manufacture of four batches of 8.5 kg each of high-purity product was undertaken (Table 1, entry 5). Again, all batches passed QC requirements confirming the reproducibility and the robustness of the process.

The sodium decanoate obtained from these batches was a white fluffy solid. For formulation purposes, it is preferable that the final product be prepared as a dense uniform solid. As a result, a simple wet granulation process was developed for densification and enhancement of the flow properties of this material. The fluffy solid (200 g, density = 0.1 g/mL) was suspended in 95% ethanol (1.6 L) and stirred vigorously for

(15) The presence of a basic solution (mixture of sodium bicarbonate/carbonate) is essential for the conversion of the acid via the sodium salt intermediate to its calcium salt see: Dynes, J. W.; Gutowski, G. J.; Lajoie, S. U.S. Patent 5,191,097, 1993; *Chem. Abstr.* **1993**, *119*, 75070.

1 h. A homogeneous nonsticky paste was obtained. The precipitate was filtered and dried to give a dense solid (175 g, 87%, density = 0.35 g/mL).

This procedure was also applied to the preparation of unnatural MCFA metal salts with odd-numbered carbon atom chain lengths (nonanoate and undecanoate). In addition, other metal salts of MCFAs such as the potassium and calcium salts were prepared by this method using potassium bicarbonate and calcium carbonate, respectively.

Conclusion

A simple, practical, one-step general procedure was developed for the preparation of MCFA metal salts. The starting materials are inexpensive, available, and easy to handle.. This approach overcomes many of the limitations previously reported for the preparation of fatty acid salts. The potential utility of this method is exemplified by the production of pilot-scale quantities of high-yield (>90%) and purity (99.9%) sodium decanoate.

Experimental Section

All HPLC chromatograms and mass spectra were recorded on a HP 1100 LC−MS Agilent instrument using a conductivity detector. An analytical Zorbax-SB phenyl column (250 mm × 4.6 mm, 5 μm) with a gradient of 25−99% acetonitrile/water containing 0.1% phosphoric acid over 10 min and a flow of 2 mL/min (temperature 30 °C) was used. The purity of sodium decanoate was assessed by HPLC analysis and ^{1}H and ^{13}C NMR. By HPLC, retention times were the following: decanoate salt, 17 min; sodium cation, 4 min; decanoic acid, 7 min.

Example 1: Preparation of Sodium Decanoate. Decanoic acid (2.5 kg, 14.5 mol) was dissolved in 95% ethanol (10 L) at room temperature. This solution was diluted with ethanol (16 L) and stirred vigorously for 15 min. Sodium bicarbonate (1.1 kg, 13 mol) was added portionwise under nitrogen to the clear solution. The pH of the reaction was 8.5. The resulting cloudy mixture was heated under reflux overnight. At the end of the reaction the pH was 6.5. The clear solution was cooled for 7 h (rate of cooling: 5 °C/h) to 45 °C (±3 °C) under vigorous stirring. A white solid precipitated which was diluted with *tert*-butyl methyl ether (25 L) in order to maintain any excess of decanoic acid in solution and to avoid the formation of a dense, difficult to filter solid. The stirring was continued for an additional 17 h, and the temperature cooled (rate of cooling: 1 °C/h) to 27 °C (±3 °C). The homogeneous white precipitate was filtered and washed with *tert*-butyl methyl ether (2 L), and the wet solid was dried for 15 h. The product was broken up into small pieces using a spatula and kept under high vacuum (60−100 mTorr) at 52 °C (±2 °C) for 17 h. The pure sodium decanoate was isolated as a white solid. Yield of product: 2.3 kg (90%); mp = 248−250 °C; ^{1}H NMR (D_2O);[16] ^{13}C NMR (D_2O);[17] LRMS (ESI): *m*/*z* 171 (acid, MH^+); HPLC: t_R = 6.6 min (purity >99.9%).

The following examples were prepared as described in Example 1.

Example 2: Sodium Dodecanoate. mp = 244−246 °C; ^{1}H NMR (D_2O);[16] ^{13}C NMR (D_2O);[18] LRMS (ESI): *m*/*z* 199 (acid, MH^+); HPLC: t_R = 7.5 min (purity >99.9%).

Example 3: Sodium Hexanoate. mp = 232−234 °C; ^{1}H NMR (D_2O);[19] ^{13}C NMR (D_2O);[20] LRMS (ESI): *m*/*z* 115 (acid, MH^+); HPLC: t_R = 4.0 min (purity >99.9%).

Example 4: Sodium Octanoate. mp = 243−245 °C; ^{1}H NMR (D_2O);[15] ^{13}C NMR (D_2O);[21] LRMS (ESI): *m*/*z* 143 (acid, MH^+); HPLC: t_R = 5.5 min (purity >99.9%).

Example 5: Sodium Nonanoate. mp = 240−244 °C; ^{1}H NMR (CD_3OD);[17] ^{13}C NMR (CD_3OD);[17] HPLC: t_R = 4.0 min (purity >99.5%).

Example 6: Potassium Nonanoate. mp = 280−282 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ: 2.14 (t, J = 7.4 Hz, 2H); 1.53−1.64 (m, 2H); 1.22−1.38 (m, 10H); 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (CD_3OD);[22] HPLC: t_R = 4.0 min (purity >99.5%).

Example 7: Sodium Undecanoate. mp = 246−250 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ: 2.14 (t, J = 7.4 Hz, 2H); 1.53−1.64 (m, 2H); 1.22−1.38 (m, 14H); 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 182.0; 38.2; 31.9; 29.7; 29.6 (2C for unresolved signal); 29.5; 29.3; 26.7; 22.6; 13.3; HPLC: t_R = 4.9 min (purity >99.5%).

Example 8: Calcium Decanoate. This compound was prepared as in Example 1 using calcium carbonate as the base. In this case more water was added to the reaction (80% more than in the reaction with decanoic acid) to solubilize the carbonate, and the resulting mixture was heated under reflux for a few days.

mp = 172−176 °C, ^{1}H NMR (CD_3OD, 400 MHz) δ: 2.18 (t, J = 7.6 Hz, 4H); 1.56−1.68 (m, 4H); 1.24−1.42 (m, 24H); 0.91 (t, J = 7.0 Hz, 6H); ^{13}C NMR (D_2O, 100 MHz) δ: 183.0, 38.0, 32.4, 30.2, 30.1, 30.0, 29.8, 26.9, 23.1, 13.9; LRMS (ESI): *m*/*z* 171 (acid, MH^+); HPLC: t_R = 6.6 min (purity >99.5%).

Acknowledgment

We thank Pierre Laurin, Franco Cesari, and Shaun D. Abbott for their thoughtful reading of the manuscript. We also acknowledge Mona Saleh, Josée Cloutier, Joël Lechasseur, Shane Stigant, Tony Ronan, John Harper, Stephen Leary, and Sue Ackroyd. We thank Lyne Marcil for the skillful preparation of this manuscript.

Supporting Information Available

Literature methods for the preparation of MCFA metal salts, determination of purity and densification of sodium decanoate.This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review November 27, 2008.

OP900038V

(16) Hoshino, T.; Imamura, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 502.
(17) Spectral Database for Organic Compounds; National Institute of Advanced Industrial Science and Technology (AIST), http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng.
(18) Mahieu, N.; Tekely, P.; Canet, D. *J. Phys. Chem.* **1993**, *97*, 2764.
(19) Kato, S.; Kageyama, H.; Takagi, K.; Mizoguchi, K.; Murai, T. *J. Prakt. Chem.* **1990**, *332*, 898.
(20) Kato, S.; Kageyama, H.; Kanda, T.; Murai, T.; Kawamura, T. *Tetrahedron Lett.* **1990**, *31*, 3587.
(21) Canet, D.; Mahieu, N.; Tekely, P. *J. Am. Chem. Soc.* **1992**, *114*, 6190.
(22) DeWeerd, R. J. E. M.; De Haan, J. W.; Van De Ven, L. J. M.; Achten, M.; Buck, H. M. *J. Phys. Chem.* **1982**, *86*, 2523.