AN EFFICIENT SYNTHESIS OF ACETIC ANHYDRIDE-d_6

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During the course of some trichothecene bioproduction studies,[1] we found it necessary to have available a supply of acetic anhydride-d_6 for preparation of the corresponding esters. Previously this material and other labeled derivatives were prepared by reaction of acetyl chloride-d_3 with anhydrous sodium acetate-d_3.[2] Other preparations involve reaction of anhydrous sodium acetate-d_3 with para-toluenesulfonyl chloride at 220°[3] and exchange of undeuterated acetic anhydride with acetic acid-d_1.[4] These methods are time-consuming, somewhat expensive, and have yields which can be expected to be less than optimum.

We have found that treatment of readily available acetic acid-d_4[5] with dicyclohexylcarbodiimide in methylene chloride provides a high yield of the anhydride in an inexpensive and simple manner.

Preliminary results suggested that the solvent was critical to the success of the reaction. Thus in ether, loss of acetic acid was accompanied by a nonvolatile residue which contained little or no anhydride. Earlier reviews of carbodiimide chemistry alluded to the effects of solvents and temperature on anhydride formation[6,7] but details are lacking. The report of acetic anhydride formation using carbon tetrachloride as solvent[8] suggests that halogenated hydrocarbons may generally encourage anhydride formation as opposed to formation of the N-acylurea.

EXPERIMENTAL

Dicyclohexylcarbodiimide (7.95 g, 38.5 mmol) was dissolved in methylene chloride (15 ml) and cooled to 0°. Acetic acid-d_4 (5.0 g, 78.0 mmol, 99.5%) in methylene chloride (15 ml) was added slowly[9] and the mixture stirred. Insoluble N,N'-dicyclohexylurea (DCU) appeared within minutes, after which the mixture was allowed to warm to room temperature and stirring was continued for 24 hr.[10] The mixture was filtered and the DCU washed with methylene chloride (10 ml). The combined filtrates were removed by distillation at atmospheric pressure and the residue distilled under vacuum[11] (60°, 4 mm) to yield pure acetic anhydride-d_6 (3.87 g, 92%). The material was characterized by glc, ir and mass spectra.

Robert A. Ellison and Frank N. Kotsonis
School of Pharmacy
University of Wisconsin
Madison, Wisconsin 53706 USA

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9) A reflux condenser was used in order to ensure no loss of volatiles. With a colder bath or very careful addition, this might not be necessary.
10) In spite of the rapid appearance of product at 0°, optimum yields were experienced with a prolonged period at room temperature.
11) Substantial losses of product occurred when attempts were made to cleanly remove DCU by successive filtration. Direct distillation from residual DCU proved very satisfactory.