

SYNTHESIS OF AROMATIC AND ALICYCLIC SIX-MEMBERED RINGS, LABELLED WITH ^{13}C IN POSITIONS 1,3,5.

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SUMMARY

The synthesis of uvitic-1,3,5- ^{13}C acid, starting from $\text{Ba}^{13}\text{CO}_3$, is described. It allows the preparation of several compounds containing the aromatic and alicyclic six-membered labelled ring on a micro scale with good yields.

INTRODUCTION

For a mass spectrometric research we needed aromatic and alicyclic compounds with the ^{13}C -atoms in specified positions in the ring. We developed the synthesis of uvitic -1,3,5- ^{13}C acid starting from BaCO_3 , enriched to 90% ^{13}C , on a medium scale. This acid allowed us to make three different substituted benzenes and the corresponding cyclohexanes, as well as several interesting intermediate products on a micro scale (0.5 mmol/purified product). The synthesis steps are rather classical ones, but it turned out to be necessary to change the experimental procedures in order to maximize the yield, calculated on ^{13}C , for small quantities of starting materials. The liquid substances were always purified by gas chromatography, the solid ones by crystallization. With the exception of the cycloalkanes the yields given correspond to the values obtained before the final purification. The analytical purity was always better than 99.5 %, checked by gas chromatography. The isotopic enrichment in ^{13}C corresponded to the enrichment of the BaCO_3 used (> 90% ^{13}C) within the limits of our mass spectrometric accuracy (± 0.5 %).

Synthesis

The synthetic route is shown in fig. 1. Na-acetate- $1-^{13}\text{C}$ was obtained from BaCO_3 (90% ^{13}C) and CH_3MgI with a 96% yield (a) {1}. By addition to a five fold excess of PBr_3 in a cooled vessel it was transformed into acetyl- $1-^{13}\text{C}$ bromide (b) {2} with 83% yield. A smaller excess of PBr_3 or addition of PBr_3 to the sodium acetate diminishes the yield because of the partial decomposition of the product by local overheating. By reaction with $\text{Cu}_2(\text{CN})_2$ the pyruvitrile- $2-^{13}\text{C}$ is obtained with 88% yield (c) {3,4}; it is hydrolyzed to pyruvamide- $2-^{13}\text{C}$ (d) by an equivalent amount of H_2O in ether saturated with HCl and then immediately further hydrolyzed to pyruvic- $2-^{13}\text{C}$ acid (e) with conc. hydrochloric acid {3,4}. The yield was 36%, the product containing about 40% impurities.

The cyclization was performed in conc. NaOH at 100° and gave 60% 1,2-dihydro-1-methyltrimesic- $1,3,5-^{13}\text{C}$ acid (f) {4,5,6}. Na oxalate- $1-^{13}\text{C}$ was isolated as a byproduct with 90% yield. The main product which contained 40% NaCl was decarboxylated in conc. sulfuric acid under N_2 to give 80% uvitic- $1,3,5-^{13}\text{C}$ -acid (g) {4,5,6}.

Part of this acid was oxidized with alkaline KMnO_4 to 85% trimesic- $1,3,5-^{13}\text{C}$ acid (h) {4}. From this acid or from uvitic acid we obtained benzene- $1,3,5-^{13}\text{C}$ (i') and toluene- $1,3,5-^{13}\text{C}$ (i) resp. in 80% yield by decarboxylation in quinoline/ CuO at 210° .

Another part of the uvitic acid was reduced by LiAlH_4 in THF to the corresponding diol (o) {7}. Diethyl ether cannot be used because of the small solubility of uvitic acid. Without further purification the diol was brominated with PBr_3 to 1-methyl-3,5-bisbromomethylbenzene- $1,3,5-^{13}\text{C}$ (p) {7} with a yield of 67%, referred to uvitic acid. The reduction of the dibromide with LiH/LiAlH_4 in THF gave 62% of mesitylene- $1,3,5-^{13}\text{C}$ (q) {7}.

Benzene, toluene and mesitylene were hydrogenated to the corresponding cycloalkanes with PtO_2 in acetic acid at atmospheric pressure (note 1). The yields were 50% for cyclohexane- $1,3,5-^{13}\text{C}$ (n) and methylcyclohexane $1,3,5-^{13}\text{C}$ (n') and 65% trans- and 5% cis 1,3,5-trimethylcyclohexane- $1,3,5-^{13}\text{C}$ (n'') after

gas chromatographic purification. The higher total yield for the latter product is explained by its lower vapor pressure at room temperature. This can strongly affect the yields on a micro scale.

The oxidation of toluene with KMnO_4 in dilute NaOH gave 83% of benzoic-1,3,5- ^{13}C acid (note 2). After catalytic hydrogenation with PtO_2 in acetic acid at normal pressure the cyclohexane-carboxylic-1,3,5- ^{13}C acid was isolated at its silver salt in 90% yield (l); this silver salt was decomposed to 1-bromo-cyclohexane-1,3,5- ^{13}C in 50% yield (m) in a Hunsdiecker-reaction with Br_2 in CCl_4 (8). Cyclohexane-1,3,5- ^{13}C could also be obtained from this compound by reduction with LiH/LiAlH_4 in THF, but the yields turned out to be smaller than by the hydrogenation of benzene because of evaporation losses.

Notes :

1. 5 m mol benzene-1,3,5- ^{13}C (toluene, mesitylene) were hydrogenated in 3 ml acetic acid and 100 mg PtO_2 at atmospheric pressure. H_2 -absorption : 320 ml in 10 h. Diluted with 20 ml pentane, filtered and washed with 30 ml $\text{NaOH}(2n)$. The org. layer was dried with Na_2CO_3 and filtered. The pentane was distilled and the product purified by preparative gas chromatography.
2. 5.6 m mol toluene-1,3,5- ^{13}C , 6 m mol KMnO_4 , 2 ml $\text{NaOH}(2n)$ and 20 ml H_2O were stirred 3 h at 90° . Unreacted toluene was removed by an azeotropic distillation. 4 m mol KMnO_4 and 2 ml $\text{NaOH}(2n)$ were added to the distillate and stirred again during 3 h at 90° . This procedure was repeated twice (with $1\frac{1}{2}$ m mol KMnO_4 , 2 ml $\text{NaOH}(2n)$ and $\frac{1}{2}$ m mol KMnO_4 , 2 ml $\text{NaOH}(2n)$).
Some NaHSO_3 was added to the joined solutions and acidified with HCl to pH 1. After filtration and drying we obtained 0.58 g (83%) benzoic-1,3,5- ^{13}C acid.

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