SYNTHESIS OF DIDEUTEROMETHYLENE HYDROCARBONS BY COPPER CATALYZED REACTION OF GRIGNARD REAGENTS

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ABSTRACT

The dilithium tetrachlorocuprate catalyzed reaction of Grignard reagents with long chain alkyl p-toluenesulfonates provides specifically labelled dideuteromethylene hydrocarbons. The tosylate esters are readily obtained by $LiAlD_4$ treatment of fatty acid methyl esters followed by tosylation in pyridine.

Keywords: Hydrocarbons, deuteromethylene hydrocarbons, organo-copper reagents Grignard reagents, dilithium tetrachlorocuprate

INTRODUCTION

Detailed analysis of the vibrational spectra of hydrocarbon chain systems in the solid state can provide information about chain conformation and organizational changes that occur during phase transitions[1]. Such information is of value in lipid membrane investigations[2]. Infrared studies on hydrocarbons having a single specific methylene group labelled with deuterium are particularly informative. In these cases it is possible to measure infrared bands associated with vibrational modes that are localized at the deuterium site and are consequently sensitive to conformation at this site. For accurate measurement of band positions it is essential to use hydrocarbons of high chemical homogeneity which also have high deuterium incorporation within the methylene group. The later requirement is a consequence of strongly interfering bands associated with the monodeuteromethylene system[3].

0362-4803/83/010135-07$01.00

Received August 10, 1982

Syntheses of lipid derivatives containing a dideuteromethylene group have proceeded via the corresponding ketone by initial reduction to monodeuterocarbinol with $NaBD_4$ followed by conversion to sulfonate ester and subsequent $LiAlD_4$ reduction to the hydrocarbon. Such a procedure was followed by Tulloch[4 5] in the preparation of several dideuterated octadecanoic acids. Other methods that also start with ketones include Raney nickel reduction of dithioketals as well as reduction of p-toluenesulfonylhydrazones[6]. These procedures are best suited to circumstances where the necessary ketonic material is already available. We have observed that ketone reductions frequently give hydrocarbons containing olefinic and other impurities and also yield products having unsatisfactory deuterium content.

This communication describes a convenient method for the synthesis of dideuteromethylene hydrocarbons that proceeds from the readily available fatty acids and which yields products having high chemical and isotopic purity.

RESULTS AND DISCUSSION

The coupling of Grignard reagents with alkyl halides[7] and toluene sulfonates[8] is very effectively catalyzed by dilithium tetrachlorocuprate. Since dideuterated toluenesulfonates of the desired chain length may easily be prepared from esters of fatty acids this method was employed in the hydrocarbon synthesis (Scheme 1). A similar procedure employing lithium dimethyl cuprate has been reported for the preparation of trans-4-octene-2,2-$^2H_2$[9].

Scheme 1

$$R\ COOCH_3 + LiAlD_4 \longrightarrow R\ CD_2\ OH \xrightarrow[\text{Pyridine}]{\text{Ts Cl}}$$

$$R\ CD_2\ O\ Ts \xrightarrow[Li_2\ Cu\ Cl_4]{R'\ MgX} R\ CD_2\ R'$$

Treatment of methyl ester with lithium aluminum deuteride was carried out in ether except in the case of methyl eicosanoate where THF was added to increase solubility. Tosylation of the resulting alcohol was conducted in pyridine[10] followed by workup with aqueous acid. Toluenesulfonate esters were stored at -20° before use to minimize potential decomposition. The reaction of the tosylates with the Grignard reagent was accomplished in THF or THF-Et_2O containing *ca.* 1% Li_2CuCl_4 at room temperature. Results are summarized in Table 1.

Table 1. Deuterated Hydrocarbons Prepared by Copper Catalyzed Coupling of Grignard Reagents

Product	Deuteromethylene Position	R in R-CD_2 OTs	R' in R' MgX	Yield(%)	Residual CHD (%)
Heptane	2	n-C_5H_{11}-	CH_3[a]-	15[c]	1.7
Tridecane	3	n-$C_{10}H_{21}$-	C_2H_5[b]-	67	3.0
Heneicosane	2	n-$C_{19}H_{39}$-	CH_3[a]-	85	3.2
Heneicosane	4	n-$C_{17}H_{35}$-	n-C_3H_7[b]-	74	3.2
Heneicosane	6	n-$C_{15}H_{31}$-	n-C_5H_{11}[b]-	50	3.2
Heneicosane	11	n-$C_{10}H_{21}$-	n-$C_{10}H_{21}$[b]-	83[d]	3.4

a) Grignard reagent prepared in Et_2O. Equal vol. of THF added with tosylate.
b) Grignard reagent prepared in THF.
c) Yield reduced by azeotrope formation of heptane/THF.
d) Containing *ca.* 10% nondeuterated eicosane.

Problems with impurity formation occurred in only two cases: In the preparation of 3,3-dideuterotridecane a small amount of 1-bromoundecane was formed. This product arose by displacement of tosylate by bromide present in the reaction mixture, and its persistance under conditions of the reaction is puzzling since alkyl bromides are reactive toward the organo-copper reagent. The bromide was removed by treatment with NH_3/MeOH followed by passage of a hexane solution of the mixture through activated alumina. A less tractable impurity arose by symmetrical coupling of the Grignard reagent during preparation of 11,11-dideuteroheneicosane with the concomitant formation of eicosane, the content of which could not be reduced below a few percent by repeated crystallization. Tamura and Kochi[7] state that homo-coupling is negligible under their conditions (0° or lower); however, lower temperature of reaction was not beneficial in our experience. Adjustment of reactant molar ratios also did not significantly affect eicosane formation. Even when a less than equivalent amount of Grignard reagent was employed, about the same proportion of C-20 product was formed. Other workers[11] have utilized inverse addition of the Grignard reagent to allylic acetates. Upon inverse addition of decylmagnesium bromide to 1,1-dideuteroundecyl p-toluenesulfonate at 0° the result was the same as that obtained under the more usual conditions. However, formation of homodimer is only a problem in those cases where respective molecular weights of products are close, and in our other synthetic examples such impurities were not noticed at all.

EXPERIMENTAL

The sequence leading to 4,4-dideuteroheneicosane is shown as typical.

1-Octadecanol-1,1-$^2H_2$ -- Methyl stearate of commercial quality was crystallized from MeOH to a purity of 99.5 + % (GLC, 3% OV-1). In 100 ml Et_2O was suspended 0.62 g (15 mmole) $LiAlD_4$ under an argon atmosphere. Methyl stearate, 4.47 g (15 mmole), was added in several portions with stirring as fast as foaming would permit. After 2 hr stirring at room temperature the mixture was treated in succession with 0.5 ml H_2O, 0.5 ml 15% NaOH and 1.5 ml H_2O to give a granular suspension of salts which was filtered off. Evaporation under reduced pressure gave 4.05 g of alcohol showing no C=O band in the infrared. This material was utilized without further purification.

1-Octadecyl-1,1-$^2H_2$ p-toluenesulfonate-- The crude carbinol from reduction of methyl stearate (ca. 15 mmole) was added to 25 ml of pyridine (dried over 4A° molecular sieves) and the mixture was cooled to 15° whereby some separation of solid occurred. To this mixture was added with stirring and cooling a solution of 3.80 g (20 mmole) of p-toluenesulfonyl chloride in 25 ml pyridine at a rate such that the temperature remained below 15°. The reaction was allowed to warm to ca. 20° over about 3.5 hr at which time it was again cooled and 10 ml of H_2O was added. After 15 min 250 ml of 1N HCl was added, and the resulting suspension was extracted with three 100 ml portions of Et_2O which were then combined and washed with two 150 ml portions of 1N HCl. After drying over $MgSO_4$ and evaporation of the ether under reduced pressure the product was taken up in 25 ml of benzene and passed through a 20 mm x 25 mm dia column of silica gel with the aid of a further 25 ml of benzene.

Evaporation of solvent then yielded 5.01 g of a colorless oil which solidified on standing. The infrared spectrum indicated the absence of hydroxyl function and showed characteristic bands at 1135 and 1365 cm^{-1} for the toluenesulfonyl group[12]. The product was not purified further and was stored at -20° before use.

Heneicosane-4,4-$^2H_2$-- A solution of propyl magnesium bromide (ca. 20 mmole) was prepared in 50 ml of THF in the usual way. To this, a solution of 0.2 mmole of freshly prepared Li_2CuCl_4[7] in 15 ml THF, was added, and the mixture was stirred 15 min at room temperature. Solid octadecyl-1,1-$^2H_2$ tosylate was added in one portion, and stirring was continued 16 hr at ambient temperature. The reaction mixture was then diluted with 100 ml of 1N HCl and extracted with three 100 ml portions of Et_2O. The combined organic phases were washed with two 100 ml portions of 1N HCl and dried over $MgSO_4$. Evaporation of solvent gave a solid which was taken up in 25 ml of hexane and passed through a 20 mm x 40 mm dia column of Al_2O_3. Upon removal of hexane 2.71 g of product was obtained which yielded 2.20 g (74%) of crystals, m.p. 40-41°, from 200 ml of 95% EtOH. GLC analysis (3% OV-1 @ 175°) showed a single major component of 99 + % purity. The infrared spectrum showed complete absence of toluenesulfonate and hydroxyl bands, and examination of the PMR spectrum revealed only signals associated with unsubstituted hydrocarbon. Mass spectral analysis showed a monodeuteromethylene content of 3.2%.

ACKNOWLEDGMENT

We thank Dr. Arnold Falick of the University of California, Berkeley for obtaining mass spectral information.

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