SYNTHESIS OF GLYCOLIC-d_2 ACID

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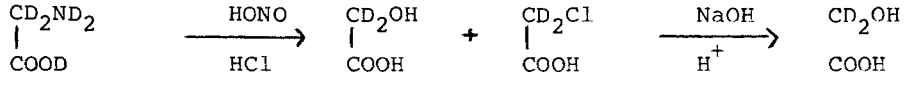
SUMMARY

Glycolic-d_2 acid, $HOCD_2CO_2H$, was prepared by the Cannizzarorearrangement of glyoxal-d_2 and by the action of nitrous acid on glycine-d_5.

KeyWords: Glycolic-$d_2$acid,Cannizzaro rearrangement, nitrous acid

We needed large amounts of deuteriated glycolic acid in order to reexamine the unusually large kinetic isotope effect of 36.5 observed during its oxidation with chromic acid at high concentra -tions[2]. Since our attempts to prepare glycolic-d_2 acid by $LiAlD_4$ reduction of diethyl oxalate[2] were unsuccessful, with glyoxal-d_2 (ca.40%) and ethylene glycol-d_4(ca.20%) being the only products formed[3], we developed two new proceedures. The first method is based on Cannizzaro rearrangement of the glyoxal-d_2 formed in the above reaction while the second method is based on the nitrous acid reaction on glycine-d_5[4], and hydrolysing the chloroacetic acid formed.



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Method 1.

$LiAlD_4$(aldrich chemical co.,98 atom%, 100 mg, 2.5 mmol) in 40 ml of dry ether was added to a solution of diethyl oxalate(1.46g, 10 mmol) in ether(40 ml) over a period of 30 minutes under dry nitrogen atmosphere at 0° C. After stirring for an additional 30 minutes, the solution was acidified with HCl(5%, 100ml), filtered, extracted with ether(3 x 50 ml) to remove unreacted diethyl oxalate, concentrated to 20 ml under reduced pressure, and stirred with NaOH (20%, 30 ml) for 20 minutes. Acidification and evaporation to dryness under vacuum gave a solid from which glycolic-d_2 acid was extracted with ether(5x 50 ml). Two crystallizations from acetone-benzene (to remove traces of oxalic acid)yielded 20 mg of glycolic -d_2 acid (10% based on $LiAlD_4$ used); mp 78-9° C (lit.[5] 78-9° C). Isotope analysis by NMR using chloroacetic acid as a standard gave a deuterium content of 99%. Anal. Calcd[6] for $C_2D_2H_2O_3$: C,30.77; H,5.13. Found: C,30.68; H,5.19.

Method 2.

$NaNO_2$(0.7 g, 10 mmol) was added to glycine-d_5[4](0.8 g, 10 mmol) in 10 ml water at room temperature. The resulting solution was acidified and maintained at pH 2 for 30 minutes by periodic additions of 10% HCl, heated to 50° C and stirred for another 30 minutes. NaOH(20%, 20 ml) was added and the mixture was stirred at 80° C for an hour to hydrolize the chloroacetic acid formed. Acidification and evaporation of the solvent under reduced pressure left a solid from which crude glycolic-$d_2$acid was extracted with acetone(5 x 20ml) Pure glycolic acid(0.2 g, 25%yield based on glycine) was obtained

by sublimation at 60°C (1 mm Hg) and two crystallizations from acetone-benzene; mp 78-9°C. NMR analysis by standard addition method gave a deuterium content of 99.5%. Anal. found: C,30.85; H,5-08.

While both methods gave identical products based on IR (Nujol; 2100,2160 cm^{-1}); mmp (78-9°C), paper chromatography (butanol-acetic acid-water, 4:1:5, R_f 0.72) and kinetic results, the second method is simpler and gives higher yields.

References and notes.

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6. Analysis performed on Perkin-Elmer 240 analyser by Micro-Tech Lab., Skokie, Illinois.