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SYNTHESIS OF n-BUTYL [3-^{13}C]ACRYLATE

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SUMMARY

A four step synthesis of n-butyl [3-^{13}C]acrylate from [^{13}C]methyl iodide is described. The procedure involves methylation of butyl acetoacetate, subsequent bromination, alkaline cleavage and, finally, dehydrobromination using cyclohexyldimethylamine. The overall yield was 5 %.

INTRODUCTION

n-Butyl acrylate specifically labelled with ^{13}C was required for studies on its oxidative metabolism in small animals. Methyl iodide which was available as a ^{13}C-labelled starting material could be used in several ways to synthesize acrylates, e.g., Wittig reaction of a glyoxylate, Grignard reaction

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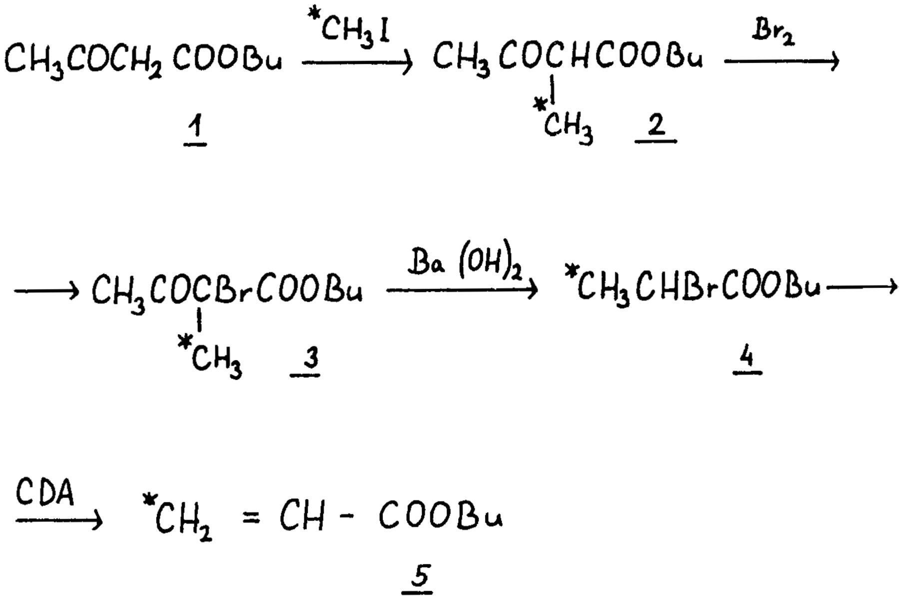
followed by dehydration and methylation of β-dicarbonylic compounds. Both Wittig and Grignard reactions failed to give desired product in sufficient yield and purity. However, methylation of acetoacetate followed by bromination and alkaline cleavage led to 2-bromopropionate in a good yield (1). An efficient method for dehydrohalogenation of 2-bromopropionate was required to successfully complete the synthesis.

RESULTS AND DISCUSSION

[^{13}C]Methyl iodide was converted to 2-bromo-[3-^{13}C]propionate (4) by the procedure described by Stotter and Hill (1). Dehydrobromination of 4 was the key step of the synthesis (Scheme). The methine hydrogen in bromopropionate 4 is strongly activated by two electron withdrawing groups so that an attack of a base on this hydrogen is highly favoured. This attack may lead to elimination of hydrogen bromide resulting in the formation of carbene instead of vinyl group. In fact, reaction of 4 with strong bases such as lithium diisopropylamide, 1,5-diazabicyclo-[4.3.0]-non-5-ene and 1,8-diazabicyclo[5.4.0]undec-7-ene led always to a mixture of products and no acrylate was found among them. Tertiary amines react with activated alkyl halides to form quaternary ammonium salts as main products. Neverthless, some sterically hindered tertiary amines may act as bases rather then nucleophiles so that elimination predominates. We found that cyclohexyldimethylamine (CDA) is a suitable eliminating reagent. The procedure described here is suitable for higher alkyl acrylates, however, the product isolation procedure (solvent extraction, chromatography) precludes the use of this method for highly volatile or low boiling acrylates.



EXPERIMENTAL

^{13}C Methyl iodide (76 % enrichment) was supplied by UVVVR, Prague. Cyclohexyldimethylamine (CDA) was a generous gift of Dr. F. Liška. Tetrahydrofuran (THF) was dried over sodium and distilled before use. A suspension of sodium hydride in mineral oil (80 % was from Aldrich (U.S.A.). All other chemicals were of reagent grade and were used as received. Gas-liquid chromatography was performed on Chrom 5 instrument (Laboratory Instruments, Prague) equipped with flame ionization detector.

n-Butyl 2-[^{13}C]methyl-3-oxobutanoate (2). To a stirred suspension of 1 g (33.8 mmol) sodium hydride in 30 ml of THF 5.1 g (32.2 mmol) of butyl 3-oxobutanoate (1) were added dropwise followed by addition of 4.8 g (33.8 mmol) of ^{13}C methyl iodide in 3 ml THF in several portions. The reaction mixture was stirred at 40°C for 3 hrs under a dry nitrogen atmosphere.

After cooling to room temperature the solvent was evaporated under reduced pressure, the residue was dissolved in 30 ml of water and extracted 6-times with 25 ml of diethylether. The combined ether extracts were washed with a solution of potassium thiosulphate, then with water and dried over magnesium sulphate. Evaporation in vacuo yielded 5.3 g (95.8 %) of oily product which was 90 % pure oxobutanoate 2 as assessed by gas-liquid chromatography. An authentic sample was used to identify this intermediate.

1-Butyl 2-bromo-2-[^{13}C]methyl-3-oxobutanoate (3). Oxobutanoate 2 (5.3 g, 27.8 mmol) was added dropwise to a stirred suspension of 920 mg sodium hydride in 30 ml of THF. After all the solid had been dissolved (carbanion formed) the solution was cooled below 0°C immersing the flask into an ice bath and 1.42 ml (27.8 mmol) of bromine in 5 ml of methylene chloride was added quickly. The reaction mixture was stirred for 1 hr under cooling and for another 1 hr at room temperature. The solvents were evaporated in vacuo and the residue was dissolved in 10 ml of water, extracted with five 25 ml portions of diethylether, the combined extracts were dried over magnesium sulphate and filtered. Evaporation of the solvent yielded 6.9 g of crude product which was purified by column chromatography on silica gel using methylene chloride as eluent. Purification yielded 5.5 g (79 %) of 3.

n-Butyl 2-bromo-[3-^{13}C]propionate (4). Oxobutanoate 3 (5.5 g, 21.9 mmol) was added to a stirred suspension of 3.75 g (21.9 mmol) of barium hydroxide in 20 ml of 1-butanol and the mixture was held below 0°C for 1 hr, followed by stirring at room temperature for an additional hour. The suspension was then filtered, the precipitate washed with butanol and ether to remove adsorbed product. Evaporation of solvent in vacuo and purification of the residue on a silica gel column using benzene as eluent yielded 2.45 g (53.5 %) of 4. The purity of this product was 98 % according to gas-liquid chromatography and ^{1}H-NMR spectrometry.

n-Butyl [3-^{13}C]acrylate (5). Dehydrohalogenation was accomplished by heating 2.45 g (11.7 mmol) of 4 with 3 ml (20 mmol) of CDA to 190 - 200°C in a sealed ampule for 3 hrs. After cooling the ampule was broken, and the reaction mixture extracted with 30 ml of pentane. The extract was washed with diluted hydrochloric acid (1:5), and with water, and dried over magnesium sulphate. The solution was filtered through glass wool, the pentane was evaporated under reduced pressure and the residue purified by column chromatography on silica gel with pentane as eluent and by vacuum distillation. Purification yielded 220 mg of acrylate 5 (15 %) which was pure according to gas-liquid chromatography (98 %) and enriched with ^{13}C up to 75.6 ± 0.5 % as determined by mass spectrometry.

REFERENCES

1. Stotter, P.L. and Hill, K.A., Tetrahedron Lett. 4067 (1972).