



Open Chemistry Journal

Content list available at: www.benthamopen.com/CHEM/

DOI: 10.2174/1874842201704010001



RESEARCH ARTICLE

A Simple, Cost-effective Synthesis of Industrially Important Long Chain Primary Alcohols

Robert Milofsky^{1,*}, James Hurley¹, Scott Heston², Nicole Hasling¹, Elise Naughton³ and Bruce Stevens¹Department of Chemistry, Fort Lewis College, Durango, CO 81301, USA²ACI Technologies, Philadelphia, PA 19113, USA³Department of Chemistry, University of Colorado, Colorado Springs, CO 80918, USA

Received: October 14, 2016

Revised: January 13, 2017

Accepted: January 17, 2017

Abstract: The hydroboration oxidation of high molecular weight α -olefins (C_{18} - C_{30+}) with sodium malonyloxyborohydride (SMB) to generate the corresponding primary alcohols is described. α -Olefins undergo hydroboration upon treatment with sodium borohydride ($NaBH_4$) and malonic acid, methyl malonic acid, dimethyl malonic acid or ethyl malonic acid, and a straightforward oxidation of these alkyl boranes yields the anti-Markovnikov primary alcohols. Following recrystallization in n-hexane, n-octane, n-decane or n-dodecane, the target alcohols were isolated in high purity (>99%). The use of SMB and its derivatives will allow synthesis of larger (C_{18} - C_{30+}) primary alcohols on an industrial scale without the costs and hazards of current methods.

Keywords: Hydroboration, Oxidation, Alkenes, Alcohols, Regioselectivity.

INTRODUCTION

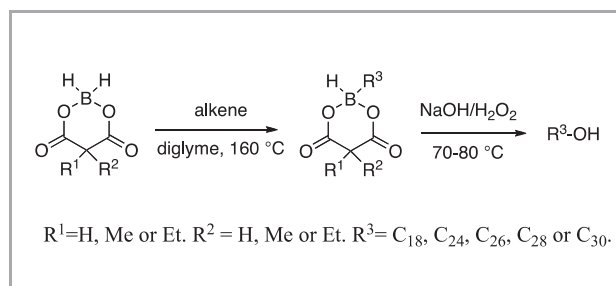
High molecular-weight primary alcohols are commonly used as additives to adhesives, paints, ink toners and personal care products [1 - 5]. These industrially important compounds also serve as precursors to esters and acids [3 - 5]. Recently, C_{24-30} alcohols have been used in pharmaceutical compositions, foodstuffs and dietary supplements and may be effective at reducing cholesterol and consequently the risk of heart disease [6]. The synthesis of these linear aliphatic primary alcohols by modification of Fischer-Tropsch catalysis has been carried out on an industrial scale since the 1920s [7]. Large-scale commercial production since the mid 1970s has been based on the polymerization of ethylene followed by *in situ* oxidation to the alcohol [8]. While effective in giving a narrow molecular weight distribution of the desired alcohols, the use of ethylene gas along with a pyrophoric catalyst (such as a Ziegler-Natta catalyst and an alkylaluminum co-catalyst) presents hazards for industrial scale production. During the past two decades, numerous approaches to the synthesis of higher molecular weight linear primary alcohols have been published. Hydroborations employing borane-THF or borane-DMS [9, 10], chloroborane adducts [11] and transition metal catalyzed hydroboration reagents [12] have generated significant interest in the field. Unfortunately, many of these reactions require reagents that are not commercially available or are not economically viable to use on industrial-scale levels. While Souto *et al.* have developed a flow method for the hydroboration/oxidation of olefins, their method has only been applied to β -pinene, 1-hexene and 1-octene [10]. Clay and Vedejs have shown that pyridine borane activated by iodine in dichloromethane can be used to hydroborate 1-dodecene with high yield at room temperature [13]. However, pyridine borane is both toxic and water-reactive, limiting its use on an industrial scale. Other synthetic routes require expensive catalysts [14] and/or have toxic side products [15]. For example, Dong *et al.* have demonstrated that primary alcohols can be prepared from terminal olefins using a palladium-catalyzed oxidation, acid-catalyzed

* Address correspondence to this author at the Department of Chemistry, Fort Lewis College, Durango, CO 81301, USA; Tel: +970-247-7467; Fax: 011-970-247-7567; E-mail: milofsky_r@fortlewis.edu

hydrolysis and ruthenium catalyzed reduction cycles [16]. In comparison to more classic hydroboration/oxidation schemes, this triple relay catalysis approach requires high catalyst loadings, and while promising, has not yet been demonstrated for the synthesis of high molecular weight primary alcohols.

Huang *et al.* reported on the efficacy of sodium malonyloxyborohydride (SMB) - a mono-functional hydroboration agent - in converting α -olefins (up to C_8) to primary alcohols [9]. SMB was found to be an effective reagent for the one-pot hydroboration-oxidation of alkenes including 1-heptene and 1-octene. While the synthesis must be carried out in an air-free environment (SMB is sensitive to oxygen), Huang *et al.* were able to use relatively mild conditions (temperatures <60 °C) to convert low-molecular weight α -olefins (1-heptene and 1-octene) in high yield and with proper regioselectivity to the corresponding alcohols [9]. Despite the efforts described above, there remains a need for the hydroboration-oxidation of higher molecular weight alkenes including C_{18-30} and higher α -olefins that is efficient, which can be carried out on an industrial scale avoiding the use of hazardous reactants and the production of toxic side products.

In this work, we report, for the first time, the use of sodium borohydride ($NaBH_4$) and several malonic acid derivatives to produce SMB and its corresponding use in the hydroboration of higher molecular weight α -olefins (C_{18-30+}). Following hydroboration, treatment with $NaOH$ and H_2O_2 in the same reaction vessel results in formation of the corresponding primary alcohols. The one-pot synthesis proceeds rapidly and efficiently under mild reaction conditions (Scheme 1). This novel method for the regioselective synthesis of high molecular weight primary alcohols in high yield and purity will lead to reduced costs and improved safety in industrial-scale synthesis. Moreover, this method yields a single primary alcohol, as opposed to current industrial-scale processes based on ethylene polymerization followed by high temperature oxidation that result in a Gaussian distribution of products [17].



Scheme 1. Hydroboration-oxidation with SMB. $R^1 = H, Me \text{ or } Et.$ $R^2 = H, Me \text{ or } Et.$ $R^3 = C_{18}, C_{24}, C_{26}, C_{28} \text{ or } C_{30}.$

With the goal of developing a procedure for the hydroboration-oxidation of high molecular weight α -olefins, a protocol for SMB hydroboration was optimized for C_{18-30+} substrates.

Representative Procedure for the Hydroboration and Oxidation of α -olefins.

A mixture of $NaBH_4$ (2.53 g, 66.1 mmol) and $C_{18}H_{36}$ (17.03 g, 71.0 mmol) were dissolved in diglyme (66 mL) under N_2 and heated to 60 °C. A solution of malonic acid (6.87 g, 66.1 mmol) in diglyme (34 mL) was slowly added to the mixture dropwise by cannula over one hour, and the mixture was then heated to reflux for 1 hour. The reaction was cooled to 60 °C, and a solution of 3 M $NaOH$ (40 mL) was carefully added followed by a solution of 30% H_2O_2 (10 mL). The reaction mixture was heated to 80 °C for 2 h and immediately acidified by the dropwise addition of 3 M HCl until the pH was 3. Upon cooling to room temperature, the solid product was collected by vacuum filtration. Recrystallization from n-hexane gave octadecan-1-ol (14.7 g, 77%) as a flaky white solid; 1H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, $J = 6.4$ Hz, 2 H), 1.54 (bs, 2 H), 1.25 (bs, 30 H), 0.87 (t, $J = 6.9$ Hz, 3 H). The product identity was further confirmed *via* analysis of the hydroboration-oxidation reaction products using High Temperature Simulated Distillation Gas Chromatography (Hi-Temp SimDis GC) [18]. A standard mixture composed of 1-octadecene (Aldrich) and octadecan-1-ol (Aldrich) allowed for peak identification in the chromatograms of the α -olefin starting material (1-octadecene) and the hydroboration oxidation product octadecan-1-ol. By integrating the peak area corresponding to the α -olefin starting material octadec-1-ene- and the peak area corresponding to the octadecan-1-ol produced in the hydroboration-oxidation reaction, we confirmed the 77% conversion of the starting α -olefin to the corresponding primary alcohol.

RESULTS AND DISCUSSION

Under optimized reaction conditions, the hydroboration-oxidation of α -olefins can be accomplished with high efficiency by *in situ* formation of SMB (or a derivative of SMB) in the presence of a high molecular weight α -olefin. The general procedure for the hydroboration-oxidation reaction involves the combination, under nitrogen, of the α -olefin and NaBH_4 in either THF or diglyme. Relatively concentrated solutions (up to 1 M) can be employed, reducing the volume of solvent required for the process. After heating the α -olefin to approximately 60 °C, the malonic acid in THF or diglyme was transferred dropwise by cannula over 60-90 minutes to the α -olefin/ NaBH_4 solution. Slow addition of the malonic acid improved the efficiency of α -olefin-to-alcohol conversion. Upon completion of the transfer, the reaction mixture was equipped with a condenser and heated to 160 °C for 1-20 hours. Next, the solution was allowed to cool to 70-80 °C at which time 3 M NaOH was added in order to hydrolyze the alkylborate salt. Addition of NaOH continued until the pH was basic as indicated by litmus paper. Oxidation to the corresponding alcohol was accomplished by the addition of H_2O_2 (30%) to the warm mixture. The solution was then stirred at 70-80 °C for an additional two hours. The final reaction mixture was acidified by adding 3 M HCl until the pH was acidic as indicated by litmus paper. The solution was then washed with water. GC and NMR analysis were carried out on the crude product, which was then purified by recrystallization in an n-alkane solvent.

In order to optimize the reaction process, the effects of the mole ratio of α -olefin to SMB were explored (Table 1).

Table 1. Effect of the ratio of α -olefin to SMB on isolated yield.

Entry ^a	α -olefin	α -olefin: SMB mole ratio ^b	Yield (%)
1	C ₂₆₋₂₈	1:3	40
2	C ₁₈	1:3	43
3	C ₂₆₋₂₈	1:2	45
4	C ₂₆₋₂₈	2:1	46
5	C ₁₈	1:2	47
6	C ₂₆₋₂₈	3:1	48
7	C ₁₈	2:1	52
8	C ₁₈	3:1	57
9	C ₁₈	1:1	70
10	C ₂₆₋₂₈	1:1	71

^aAll compounds have been characterized by GC and ¹H NMR. ^bAll reactions carried out under N₂ using THF. Cannula additions were carried out dropwise over the course of 45-60 minutes. Following the cannula transfer, the reaction mixture was heated to 160 °C for 5 hours.

Initial attempts focused on utilization of the α olefin as the limiting reagent (Table 1), entries 1, 2, 3 and 5). However, under these conditions, typical yields were only in the 40-50% range. Notably, employing a large excess of α olefin relative to SMB also led to low conversions (Table (1) entries 4, 6, 7, and 8). In practice, a 1:1 mol equivalent of α -olefin:SMB proved to be the most efficient (Table (1), entries 9 and 10) with respect to the yield of the corresponding primary alcohol.

While Huang *et al.* employed longer reaction times (5-36 hours) for the hydroboration of smaller (C₆-C₈) α -olefins [9], we have found that reactions in diglyme proceed to completion within 1.5 hours (Table 2).

Table 2. Effect of reaction time on α -olefin conversion (%).

Entry ^a	α -olefin	Reaction time (h)	α -olefin conversion (%) ^b
1	C ₁₈	19	59
2	C ₁₈	5	70
3	C ₁₈	1	76.5
4	C ₂₆₋₂₈	22	59
5	C ₂₆₋₂₈	5	62
6	C ₂₆₋₂₈	1	67
7	C ₃₀₊	19	60 ^p
8	C ₃₀₊	1.5	67 ^p

^aAll reactions were carried out under N₂ using diglyme as the solvent. The α -olefin:SMB ratio was 1:1 for all entries. Other conditions are identical to Table 1. ^b% conversion is approximate.

As illustrated in Table 2, the reaction proceeded smoothly for all of the α -olefin substrates (C_{18} , C_{26-28} and C_{30+}) tested. It is important to note that the α -olefin starting materials (Chevron Phillips) for entries 4-8 (Table 2) are mixtures of α -olefins, vinylidenes and other hydrocarbons. In fact the C_{30+} reagent only contains 55% n- α -olefin (carbon no. 24-30+) while the C_{26-28} contains upwards of 86% n- α -olefin by weight. Nonetheless, reaction conditions consistently resulted in the conversion of 60-70% of the available α -olefin to the desired primary alcohol. Following separation of the unreacted alkene from the primary alcohols by recrystallization, the product purity ranged from 96-99% primary alcohol. Product purity was determined by Hi-Temp SimDis GC, comparing the retention time of the product to that of a known standard. NMR and melting point data supported the GC data. For example, 1-hexacosanol gave ^1H NMR (400 MHz, CDCl_3) δ 3.63 (t, $J=6.4$ Hz, 2 H), 1.54 (bs, 2 H), 1.25 (bs, 46 H), 0.87 (t, $J=6.9$ Hz, 3 H) and a m.p. of 79-81 °C. The relatively short reaction times demonstrated here compared to earlier work on smaller α -olefins [9] suggests that the work discussed here will lead to a substantial reduction in costs associated with the industrial scale synthesis of high molecular weight primary alcohols.

While the C_{30+} α -olefin feedstock from Chevron Phillips contains a wide range of α -olefins, internal olefins and branched olefins ranging from C_{20} - C_{36} and higher, we found that the SMB-based hydroboration-oxidation reaction proceeded smoothly even with such a complex starting material. This result is indicative of the robustness of the procedure. Products formed by the SMB-based hydroboration oxidation reaction of the C_{30+} α -olefin feedstock were also analyzed using Hi-Temp SimDis GC [18]. A boiling point calibration standard (Agilent) in concert with C_{20} , C_{24} , C_{26} , C_{28} and C_{30} alcohol standards (Aldrich) allowed for peak identification in the chromatograms of the C_{30+} α -olefin starting material and the hydroboration oxidation products. By integrating the peak areas corresponding to the C_{30+} α -olefin starting material and the peak areas corresponding to the corresponding alcohols produced in the hydroboration-oxidation reaction, we estimate that >70% of the available α -olefins were converted to the corresponding primary alcohols. ^1H NMR data support the GC results [17].

As a final step in the optimization of the reaction conditions, the effect of substituted malonic acids on the yield and final product purity of the SMB-based hydroboration-oxidation were explored. 1-octadecene was employed as a model substrate since it is readily available in high purity (Chevron Phillips). Three different malonic acids (dimethylmalonic acid, methylmalonic acid and ethylmalonic acid), all commercially available (Aldrich) were examined. Employing any substituted malonic acid may have led to a small increase in purity of the final product as determined by GC (Table 3) and confirmed by ^1H NMR. Finally, recrystallization (1x) in a variety of hydrocarbon solvents (n-hexane, n-octane, n-decane and n-dodecane) allowed for the separation of the target alcohol from the remaining starting material. Preliminary data suggests a slight improvement in overall yield when the larger n-alkanes are used in the recrystallization procedure, although product purity remains equally high in all of the solvents tested.

Table 3. Efficiency of malonic acid derivatives.

Entry ^a	Malonic acid derivative	α -olefin conversion (%)	ROH purity (%) ^b
1	Malonic acid	76.5	97.1
2	Methylmalonic acid	76.3	99.9
3	Dimethylmalonic acid	75.5	99.9
4	Ethylmalonic acid	83.8	99.9

^aAll conditions are identical to Table 2. ^bFollowing recrystallization in n-hexane, n-heptane, n-octane, n-decane or n-dodecane.

CONCLUSION

In summary, we have reported a relatively inexpensive, safe and effective means of hydroborating high molecular weight α -olefins. Oxidation with H_2O_2 produced the corresponding primary alcohols in high yield and purity. The efficacy of SMB and derivatives of SMB with respect to the hydroboration of high molecular weight α -olefins has been demonstrated. Easy purification and rapid characterization by Hi-Temp SimDis GC will likely make the method reported in this work valuable in the large-scale synthesis of high molecular weight primary alcohols.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by S&S Chemical and Fort Lewis College.

REFERENCES

- [1] Klinkhammer, M.E.; Wortley, R.B.; Strash, T.A. Cleaning composition having high self-adhesion and providing residual benefits. USA Patent 20100093586 A1, 2010.
- [2] Tanimoto, S.; Kato, M.; Fujiwara, N. Production of aqueous resin emulsion. Japanese Patent 2000128909, 2000.
- [3] Baker, T.J.; Woods, J.H.; Zerr, J.R. Additive composition for water-based inks. USA Patent RE34,792, 1994.
- [4] Gunstone, F.D. Chemical reactions of fatty acids with special reference to the carboxyl group. *Eur. J. Lipid Sci. Technol.*, **2001**, *103*, 307-314. [[http://dx.doi.org/10.1002/1438-9312\(200105\)103:5<307::AID-EJLT307>3.0.CO;2-D](http://dx.doi.org/10.1002/1438-9312(200105)103:5<307::AID-EJLT307>3.0.CO;2-D)]
- [5] Vanbesien, D.W.; Turek, C.M.; Bamsey, N.M.; Tracey, C.L.; Chopra, N.; Belelie, J.L.; Iftime, G. Phase change inks comprising linear primary alcohols. USA Patent 20140118436 A1, 2014.
- [6] Perez, P.P. High molecular weight primary aliphatic alcohols obtained from beeswax and pharmaceutical use thereof. USA Patent 6,225,354, 2001.
- [7] Henrici-Olive, G.; Olive, S. The Fisher-Tropsch synthesis: Molecular weight distribution of primary products and reaction mechanism. *Angew. Chem.*, **1976**, *15*, 136-141. [<http://dx.doi.org/10.1002/anie.197601361>]
- [8] Britovsek, G.J.P.; Cohen, S.A.; Gibson, V.C. Chain growth reaction process. USA Patent 7,767,771, 2010.
- [9] Huang, S.W.; Peng, W.L.; Shan, Z.X.; Zhao, D.J. A new facile approach to highly selective hydroboration of alkenes with sodium malonyloxyborohydride. *New J. Chem.*, **2001**, *6*, 869-871. [<http://dx.doi.org/10.1039/b100228g>]
- [10] Souto, J.A.; Stockman, R.A.; Ley, S.V. Development of a flow method for the hydroboration/oxidation of olefins. *Org. Biomol. Chem.*, **2015**, *13*(13), 3871-3877. [<http://dx.doi.org/10.1039/C5OB00170F>] [PMID: 25714697]
- [11] Kanth, J.V.; Brown, H.C. Hydroboration. 97. Synthesis of new exceptional chloroborane Lewis base adducts for hydroboration. Dioxanemonochloroborane as a superior reagent for the selective hydroboration of terminal alkenes. *J. Org. Chem.*, **2001**, *66*(16), 5359-5365. [<http://dx.doi.org/10.1021/jo015527o>] [PMID: 11485456]
- [12] a. Evans, D.A.; Fu, G.C. The rhodium-catalyzed hydroboration of olefins: A mechanistic investigation. *J. Org. Chem.*, **1990**, *55*, 2280-2282. [<http://dx.doi.org/10.1021/jo00295a007>]
b. Evans, D.A.; Muci, A.R.; Stummer, R. Samarium (III)-catalyzed hydroboration of olefins with catecholborane: A general approach to the synthesis of boronate esters. *J. Org. Chem.*, **1993**, *58*, 5307-5309. [<http://dx.doi.org/10.1021/jo00072a007>]
- [13] Clay, J.M.; Vedejs, E. Hydroboration with pyridine borane at room temperature. *J. Am. Chem. Soc.*, **2005**, *127*(16), 5766-5767. [<http://dx.doi.org/10.1021/ja043743j>] [PMID: 15839656]
- [14] a. Bijpost, E.A.; Duchateau, R.; Teuben, J.H. Early transition metal-catalyzed hydroboration of alkenes. *J. Mol. Catal.*, **1995**, *95*, 121-128. [[http://dx.doi.org/10.1016/1381-1169\(94\)00013-1](http://dx.doi.org/10.1016/1381-1169(94)00013-1)]
b. Fu, G.C. *Transition Metal-Catalyzed Hydroboration of Olefins in Transition Metals for Organic Synthesis: Building Blocks for Fine Chemicals*, 2nd ed; Wiley-VCH: Germany, **2004**.
- [15] Alexandre, F.R.; Pantaleone, D.P.; Taylor, P.P.; Fotheringham, I.G.; Ager, D.J.; Turner, N.J. Amine-boranes: Effective reducing agents for the de-racemisation of dl-amino acids using l-amino acid oxidase from *Proteus myxofaciens*. *Tetrahedron Lett.*, **2002**, *43*, 707-710. [[http://dx.doi.org/10.1016/S0040-4039\(01\)02233-X](http://dx.doi.org/10.1016/S0040-4039(01)02233-X)]
- [16] Dong, G.; Teo, P.; Wickens, Z.K.; Grubbs, R.H. Primary alcohols from terminal olefins: Formal anti-Markovnikov hydration via triple relay catalysis. *Science*, **2011**, *333*(6049), 1609-1612. [<http://dx.doi.org/10.1126/science.1208685>] [PMID: 21921194]
- [17] Hasling, N.; Naughton, E.; Hurley, J.; Milofsky, R.; Stevens, S. Synthesis of high molecular weight primary alcohols. USA Patent Appl. 20110160495 A1, 2011.
- [18] Vickers, A.K. Higher-Temperature Simulated Distillation with DB-HT Sim Dis Columns. Available from: <http://www.agilent.com/cs/library/applications/5988-7929EN.pdf> [accessed December 8, 2016].