AN EFFICIENT SYNTHESIS OF [2-^{13}C]MONOBROMOACETIC ACID

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Received May 3, 1976
Revised July 1, 1976

SUMMARY

[2-^{13}C]-Monobromoacetic acid was prepared in good yield by the bromination of acetic acid in the presence of phosphorous trichloride by appropriate modification of the method of Marvel.[1] A by-product of this method was found to be bromoacetyl bromide, which could be avoided by hydrolysis to the required product by a modified work-up procedure. Pure monobromoacetic acid was obtained by sublimation.

Key Words: Bromination, Carbon-13, Acetic Acid, Sublimation

Alkylation of active-site functional groups with monobromoacetic acid is commonly employed in inhibition studies on enzymes.[2] During the course of our work in which we are using ^{13}C-labelled inhibitors as probes of active-site environment, we require 90% isotopically-enriched monobromoacetic acid. Preparation of 75% isotopically enriched [2-^{13}C]-monobromoacetic acid by bromination of 90% isotopically enriched [2-^{13}C]acetic acid has already been described,[3] but the method suffers from dilution of the label by exchange with isotopically unenriched acetic anhydride used in the reaction. Consequently, we examined a number of preparations of monobromoacetic acid from acetic acid or sodium acetate to assess the potential for convenient adaptations, e.g. (a) the use of dioxan dibromide, (b) reaction of N-bromosuccinimide with acetyl chloride in thionyl chloride, with subsequent hydrolysis to the acid.[4] However, the most consistent and efficient route was found to be reaction with bromine/phosphorous trichloride in the absence of solvent, under the conditions described below. A by-product of the reaction is bromoacetylbromide, but this

is converted to product by a modified work-up procedure. Sublimation in vacuo provides the most convenient method of purification of this reactive and highly hygroscopic product.

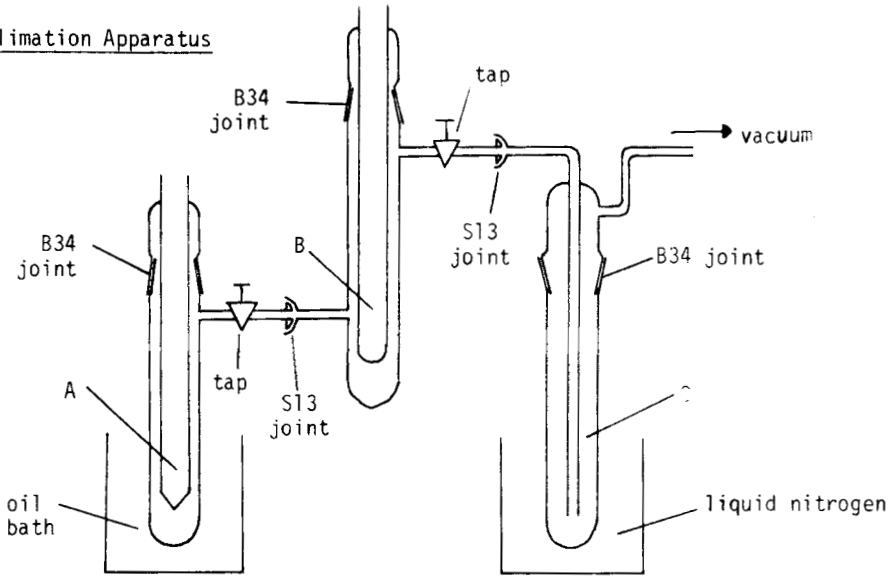
EXPERIMENTAL

To [2-^{13}C]acetic acid (0.5 g, 90% isotopically enriched ex Merck, Sharp and Dohme Isotopes, lot no. A/13) in a 5 ml. 2-necked round-bottomed flask fitted with a reflux condenser and a calcium chloride guard-tube, was added phosphorous trichloride (50 µl, freshly distilled, b.p. 76°/757 mm) and bromine (0.18 ml, dried over conc. sulphuric acid, followed by distillation). The reaction mixture was stirred (magnetic stirrer), whilst heated in an oil bath at 70°. After disappearance of the red bromine colour (∿ 1 h), more bromine (0.18 ml) was added, followed after 2 h by a further addition (0.15 ml). After heating for a further 6 h (9 h in total), the reaction mixture was cooled and any excess bromine evaporated by passage of nitrogen gas. Water (1 ml) was added and the reaction mixture washed into a 10 ml round-bottomed flask (final volume 4 ml). The pH of the aqueous solution was adjusted to 8.5 with solid sodium bicarbonate and after 2 mins, the solution was carefully acidified to pH 1.5. After evaporation (rotary evaporator, 15 mm Hg, at 20°), the damp solid residue, consisting largely of sodium chloride but containing the required product, was dried in a desiccator over silica gel for 36 h at 5 mm Hg. The dried solid was transferred to the sublimation apparatus illustrated in the Figure. To ensure transfer of the last traces, additional dry sodium chloride was used as a carrier.

Sublimation was conducted at 0.1 mm Hg in an oil bath at 50°C onto a cold-finger (A) cooled with acetone/solid carbon dioxide. Two additional traps (B, C) were cooled with liquid nitrogen. After completion, the apparatus was vented with pure, dry argon and the solid sublimate scraped from the cold-finger (A) and collected under a blanket of argon.[5] Additional product was obtained by washing (A) and traps (B) and (C) with

Figure:

Sublimation Apparatus



anhydrous diethylether, addition of solid sodium chloride to the resulting solution, followed by evaporation and resublimation as before. The product was stored under argon at -30°. The yields of 9 experiments, including cold-runs, was in the range 74 - 79% of product isolated as a white solid, m.p. 47 - 48° (lit. 49 - 50°)[4] The isotopic enrichment as determined by mass spectrometry was 91±2%. The ^{13}C.m.r. spectra confirmed the absence of labelled impurities, and overall chemical purity was confirmed by gas chromatography (5ft 10% SE-30 on Chromosorb W at 140°). A test for total phosphorus[6] demonstrated the absence of contamination from this source.

REFERENCES

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(2) Climie I.J.G., Evans D.A., and Akhtar M., J.C.S. Chem. Comm. 1975, 160.

(3) Nigen A.M., Keim P., Marshall R.C., Morrow J.S., Vigna R.A., Gurd F.R.N., J. Biol. Chem., 248, 3724 (1973).

(4) Harpp D.N., Bao L.Q., Black C.J., Gleason J.G., Smith R.A., J. Org. Chem., 40, 3420, (1975).

(5) Rubber gloves are required whenever handling monobromoacetic acid due to its extremely hygroscopic nature.

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