AN IMPROVED SYNTHESIS OF METHYL PROPIOLATE-1,2,3-$^{13}C_3$

Daniel F. Lieberman and Sun-Shine Yuan

KOR INCORPORATED
56 Rogers Street, Cambridge, MA 02142 (U.S.A.)

SUMMARY

An high yield synthesis of the title compound from $^{13}CO_2$ is described. A key to the success is direct formation of the ester from the intermediate lithium propiolate-$^{13}C_3$.

Key words: Methyl Propiolate, Direct Alkylation, Carbon Labelling.

INTRODUCTION

Propiolate esters are finding wide use as three carbon synthons in a variety of biological and other useful compounds. Propiolate esters are utilized in (2π + 2π), (2π + 4π), and ene type cycloadditions (1-6). Carbon and heteroatom nucleophiles add to methyl propiolate to produce substituted acrylates (7-9). The anion of methyl propiolate attacks electrophiles, such as aldehydes and ketones, producing 2-yn-4-ols (9). The latter reaction type is useful in steroid synthesis (6,10).

DISCUSSION

0362-4803/82/040605-06$01.00
© 1982 by John Wiley & Sons, Ltd.

Received July 16, 1981
Revised December 16, 1981

The synthesis of methyl propiolate-$^{13}C_3$ (3) presented here resulted from a continuing effort to improve upon the reproducibility, yield, and safety of literature preparations in the addition of carbon dioxide to the acetylide anion. Other easily obtainable labelling patterns via this sequence are 1-^{13}C and 2,3-$^{13}C_2$ propiolates (Scheme 1). The reaction producing 3 is practical when run on scales approaching one mole.

$$^{13}CO_2 \rightarrow \underset{\underline{1}}{H{-}^{13}C{\equiv}^{13}CH} \rightarrow \underset{\underline{2}}{H{-}^{13}C{\equiv}^{13}C{-}^{13}CO_2Li} \rightarrow \underset{\underline{3}}{H{-}^{13}C{\equiv}^{13}C{-}^{13}CO_2CH_3}$$

SCHEME 1

The use of sodium acetylide is ruled out *a priori* because of its explosion hazard and the capriciousness of yields generally obtained by this route (11-12). Lithium acetylide provides a convenient and safer alternative. However, the yield of methyl propiolate via Dawson and Dunlap's (13) *n*-butyllithium route is only 51% based on acetylene. These authors use diazomethane as the esterifying agent. In this laboratory the application of diazomethane resulted in significant yield reductions, owing to its probable dipolar addition to the triple bond of propiolic acid.

In the protocol described below the competing side reactions during esterification are obviated so that 3 can be isolated in 85-90% yield.

EXPERIMENTAL

Carbon-^{13}C dioxide (90 mol % ^{13}C) was obtained from KOR

Inc. Methyl propiolate was obtained from Farchan Division of Story Chemical Company. Gas liquid chromatography was performed on a Bendix-3000 equipped with a 6 ft. x 2mm glass column packed with 10% OV-17 on Gas Chrom-Q 100/120 mesh; oven 20°C, flame ionization detector, at 20psi flow rate.

Proton magnetic resonance (PMR) data were recorded on a Varian EM 360, with tetramethylsilane as internal standard. Carbon magnetic resonance (CMR) data were recorded on a Bruker HFX 100 at 22 Megahertz (in $CDCl_3$). Mass spectra data were acquired with a Varian-Mat 44.

Acetylene-$^{13}C_2$ (1). Prepared by the method of Whaley and Ott (14, see also 15). To a stainless steel chamber (150 x 900 mm) with external thermocouple and heater was added lithium (336 g, 48 mol). Vacuum was applied while the reaction chamber was brought to 650°C. Following isolation from the vacuum system, carbon-^{13}C dioxide (144 L, 6 mol) was pulsed onto the lithium at such a rate to keep the chamber between 650-700°C (time approximately 6 hr). After addition of all the carbon-^{13}C dioxide the temperature was raised to 750-800°C for 1 hour, with the reaction chamber open to the vacuum system. After cooling, the lithium acetylide-$^{13}C_2$ was carefully hydrolyzed with 8L CO_2-free distilled water. In collecting 1 water vapor was trapped with a Dry Ice/acetone trap, 1 was trapped in a pair of liquid nitrogen traps, and hydrogen was removed via the vacuum system. The product was further dried by passing it through a U-tube containing P_2O_5 on glass wool and stored in gas bottles at subatmospheric pressure. Yield 68.5 L, 95% based on carbon-^{13}C dioxide.

<u>Methyl Propiolate</u>-$^{13}C_3$ (<u>3</u>). Lithium propiolate-$^{13}C_3$ (<u>2</u>) was prepared by the method of Dawson and Dunlap as follows: In a 2 L 3 neck flask with magnetic stirring <u>1</u> (8.6 L, 0.36 mol) was frozen at -196°C. To this was transferred by cannula 750 mL prechilled (-78°C) dry tetrahydrofuran (THF), brought to -78°C and placed under positive N_2 pressure. One hundred and fifty milliliters <u>n</u>-butyllithium (2.4 M in hexane) in a 250 mL pressure-equalizing funnel was introduced over 40 minutes.

In a 3 L 3 neck flask with sealed mechanical stirring, carbon-^{13}C dioxide (8.6 L, 0.36 mol) was frozen at -196°C. To this was transferred by cannula 500 mL prechilled (-78°C) dry THF, brought to -78°C and placed under positive N_2 pressure. The solution of lithium acetylide-$^{13}C_2$ was transferred by cannula into the carbon-^{13}C dioxide solution. As the addition proceeded, a white precipitate indicated the formation of <u>2</u>. Addition was complete in 10 min. After 1 h at -78°C the suspension was brought to 25°C; 2,6-di-<u>tert</u>-butyl-4-methylphenol (50 mg, 0.2 mmol) was added as inhibitor and 600 mL tetraglyme was added for solvent exchange. The THF was removed under reduced pressure with some difficulty.

To the suspension of <u>2</u> in tetraglyme was added tetrabutylammonium hydrogen sulfate (2 g, 6 mmol) and methyl <u>p</u>-toluenesulfonate (110 mL, 0.72 mol). After stirring overnight in a sealed flask, the title compound was distilled at 55°C, 1 Torr to produce 27.6g; yield 89%. Yields ranged from 85-90% over four runs on acetylene-$^{13}C_2$ and carbon-^{13}C dioxide.

GLC data: Retention time; methyl propiolate 7.25 min., <u>3</u> 7.25 min.

^1H NMR data in ppm: 3.80 d, J=4Hz methyl H; 3.31 dd, J=259, 5Hz acetylenic H; 3.31 dd, J=310, 5Hz acetylenic H.

^{13}C NMR data in ppm: 153.585 dd, J=78.13, 66.40Hz C#1; 153.585 d, J=125.0Hz C#1; 76.879 t, J=15.62Hz C#3; 73.672 dd, J=44.92, 29.30Hz C#2.

MS data (m/e, relative intensity): methyl propiolate: (84, 0.58) M^+; (69, 1.72) M^+-15; (53, 100) M^+-31. Compound <u>3</u>: (87, 0.60) M^+; (72, 4.06) M^+-15; (56, 100) M^+-31.

ACKNOWLEDGEMENTS

We are grateful to Drs. A. M. Ajami, J. C. Bradley, and J. D. Cutting for helpful discussion and to G. J. T. Labelle and K. L. Maruca for technical assistance.

REFERENCES

1. Clark, R. D. and Untch, K. G.-J. Org Chem. <u>44</u>: 248 (1979).

2. Salomon, R. G., Burns, J. R. and Dominic, W. J. - J. Org. Chem. <u>41</u>: 2918 (1976).

3. Snider, B. B., Rodini, D. J., Conn, R. S. E. and Sealfom, S. - J. Amer. Chem. Soc. <u>101</u>: 5283 (1979).

---

4. Acheson, R. M. and Paglietti, G. - Heterocycles 12: 695 (1979).

5. Tanimoto, S., Matsumura, Y., Sugimoto, T. and Okano, M. - Tetrahedron Lett. 2899 (1977).

6. Dauben, W. G. and Brookhart, T. - J. Amer. Chem. Soc. 103: 237 (1981).

7. Wildeman, J., Borgen, P. C., Pluim, H., Rouwette, P. H. F. M. and van Leusen, A. M. - Tetrahedron Lett. 2213 (1978).

8. Truce, W. E. and Tichenor, G. J. W. - J. Org. Chem. 37: 2391 (1972).

9. Corey, E. J., Kim, C. U., Chen, R. H. K. and Takeda, M. - J. Amer. Chem. Soc. 94: 4395 (1972).

10. Hodosan, F. P., Serban, N., Balogh, A., Jude, I., Mantsch, O. C. and Bodor, N. S. - U. S. Pat. #3,734,938, cf. Chem. Abstr. 79: 42,759 r (1973).

11. Patcher, I. J. - U. S. Pat. #2,799,703, cf. Chem. Abstr. 52: 1,206 b (1958).

12. Tedeschi, R. J. and Moore, G. L. - U. S. Pat. #3,541,144, cf. Chem. Abstr. 74: 31,549 t (1971).

13. Dawson, W. H. and Dunlap, R. B. - J. Labelled Compounds and Radiopharmaceuticals 16: 335 (1979).

14. Whaley, T. W. and Ott, D. G. - J. Labelled Compounds 10: 461 (1974).

15. Tamers, M. A. - U. S. Pat. #4,009,219, cf. Chem. Abstr. 86: 171,063 c (1977).