

SYNTHESIS OF MICROAMOUNTS OF KETONES FROM CARBOXYLIC ACIDS:

1-PHENOXY-2-BUTANONES-2-¹⁴C.

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SUMMARY

A technique using acetic acid as a co-reactant for synthesizing microamounts of radiolabelled ketones from carboxylic acids with ethyl lithium is described. The acetic acid forms methyl ethyl ketone, a compound easily separated from the radiolabelled products.

Key Words: Carbon-14, ketones, microsynthesis

INTRODUCTION

A valuable method for the synthesis of ketones from carboxylic acids uses alkyl lithium (1): $\text{RCO}_2\text{H} + 2\text{R}^1\text{Li} \rightarrow \text{RR}^1(\text{OLi})_2 \rightarrow \text{RCOR}^1$. When alkyl lithium is present in excess, however, equally active side reactions of the product and intermediate occur (2). Because of these reactions and the difficulty of handling microamounts of alkyl lithium, this method for synthesizing radiolabelled ketones is not always practical. In that radiolabelled ketones were necessary in our study of the structure-activity relationship of xenobiotic transport in plants (3), I developed a technique for synthesizing microamounts of 1-(4-fluorophenoxy)-2-butanone-2-¹⁴C and 1-(4-chlorophenoxy)-2-butanone-2-¹⁴C in 22 to 91% yields. The technique may be of general use for synthesizing other ketones in microamounts.

This simple but critical technique involves the addition of a short chain carboxylic acid to the phenoxyacetic acid being treated with the alkyl lithium. The co-reactant permits use and handling of easily measured quantities of alkyl lithium in the reaction. Without the co-reactant, the small quantities of

alkyl lithium needed in the microsyntheses would be of dubious species because of the alkyl lithium reaction with trace moisture and air in the vessel. The mixed carboxylic acids are then treated with a slight excess of alkyl lithium. The co-product, a volatile unlabelled ketone, is readily separated from the less volatile radiolabelled product.

EXPERIMENTAL

1-(4-fluorophenoxy)-2-butanone-2-¹⁴C. *p*-Fluorophenoxyacetic-1-¹⁴C acid (4), 3.66 μ Ci (0.211 mg at sp. act. 2.95 mCi/mmole) was mixed with 105 mg (0.1 ml) glacial acetic acid in a solution in 15 ml anhydrous tetrahydrofuran. Total acid equivalent was 1.75 mmoles. To the rapidly stirred and cooled (0-10° C) solution were added 4.2 mmoles (120%) ethyl lithium in benzene (Ventron Corp., Alfa Div.). The mixture was stirred for 2.5 hours, decomposed with 10 ml 1N hydrochloric acid, and extracted with methylene chloride. The organic layer was washed with 10 ml 5% sodium bicarbonate, dried over magnesium sulfate, and evaporated to dryness to yield 0.8 μ Ci (22%) 1-(4-fluorophenoxy)-2-butanone-2-¹⁴C. The compound was authenticated by thin layer co-chromatography with known unlabelled compound on a silica gel G plate using a solvent mixture of hexane, ethyl acetate, and formic acid (20:5:1). The R_F of the ketone is 0.7. The average yield of 4 runs of 1-(4-fluorophenoxy)-2-butanone-2-¹⁴C was 25%.

A similar experiment with 3.5 μ Ci of *p*-chlorophenoxyacetic-1-¹⁴C acid (sp. act. 3.1 mCi/mmole) yielded 3.2 μ Ci 1-(4-chlorophenoxy)-2-butanone-2-¹⁴C. The yields of 2 runs of 1-(4-chlorophenoxy)-2-butanone-2-¹⁴C were 51 and 91%.

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