Improved Method of Preparation of α-Substituted Fatty Acids[1]

WARNER M. LINFIELD, ROBERT A. BARAUSKAS and **FRANK D. SMITH**, Eastern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, Philadelphia, PA 19118

ABSTRACT

The previously published methods for the syntheses of α-substituted fatty acids, as developed by Pfeffer et al. and Konen et al., were improved by using the dimethylamides instead of the free carboxylic acids and changing the solvent system to eliminate hexamethylphosphoramide, a known carcinogen. The improved method cuts the use of metalating agent in half, drastically reduces refrigeration requirements, and permits the preparation of larger batches. A Grignard reagent can be used in place of *n*-butyllithium as metalating agent but gives substantially poorer yields. The syntheses of α-hydroxylauric acid and α-butyllauric acid are described.

INTRODUCTION

Previous investigators have shown that various α-substituted carboxylic acids can be made through α-anion reactions. Creger showed that metalation with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by reaction with alkyl halides and subsequent acidification provided a general method (1) according to the following scheme:

$$RCH_2COOH \xrightarrow{2LDA} \overset{Li}{(RCHCOOLi)} \xrightarrow[2)\ H+]{1)\ R'I} RCHR'COOH$$

Pfeffer et al. (2,3) found that the use of THF with cosolvent hexamethylphosphoramide (4) (HMPA) increased yields of mono α-substituted acids. α-Methylol derivatives of long-chain acids were prepared by reaction of α-methalated acids with formaldehyde. The intermediate methylol derivative after dehydration afforded substituted acrylic acids (5) according to the following scheme:

$$\overset{Li}{RCHCOOLi} + HCHO \xrightarrow{[H^+]} RCH(CH_2OH)COOH \xrightarrow[H_3PO_4]{heat} RC\overset{CH_2}{\overset{\|}{C}}OOH$$

α-Hydroxy and α-hydroperoxy acids were made by oxidation of α-lithiated long-chain acids (6).

α-Metalation of amides by use of *n*-butyllithium has been studied by several investigators. Various short-chain dimethylamides were reacted with lithium diethylamide in benzene-HMPA and the resulting α-anions were alkylated (7). Some short-chain aliphatic, arylalkanoic and alicyclic amides were reacted with lithium dialkylamides and the α-metalated amides were oxidized (8,9). Rathke and Lindert (10) prepared the α-carbanions of various *tert*-butyl and ethyl esters with one equivalent of lithium isopropylcyclohexylamide and, after reaction with alkyl halides, obtained esters of the α-alkylated acids.

The synthetic routes developed by Pfeffer et al. (2,3,5) and Konen and coworkers (6) are quite elegant and give generally high yields. However, extremely low reaction temperatures had to be maintained, and because of the exothermic nature of each reaction step, scale-up of batch size beyond 10 g was virtually impossible.

The objective of this study was to make the synthetic procedure of the above workers safer and more practical so that the batch size could be increased, and to render the synthesis economically more attractive by the elimination of HMPA, by drastic reduction of the amount of metalating agent used and by cutting back on the extreme refrigeration required in the previously reported procedures.

EXPERIMENTAL SECTION

Materials

n-Butyllithium was purchased from the Alpha Division, Ventron Corp., Danvers, MA. Dimethylamine, diisopropylamine, 1-iodobutane, THF, lauroyl chloride, phenylmagnesium bromide and palmitoyl chloride were supplied by Aldrich Chem. Co., Milwaukee, WI. Skellysolve C (bp 88-98 C) was supplied by the Getty Oil Co., Tulsa, OK. All materials except THF were used as received. THF was dried over sodium metal and distilled from freshly cut sodium before use.

Analytical Procedures

Neutral equivalents were determined by titration in aqueous alcohol with standard base and were found in all cases to agree with theoretical values within experimental error. Analysis by gas liquid chromatography (GLC) was accomplished by means of a Hewlett-Packard Model 5750 gas liquid chromatograph equipped with a digital integrator. The column used for analysis of amides was ¼ in. × 4 ft, 316 SS, packed with 20% OV1 on 60-80 mesh Chromosorb W. Acids were analyzed on a silanized 1/8 in. × 4.5 ft 316 SS column packed with 7.5% stabilized ethylene glycol adipate containing 2% phosphoric acid on 90-100 mesh Anakrom ABS.

Synthetic Procedures

Synthesis of dimethylamides. The dimethylamides were prepared via the Schotten-Baumann reaction (11). The dimethylamide of lauric acid was a liquid and dimethylpalmitamide had a melting point of 39-40 C. Analysis by GLC showed that both amides were over 99% pure.

Example I: synthesis of α-hydroxy N,N-dimethyllauramide and α-hydroxylauric acid. Anhydrous THF (50 mL) and diisopropylamine (6.2 g, .069 mol) were added to

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a dry nitrogen-flushed 3-neck 250-mL flask, fitted with a gas dispersion tube supplied with dry nitrogen, a thermometer and a magnetic stirrer. *n*-Butyllithium in hexane (26.7 mL of 2.1 M, .056 mol) was added to the solution at such a rate that the temperature did not exceed -20 C. Dimethyllauramide (11.6 g, .051 mol) was added while maintaining the temperature below 0 C. The solution temperature was then allowed to rise to room temperature, and oxygen was bubbled in for 20 min.

The solution was evaporated to dryness, 30 mL of water was added, and the mixture was acidified with hydrochloric acid. The product was extracted with 50 mL of ether. The ether extract was washed with water until neutral and analyzed by GLC which showed that no unreacted dimethylamide was present. After crystallization from 60 mL of acetone at -28 C, α-hydroxydimethyllauramide (10.6 g, mp 42.5-43 C) was obtained in an 85% yield. Its infrared (IR) spectrum showed the characteristic absorptions at 1740 and 3440 cm^{-1}.

α-Hydroxydimethyllauramide from above (7.5 g, .031 mol) was hydrolyzed by heating with potassium hydroxide (50% aqueous, 30 mL), distilled water (100 mL), and isopropyl alcohol (75 mL), at 160 C for 4 hr in a pressure vessel. The cooled hydrolysis mixture was acidified. Crude α-hydroxylauric acid was extracted with ether and the extract was washed with water until neutral. After solvent evaporation the product was crystallized from 35 mL of acetone at -28 C, and α-hydroxylauric acid (5.6 g, mp 73-74/ lit 73-74) (12) was obtained in an 85.6% yield.

Example II: synthesis of α-butyl N,N-dimethyllauramide and α-butyllauric acid. Benzene (80 mL) was dried by refluxing 1 hr in a 250-mL 3-neck flask, equipped with a Dean-Stark tube, condenser, a gas dispersion tube supplied with dry nitrogen, a magnetic stirrer, and a heating mantle. Diisopropylamine (10 g, .099 mol) was added and followed by *n*-butyllithium in hexane (31.6 mL of 3.4 M, .076 mol) while maintaining the temperature below 20 C. Dimethyllauramide (15.0 g, .066 mol) was then added at once and the solution was heated at reflux 3 min and cooled to room temperature. 1-Iodobutane (18 g, .099 mol) was added, and the solution was stirred for 3 hr at room temperature. Analysis by GLC showed that no unreacted amide was present. The product was isolated by acidifying the benzene solution, washing until neutral, and drying. The crude α-butyl dimethyllauramide (18.7 g, 100% yield) obtained was shown by GLC to have a purity of 99.9%.

α-Butyl dimethyllauramide (10 g, .035 mol) was hydrolyzed in a pressure vessel as described for example I. The hydrolysis product was acidified and extracted with ether. The ether extract was washed with water until neutral, dried and evaporated. Crude α-butyllauric acid (8.5 g, fp 10.2 C) was obtained in 94% yield. Its neutral equivalent was within 1% of theory.

Example III: synthesis of α-hydroxylauric acid with the aid of phenylmagnesium bromide. Diisopropylamine (16 g, 0.158 mol) was dissolved in Skellysolve C (160 mL) in a reaction flask which was kept flushed with a gentle stream of nitrogen. An ether solution of phenylmagnesium bromide (68 mL of 2.3 M, 0.156 mol) was added and the mixture was refluxed for 20 min. A white precipitate formed during the reflux period. The N,N-dimethylamide of lauric acid (26.8 g, 0.118 mol) was then added and the mixture was refluxed for 2 hr. During this period, the precipitate gradually dissolved. The nitrogen flow was stopped and the reaction vessel was provided with a 12-in. Vigreaux column. Solvent was distilled off until the vapor temperature reached 90 C. The reaction mixture was then cooled to room temperature, additional Skellysolve C (50 mL) was added, and oxygen was bubbled into the reaction mixture. During the oxygen addition, the apparatus was heavily shielded, and cooling in an ice bath was required to maintain the reaction at 20-25 C. After 1 hr of reaction at that temperature, the material was heated to reflux for 2 hr while maintaining the oxygen flow. The reaction mixture was then cooled to 50 C, and hydrochloric acid (4 N, 150 mL) was added with good agitation. The reaction product was placed in a separatory funnel, and the lower layer (aqueous) was drawn off and discarded. The upper layer was washed with two successive portions of distilled water (100 mL), and the solvent was stripped off in a rotary evaporator under a vacuum of 23 mm until the temperature of the product reached 100 C. The crude amide was hydrolyzed by heating with potassium hydroxide as already described. The cooled hydrolysis mixture was acidified and extracted with hexane (200 mL). After drying over anhydrous sodium sulfate, the hexane solution was cooled to -30 C. The crystals which had formed were filtered off and recrystallized from hexane. The α-hydroxylauric acid thus obtained (6.4 g, 25% of theoretical yield) and gave a neutral equivalent within 1% of theory. The IR spectrum and melting point agreed with those of the preparation of example I.

RESULTS AND DISCUSSION

Use of fatty acid dimethylamide in place of the fatty acid as the starting material cut the requirement of *n*-butyllithium agent in half because of the elimination of the acidic proton of the carboxyl function. In view of the very high cost of *n*-butyllithium, the introduction of two additional reaction steps (amidation, hydrolysis) into the synthetic methodology is economically worthwile.

Formation of the α-anion of the fatty acid dimethylamide was accomplished readily in the absence of HMPA using either THF or benzene as solvent. Since THF tends to form peroxides, benzene (13) is the preferred and a safer solvent with respect to explosive hazard. Drying of equipment and starting amide can be readily accomplished by azeotropic distillation with benzene.

The α-anion formation of the fatty amide in benzene or THF and subsequent reaction to form the α-substituted derivative require only moderate refrigeration, and, if the synthesis is carried out with the aid of a Grignard reagent, the reaction mixture has to be heated. The three examples described in the Experimental Section are typical of the general synthetic methodology.

The procedure of Creger is applied to the metalation of dimethylamide of the fatty acid; hence, only one equivalent of *n*-butyllithium needs to be used (example I). LDA and the fatty acid dimethylamides are soluble in THF and benzene, and HMPA is not needed. Reaction at -30 C of diisopropylamine with *n*-butyllithium in THF appears to be instantaneous as is subsequent reaction with the fatty acid amide. Treatment of the α-anion solution with oxygen does not result in color development, which appears to be an indication of side reactions and reduced yields. GLC analysis of the reaction product shows absence of unreacted dimethylamide or other chromatographable impurities. When the α-anion synthesis in THF is carried out at 15-20 C, discoloration, charring and reduced yield are obtained, probably due to attack on THF by lithium diisopropylamide (14). The reactivity in THF as well as the potential hazard of peroxide formation makes this solvent less attractive in the α-anion synthesis.

Use of benzene in place of THF (example II) results in a simplified procedure and eliminates the hazard of peroxide formation. Benzene is not attacked by LDA, but α-anion formation in benzene is much slower than in THF. Thus,

reaction of dimethylamides of fatty acids with LDA in benzene solution at room temperature is incomplete but is completed by heating at reflux for a few minutes. Heating is not deleterious since the α-anions of fatty amides, unlike those of the acids, are thermally stable. To attain high yields of α-substituted products, it is imperative that the reaction between LDA and dimethylamide be as complete as possible prior to addition of an alkyl halide, otherwise LDA may attack the halide and give rise to olefins (5). The yield of α-alkylated amides is also reduced if the reaction between α-anion and alkyl halide is carried out above room temperature. Thus, when the reaction is carried out at reflux, the yield drops to 50%.

Because of the high cost of *n*-butyllithium, less costly bases were investigated. Lithium amide, metallic lithium, sodium amide, metallic sodium and sodium hydroxide were found to be ineffective in producing the desired α-anions of fatty acids or amides.

Phenylmagnesium bromide is commercially available at about one-half the cost of *n*-butyllithium and was thought to be effective in abstracting the α-proton. Since the Grignard reagent can be prepared in situ from magnesium metal and bromobenzene, its use seemed attractive. Although Ivanov et al. (15) prepared organomagnesium derivatives via reaction of Grignard reagents with acids of the type $RC{\equiv}CCH_2COOH$, metalation of a fatty acid dimethyl amide with bromomagnesium diisopropylamine (from diisopropylamine and a Grignard reagent) has not been previously reported.

Phenylmagnesium bromide proved to be far less reactive than *n*-butyllithium, so that the reaction with diisopropylamine requires heating to reflux to form the proton-abstracting intermediate, presumably $BrMgN(iso\text{-}C_3H_7)_2$. Either benzene or an aliphatic hydrocarbon solvent can be used. Skellysolve C is preferred because it is higher boiling and has a higher flash point than benzene. As with *n*-butyllithium, it is necessary to have as much of the Grignard reagent as possible reacted with diisopropylamine before the fatty acid amide was added. After the α-anion of the amide was formed, we attempted reaction with various reagents, such as iodomethane, iodobutane, carbon dioxide, paraformaldehyde and oxygen. Although we were able to show formation of the desired product with all of these reactants by means of GLC, the yields were of the order of 10% or less except with the reaction of oxygen reported here in example III. Because of the laborious product isolations and the existence of high yield syntheses of α-substituted fatty acids or α-alkyl acrylic acids (16), the reactions of these reagents with the Grignard salts are not described here.

Since we did not check the normality of the commercial Grignard reagent solution, some of the failures to attain high yields could be attributed to an actual normality less than that stated on the label. Because of the absence of turbidity or precipitate in the solution and the lack of pressure, we assumed the reagent to be properly standarized by the manufacturer. Also, the use of a substantial excess of Grignard reagent in a few instances failed to raise the yields. Thus, it appears that the proton abstraction with the Grignard reagent is far from quantitative, and the reactivity of the magnesium salt of the α-anion is far less than that of the analogous lithium salt. In all experiments carried out with the Grignard reagent, we were able to recover large amounts of the starting amides or the analogous fatty acids. It should be noted that in the oxidation step (examples I and III), care should be taken to shield the operator from a possible explosion. Lower boiling solvents, such as diethyl ether, should be distilled off to reduce this hazard. In the synthetic routes described, acid hydrolysis takes at least 16 hr, whereas alkaline hydrolysis in a pressure vessel as described here requires only 4 hr; thus, only the latter has been described.

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