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Novel Synthesis of Long-Chain Primary Alkyl Compounds

Thomas Gibson* and Linda Tulich

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45247

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A method has been developed for the efficient laboratory-scale synthesis of long-chain compounds involving the metathesis of α-olefins to long-chain internal olefins, followed by hydrozirconation. The latter process gives the terminally substituted zirconium alkyl exclusively, which can be converted to a wide variety of functional groups. This paper deals exclusively with the formation of long-chain primary iodides.

A multitude of methods has been developed over the past 60 or 70 years for the synthesis of straight-chain compounds with chain lengths in excess of 20 carbon atoms (for a recent review, cf. ref 1). Almost all of these syntheses have been based on a strategy which involves chain extension of readily available alkyl derivatives by anywhere from 1 to 12 carbons by reaction with a bifunctional molecule (eq 1). This strategy suffers from the

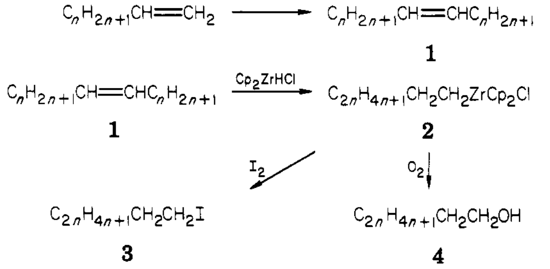
$$RX + Y(CH_2)_MZ \rightarrow R(CH_2)_MZ \qquad (1)$$

necessity for extensive repetition in order to reach chain lengths longer than 30, resulting in low yields because of the manipulations involved. This can be avoided by the use of difunctional compounds with longer chain lengths ($M \geq 6$), but this limits the utility of the method because of the wide spacing between the homologues obtained.

We have developed an alternative strategy which utilizes a single, readily available organic starting material and which provides direct access to all of the even numbered chain alkyl compounds up to chain lengths of 42 carbon atoms in two simple steps. Overall yields are good, the purity of the final products is very high, and a variety of terminal functional groups is accessible without extensive manipulation.

Our strategy involves the two steps shown in Scheme I, in which the basic chain is formed via olefin metathesis,[2] and functionality is moved to the end of the chain by hydrozirconation.[3-5] Metathesis of α-olefins, readily available commercially in high purity in chain lengths up to 22 carbons, provides the long chain internal olefins **1** in good yield and high purity. Conversion of **1** to the terminally substituted zirconium compounds **2** is accomplished by hydrozirconation followed by reaction with a suitable electrophile. For example, primary alkyl iodides **3** (X = I) can be obtained in high purity in 70–80% yields from the internal olefins, or the alcohols **4** can be obtained by reaction with oxygen.[4,5]

Scheme I



The olefin metathesis reaction has been thoroughly reviewed.[2] Many catalysts, both homogeneous and heterogeneous, have been employed, but few appear to work efficiently with α-olefins. After some experimentation, we have developed a convenient catalyst based on a modification of the $WCl_6/SnMe_4$ system previously employed for the metathesis of unsaturated esters.[6] In our hands, use of the $WCl_6/SnMe_4$ combination for the metathesis of terminal olefins resulted in contamination of product with substantial amounts of the olefin with one less carbon atom, e.g., eq 2. Examination of recovered α-olefin showed

$$C_8H_{17}CH{=}CH_2 \xrightarrow[Me_4Sn]{WCl_6} C_8H_{17}CH{=}CHC_8H_{17} + C_8H_{17}CH{=}CHC_7H_{15} \qquad (2)$$

the presence of the isomer resulting from movement of the double bond to the 2-position, suggesting that the contaminant was the result of acid-catalyzed isomerization of α-olefin followed by cross metathesis. Mass spectral analysis of crude product confirmed this conjecture. Previous work had shown that metathesis of olefins in benzene with WCl_6 as catalyst resulted in solvent alkylation but that the acidity of the catalyst could be moderated and alkylation eliminated by the addition of mild Lewis bases such as esters[7] and phosphines,[8] which did not interfere with the metathesis. In our system, we found ethyl acetate to be a sufficient modifier which reduced the formation of side product to the order of 1–2%. Reaction of an α-olefin with the $WCl_6/SnMe_4$/EtOAc combination without solvent at 80 °C occurs rapidly to give about 50% conversion in 30 min. After 16–18 h, conversion is about 80%, and the catalyst is completely inactive. By addition of fresh batches of catalyst in 30–60-min intervals, approximately 80% conversion can be attained in 1.5–3 h. The crude product, after removal of unreacted α-olefin by distillation, consists of a mixture of cis and trans isomers of the internal olefin, without contamination by other compounds except for small amounts of the next lower homologue. Table I summarizes the yields of pure, recrystallized, trans isomer for a number of chain lengths, and a representative example of the reaction and workup

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Table I

α-olefin	amt, mol	product	yield,[a] %	purity,[b] %	mp, °C	mol wt[c]
1-tridecene	3.0	12-tetracosene	50	99.5	36	336 ± 1
1-tetradecene	3.0	13-hexacosene	31	99.8	41	364 ± 1
1-pentadecene	2.3	14-octacosene	36	97.5	49	392 ± 1
1-hexadecene	2.6	15-triacontene	50	98.8	53	420 ± 1
1-octadecene	0.7	17-tetratriacontene	49	96	61	476 ± 1
1-docosene	0.66	21-dotetracontene	58	~90	74	589 ± 1

[a] Yield of trans olefin, recrystallized to constant melting point. [b] Determined by gas chromatographic analysis: 5 ft × 1/4 in. column, SE-30; 166–300 °C (10 °C/min). [c] Field-ionization mass spectrometry, M^+.

Table II[a]

olefin	amt, mol	time, h	olefin/iodide ratio[b]	product	yield,[c] %	mp, °C	ref[d] mp, °C
12-tetracosene	0.78	64	8:92	1-iodotetracosane	75	53–54	54
13-hexacosene	0.14	89	15:85	1-iodohexacosane	80	58–60	59
14-octacosene	0.13	168	46:54	1-iodooctacosane	30	64–65	63
15-triacontene	0.66	48	12:88	1-iodotriacontane	74	65–66	67
17-tetratriacontene	0.067	168	33:67	1-iodotetratriacontane	49	73–74	72
21-dotetracontene	0.05	144		1-iododotetracontane	68	82–83	

[a] Reactions at 40 °C in THF with 2.0 equiv of Cp_2ZrCl_2 and 1.0 equiv of Vitride (2.0 equiv of H)/mol of olefin, followed by 2.0 equiv of I_2. [b] Determined by integration of the ^1H NMR spectrum, only primary iodide detectable. [c] Recrystallized product, free of olefin. [d] Reference 14. The alkyl iodides from chains of 22–30 carbons are reported to exist in two forms, the stable β-modification and metastable α-modifications, melting 3–6 °C lower. The melting points reported here are for the β-modifications.

is given in the Experimental Section. Oxidative cleavage[9] of the olefins followed by esterification of the resultant acid gave in each case a single ester with a chain length corresponding to the position of the double bond in the center of the chain. Gas chromatographic analysis of the esters failed to detect the presence of any homologues.

Numerous methods have been developed for the metal hydride mediated movement of double bonds to terminal positions. Pyrolysis of tri-*sec*-alkylboranes in refluxing diglyme causes isomerization to the primary boranes, which can be converted to the alcohols or olefins.[10,11] However, substantial secondary compounds remain to contaminate the product, and purification can be difficult with long chains.[5,11] Sato has recently developed an aluminum hydride mediated process, catalyzed by titanium or zirconium compounds,[12] but we were unsuccessful in applying this method to the olefins in Table I. A more promising approach appeared to be the stoichiometric hydrozirconation/isomerization of olefins recently developed by Wailes[3] and Schwartz[4] which utilizes the dicyclopentadienylzirconium hydride (**6**, eq 3). Schwartz carried

$$\underset{\mathbf{5}}{Cp_2ZrCl_2} + {}^1/_4LiAlH_4 \rightarrow \underset{\mathbf{6}}{Cp_2ZrHCl} + LiCl + AlCl_3 \quad (3)$$

out the reaction of various olefins with **6** on a small scale, in which the reagent was isolated from the reaction of the dichloride **5** with lithium aluminum hydride or Vitride $[NaAlH_2(OCH_2CH_2OCH_3)_2]$. The reagent is insoluble in most solvents and can be washed free of salts under an inert atmosphere but is difficult to handle on a large scale. In our hands, reaction of this compound with *trans*-4-octene in benzene or THF (followed by treatment with *N*-bromosuccinimide) gave variable yields of 1-bromooctane in the range of 30–60%. Attempts to carry out the reaction by addition of olefin to the reagent in situ were unsuccessful when lithium aluminum hydride was used for formation of **6**. However, alkoxy hydrides such as Vitride, lithium trimethoxyaluminum hydride, and lithium tri-*tert*-butoxyaluminum hydride were effective in situ. Good yields of terminal iodides were obtained when the appropriate amount of an alkoxyaluminum hydride is added to a mixture of olefin and **5** in THF at room temperature, followed by heating at 40 °C for variable lengths of time and, finally, addition of iodine. Use of 1 equiv of **5**/mol of olefin usually gives about 30–50% yields of iodides, while 70–80% yields can be obtained with 1.5–2 equiv. Attempts to carry out this process at temperatures above about 50 °C result in generation of deep purple solutions and reduced yields, apparently because of decomposition of the reagent or an intermediate. In most instances, the formation of 5–15% of saturated hydrocarbon was noted. This could arise from reduction of olefin by the zirconium hydride,[3] abstraction of hydrogen from solvents by the alkylzirconium, or hydrolysis by moisture in the argon. The latter possibility is excluded by the observation that the amount of hydrocarbon formed is not dependent on reaction time. We are now in the process of investigating the effect of solvent on this side reaction. Schwartz has shown that the alkylzirconium intermediate undergoes rapid metal exchange with aluminum chloride to give aluminum alkyls, which do not migrate readily along a chain.[13] Apparently the aluminum chloride generated during the formation of **6** with $LiAlH_4$ interferes in the subsequent hydrozirconation, while the oxygenated aluminum chlorides formed from Vitride etc. do not. Results for the preparative-scale formation of terminal iodides from the long-chain olefins of Table I are given in Table II, and complete experimental details can be found in the Experimental Section. It should be noted that, while the relatively expensive reagent Cp_2ZrCl_2 is used in this reaction, its recovery from the reaction product is relatively simple.

In summary, we have applied two modern organometallic synthetic methods, which are very convenient to use on a laboratory scale, to the simple preparation of long-chain compounds. While in this paper we have dis-

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cussed only the preparation of the iodides, the method could, through suitable modification in the last step, be applied to the formation of alcohols, bromides, chlorides, and odd chain length aldehydes or carboxylic acids.[13] The iodides are useful intermediates and can be used to alkylate a wide variety of substrates, e.g., malonate, to provide ready access to long-chain carboxylic acids and related compounds.

Experimental Section[15]

General Procedure for Metathesis of α-Olefins. Olefin (3 mol), dried by distillation from CaH_2, is placed in a flame-dried, three-necked flask of at least 2-L capacity, and the flask is thoroughly flushed with argon and heated to 80 °C. Through an open side arm, with a strong flow of argon to prevent contamination with oxygen, is added 15 mmol of WCl_6 (preweighed under argon into sealed vials), 60 mmol of ethyl acetate (dried by percolation through silica gel), and 30 mmol of tetramethyltin. After a few minutes, vigorous evolution of ethylene begins, and the temperature of the liquid rises somewhat. At this stage foam can be a problem, and good stirring is required, as well as a condenser. After 0.5–1.0 h the foaming subsides, and analysis usually indicated about 50% conversion. If the reaction is allowed to continue, conversions of 70–80% are usually obtained after overnight heating. Alternatively, fresh batches of catalyst can be added at 1-h intervals, in which case similar conversions are obtained after 3 h. The reaction can be monitored by quenching an aliquot with concentrated NH_4OH, extraction with hexane, and GC analysis (5 ft × $^1/_4$ in. SE-30; 150–300 °C, 10 °C/min). After cooling to room temperature, the reaction mixture is quenched with 200 mL of concentrated NH_4OH, extracted with hexane, and dried over $MgSO_4$. After removal of untreated α-olefin by vacuum distillation, the crystalline residue is crystallized from acetone. Two crystallizations give essentially pure trans olefin in 30–50% yields, usually contaminated with ca. 1% of the next lower homologue. Further crystallizations of the mother liquors give varying amounts of cis/trans mixtures, usually of sufficient purity to be used in the hydrozirconation step. Alternatively, the entire crude reaction product, after removal of unreacted α-olefin, can be used in the hydrozirconation reaction.

Hydrozirconation/Iodination, General Procedure. Zirconocene dichloride (386 g, 1.32 mol) is dissolved in 3 L of dry THF in a flame-dried, three-necked, 5-L Morton flask fitted with a paddle stirrer, a rubber septum, and an immersion thermometer controlling a Thermo-Watch. Heat is provided by a heating mantle. After the flask is flushed with argon, Vitride (0.66 mol, 70% in toluene) is added at a moderate rate directly from the bottle via a flexible tube with needles at each end, pressure being supplied from an argon tank reduced to about 5 psig. After about 1–2 h at room temperature, olefin (0.66 mol) is added via flexible rubber tubing, and the mixture heated to 40 °C (alternatively, the olefin can be introduced with the Cp_2ZrCl_2). The reaction is monitored at periodic intervals by withdrawal of a small sample, quenching with iodine, and filtration through a short column of silica gel. The extent of conversion to iodide can be determined directly by ^{1}HMR analysis of the crude product. When no more change occurs (1–6 days), iodine (333.5 g, 1.32 mol) is added after the reaction mixture is cooled in an ice bath. After the mixture is stirred 4 h at room temperature, the THF is distilled and replaced with hexane, which precipitates the zirconium-containing byproducts. Filtration, followed by percolation through 500 g of silica gel in a sintered-glass filter, gives the crude iodide contaminated with varying amounts of olefin. Crystallization from acetone (up to C_{30}) or hexane (C_{34} and C_{42}) gave the results in Table II. Spectral data (^{1}H NMR, ^{13}C NMR, and mass spectra) are consistent with the presence of only primary iodide and, in some instances, small amounts of the saturated hydrocarbon. The zirconocene dichloride can be recovered by treatment of the insoluble material with charcoal in chloroform, filtration, and treatment with anhydrous HCl to regenerate the dichloride.

Registry No. 5, 1291-32-3; **6**, 37342-97-5; 1-tridecene, 2437-56-1; 1-tetradecene, 1120-36-1; 1-pentadecene, 13360-61-7; 1-hexadecene, 629-73-2; 1-octadecene, 112-88-9; 1-docosene, 1599-67-3; (*E*)-12-tetracosene, 76665-54-8; (*E*)-13-hexacosene, 76665-55-9; (*E*)-14-octacosene, 76665-56-0; (*E*)-15-triacontene, 76665-57-1; (*E*)-17-tetratriacontene, 76665-58-2; (*E*)-21-dotetracontene, 76665-59-3; 1-iodotetracosane, 62127-55-3; 1-iodohexacosane, 52644-81-2; 1-iodooctacosane, 62154-80-7; 1-iodotriacontane, 62154-82-9; 1-iodotetratriacontane, 62154-85-2; 1-iodotetracontane, 76665-60-6; (*E*)-4-octene, 14850-23-8; 1-bromooctane, 111-83-1.

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[15] Melting points were determined on a microscope equipped with a hot stage and are corrected. Infrared spectra were determined with a Perkin-Elmer Model 257 spectrometer, ^{1}H NMR spectra were obtained on a Varian Model HA-100 spectrometer, ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer, and mass spectra were obtained on a Varian-MAT SM-1 spectrometer. α-Olefins were obtained from Aldrich or Humphreys, zirconocene dichloride from Arapahoe, tetramethytin from Aldrich, and tungsten hexachloride from Alfa-Ventron. Vitride (70% in toluene) was obtained from Hexcel Chemical Specialties.

Asymmetric Addition of Thioglycolic Acid to Nitro Olefins Catalyzed by Cinchona Alkaloids

Norio Kobayashi* and Kiyoko Iwai

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

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Thioglycolic acid (**1**) has been shown to undergo asymmetric addition to (2-nitroethenyl)benzene (**2**) in the presence of a cinchona alkaloid as a catalyst. By selection of reaction conditions, enantiomeric yields of up to 58% were obtained. Evidence is presented which supports the idea that the interaction between the carboxyl group of **1** and the active site of the catalyst (quinuclidine nitrogen) exerts a favorable effect on the extent of asymmetric induction. When methyl 7-nitrohept-6-enoate (**10**) was used as an acceptor, (*S*)-**13** was obtained in 37% ee with quinine catalyst. Also studied was the asymmetric addition of **1** to 1-methoxy-2-(2-nitroethenyl)benzene (**8**) and (2-nitro-1-propenyl)benzene (**9**).

The catalytic asymmetric addition of thiols to α,β-unsaturated compounds is a reaction that possesses a potential applicability to the synthesis of physiologically active substances having a chiral center at the α- or β-

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