

2-DEUTEROMETHYLATION OF KETONES

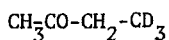
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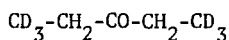
SUMMARY

A methods of obtaining 2-deuteromethyl ketones by deuteromethylation of the corresponding β -ketesters, is described and proposed as a general method for β -deuterium labeling of ketones.

In the course of another investigation [1] the need arose for the β -deuterated ketones 2-butanone-4,4,4,-d₃ I and 3-pentanone-1,1,1,5,5,5,-d₆ II . While the former was unknown, the latter has been prepared two decades ago [2] but by a rather cumbersome and expensive procedure.



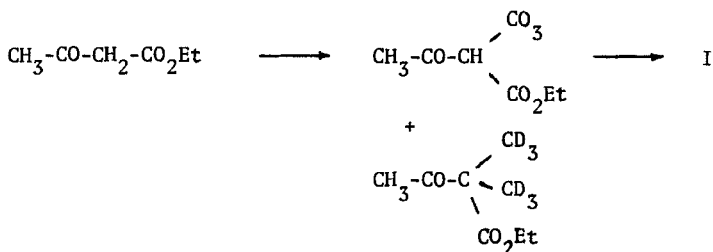
I



II

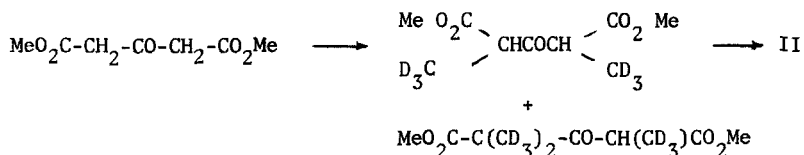
We became aware that, while well established procedures for the preparation of α -deuteriated ketones are known and were amply documented [3,4] the information on β -deutero ketones was relatively scarce [3,4]. In fact no general method for securing 2-deuteromethyl or -alkyl ketones, was available and we thought it worth pursuing.

The basic process underlying our method is alkylation of β -ketoesters with a suitable deuterioalkyl halide followed by hydrolysis and decarboxylation. Since we needed deuteromethyl compounds I and II , we used methyl iodide-d₃ in the alkylation procedure.



Thus, deuteromethylation of ethyl acetoacetate, using sodium hydride, followed by acid hydrolysis-decarboxylation of the product, gave a 23% overall yield of I accompanied by some dimethylated product. The latter could not be avoided by use of sodium methoxide instead of sodium hydride, which suggests that second attack occurred only on the tertiary carbon.

For the synthesis of II, another sequence was first tried, viz. reduction of acetone dicarboxylic ester by LiAlD_4 , transformation of the resulting diol into the ditosylate and reduction of the latter again with LiAlD_4 , but this was abandoned because of very poor yields.



Hence, deuteromethylation of dimethylacetone dicarboxylate gave a mixture of mono- and dideuteromethylated diesters, which underwent hydrolysis-decarboxylation to a corresponding mixture of ketones from which II was isolated by preparative g l p c in an overall yield of 27%.

We suggest that a variety of β -deutero ketones can be secured by this method using appropriate deuterio-alkyl iodides or bromides with selective carbanion substrates.

EXPERIMENTAL

2-Butanone-4,4,4,-d₃ I

Ethylacetoacetate (9 g., 0.069 mole) was added, with cooling and

stirring, to a suspension of NaH(ca. 3.5 g, 0.15 mole) in 75 ml. benzene and 25 ml. dimethylformamide[5]. To this reaction mixture, a solution of methyl iodide - d_3 (10 g, 0.069 mole) in 50 ml. benzene was added slowly and with stirring, which was then continued for 14 hrs. After filtering the solution was washed with HCl aq. and sat. NaCl aq., dried and the solvent removed. The residue was distilled in vacuo (24 torr): 1st fr. b.p. 84-90° (1.2 g); 2nd fr. b.p. 90-92° (7.7g). Both fractions contain the monodeuteromethylated ester as the major component and were unified for further processing.

A solution of the above product (8.9g) in 15 ml. acetic acid 20 ml. water and 1.5 ml. sulfuric acid was refluxed for 14 hrs. NaOH aq. was added with pH 8 followed by continuous extraction with ether for 24 hrs. After drying, the ether was removed in a fractional distillation and the residues separated by preparative glpc (15% carbowax-20M on Chromosorb P at 60°). Yield: 0.9g (23%) I and 0.35g (12%) 3-deuteromethyl- I as well as 0.2g of a third, unidentified product. Similar results were obtained when sodium methoxide was used instead of sodium hydride in the alkylation procedure.

Satisfactory NMR- and Mass spectrometric analyses were obtained.

3-Pentanone-1,1,1,5,5,5,- d_6 II

To a mixture of dimethylacetonedicarboxylate (6.2 g, 0.035 mole) and methyl iodide- d_3 (Miles-Yeda) (10 g., 0.07 mole) in 10 ml. absolute methanolic solution of sodium methoxide (from 1.7 g sodium in 20 ml. methanol) was added during one hour[6]. The reaction mixture was further stirred for 14 hrs. at room temperature followed by methanol removal on a rotatory evaporator. Water was added and the resulting mixture extracted with ether. After drying, filtering and removal of the ether, 6.2g of crude residue were distilled in vacuo, b.p. 60-62°/0.01 torr, to give 5.66g of distillate. The latter turns out to be a mixture of

mono- and dideuteriomethylated diester which was further processed as such rather than separated at this stage.

The solution of the above mixture in 25 ml. acetic acid containing 3 ml. sulfuric acid was refluxed for 14 hours. The solution was brought to pH 8 by addition of NaOH aq., and was continuously extracted with ether during 24 hrs. After drying, the ether was removed in a fractional distillation and the residue separated by preparative g l p c (8% XE- 60 on Chromosorb P at 50°C). A yield of 0.9g (27%) 3-pentanone-1,1,1,5,5,5,-d₆ II and 0.7g (26%) 2-deuteromethyl- II was obtained. Attempts to avoid or reduce formation of the latter, failed.

Satisfactory NMR- and Mass spectrometric analyses were obtained.

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