Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXV, No. 11

GEMINALLY ^{13}C-LABELLED VINYL IODIDES; E-2'-IODO-4-METHOXYPHENYL[2'-^{13}C]ETHENE FROM [^{13}C]IODOFORM

Karen V. Baker, John M. Brown and Neil A. Cooley
Dyson Perrins Laboratory, South Parks Road, OXFORD OX1 3QY

SUMMARY

[^{13}C]Iodoform has been synthesised from [^{13}C]acetophenone and converted into the title compound by preparation of its chromium [III] derivative and reaction with 4-methoxybenzaldehyde. Purification was effected by recrystallisation from MeOH, or silica chromatrography.

Key words: Iodovinyl, iodoform, chromium (II), condensation.

INTRODUCTION

In the course of studies on the mechanism of carbon-carbon bond formation *via* catalytic cross-coupling (1), samples of ^{13}C- labelled vinyl halides were needed. Whilst most existing methods for preparation of vinyl halides were unsuitable, either through lack of stereoselectivity or difficulty in label incorporation, the recent chromium chemistry of Takai seemed much more promising (2). By this route, benzaldehyde was converted into 2-iodostyrene (E : Z, 94:6) by reaction with the species formed on admixture of iodoform and anhydrous chromium chloride in tetrahydrofuran. This required the development of a synthesis of [^{13}C]iodoform, following a similar route to that adopted by Siegel and Seebach for the preparation of [^{13}C]bromoform (3,4). This is more efficient than the indirect method previously described (3). Further, the ^{13}C label is fully utilised; in a related route to [^{14}C]iodoform from [^{14}C] acetone, half the isotope is converted into [^{14}C$_1$] acetic acid (5).

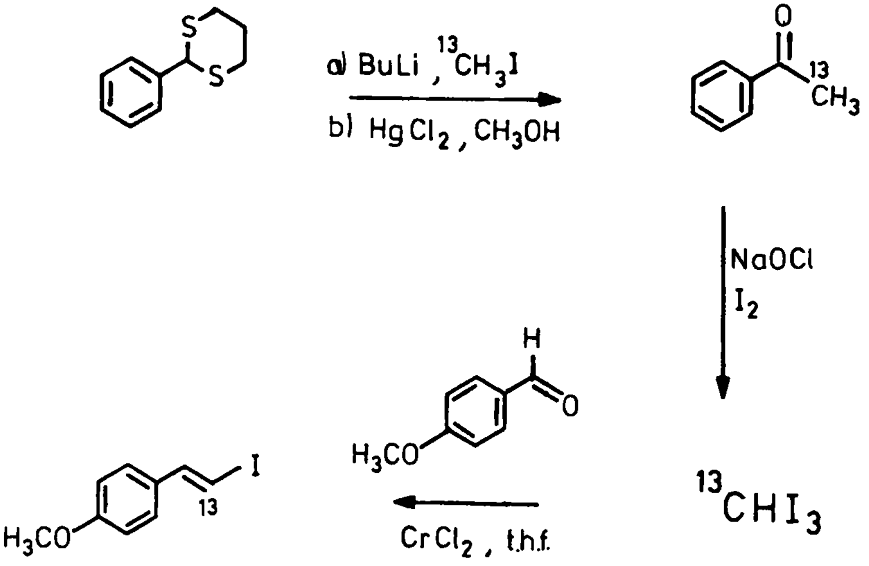
0362–4803/88/111229–05$05.00

Received February 26, 1988
Revised April 6, 1988

DISCUSSION

Following the detailed description of Siegel and Seebach (3), 2-phenyl-1,3-dithiane was methylated with [^{13}C]methyl iodide. This was converted into crude [^{13}C]acetophenone which was not purified further. Using commercial acetophenone, optimisation of the iodoform reaction was carried out (5). It was found that addition of bleach to acetophenone dissolved in a mixture of water and diethylene glycol containing an excess of KI at 0°C gave a pure product on dilution with water, and subsequent reprecipitation from aqueous ethanol.

It was confirmed that the reaction between 4-methoxybenzaldehyde and the $CrCl_2/CHI_3$ reagent indeed gave rise to E-iodo-(4-methoxy)styrene (Scheme). The product was obtained analytically pure by flash column chromatography. Before preparation of the labelled compound, some effort was made to optimise conditions for economical usage of ^{13}C enriched material. In Takai's original work, the haloform is employed in twofold excess over the aldehyde, and this is clearly unsuitable. Through systematic variation it was discovered that high yields of product could be obtained with a 1:1 ratio of reactants in the presence of a substantial excess of $CrCl_2$ - consequently these conditions were adopted in



preparation of the isotopically enriched compound. This labelled vinyl iodide is stable in the crystalline state when stored at -20° over a period of weeks, but some polymerisation is apparent at higher temperatures.

EXPERIMENTAL

All reactions were carried out using purified solvents employing inert atmosphere techniques where appropriate. [^{13}C]Methyl iodide was purchased from Aldrich, in 99% isotopic purity.

[^{13}C]Iodoform

A solution of 2-phenyl-1,3-dithiane (1.39 g., 7.1 mmol) in tetrahydrofuran (12 cm^3) was cooled to -78°C under an atmosphere of argon and treated with butyllithium (4.7 cm^3, 1.6 M in hexane). After stirring for 1h. at -78°C, iodomethane (1.0 g, 70 mmol, 99% ^{13}C) was added, resulting in an immediate colour change from green to pale yellow. The temperature was raised to -30°C and stirring continued for 8 h. After warming to ambient temperature 0.1M HCl (30 cm^3) was added. The aqueous phase was extracted with 1:1 CH_2Cl_2/ pentane (3 x 20 cm^3), and the combined organic layers dried over anhydrous $MgSO_4$. Solvent was removed in vacuo at 20° giving a pale yellow oil, pure by ^{2}H N.m.r. (3) This was dissolved in 1% aqueous methanol (50 cm^3) then $HgCl_2$ (2.80 g., 97 mmol) and red HgO (1.12 g, 51 mmol) added. The mixture was refluxed for 3 h., and solvent removed through a short Vigreux column to a final volume of 10 cm^3. This mixture was dissolved in aqueous KI (ca 1M., 20 cm^3) and diethylene glycol (15 cm^3) and stirred at -10° during addition of bleach (30 cm^3, "10-14% available Cl_2") over 15 m.. After a further 10 m. the reaction mixture was allowed to warm to 20°C and water (100 cm^3) added immediately. The resulting yellow solid was isolated by filtration and redissolved in EtOH (100 cm^3). Slow addition of water (200 cm^3) and filtration in vacuo gave [^{13}C]iodoform as pale yellow prisms, 1.26 g., 46%, m.p. 120-2° (lit 119° (6)).

E 2'-Iodo-4-methoxyphenylethene

To a grey suspension of CrCl$_2$ (0.686 g, 5.55 mmol) in thf (10 cm^3, distilled off sodium benzophenone) was added a solution of CHI$_3$ (0. 730 g., 2.87 mmol) and 4-methoxybenzaldehyde (0.159 g., 0.92 mmol) in thf (5 cm^3) at 0°C. The mixture was stirred for 3 h. at 0°C then poured into H$_2$O (25 cm^3) resulting in a colour change from dark brown to dark green, and extracted with Et$_2$O (3 x 10 cm^3). The combined extracts were dried over MgSO$_4$ and concentrated in vacuo. The remaining dark yellow oil was adsorbed on silica gel (2.0 g, 60μ flash column grade) with the aid of a small amount of CH$_2$Cl$_2$. The adsorbate was transferred to a silica chromatography column and eluted with hexane giving recovered CHI$_3$ (0.201 g.) Further elution with hexane/ether (15:1) gave 2'-iodo-4-methoxyphenylethylene (0.177 g., 74%) m.p. 62-64°C. Found C = 41.7, H = 3.74; C$_9$H$_9$IO requires C = 41.5, H = 3.46%. NMR (^{1}H, CDCl$_3$) δ 7.37 (1H, d, H1' $J_{1',2'}$ = 15 Hz) 7.24 (2H, ABq, H2 $J_{2,3}$ = 8 Hz) 6.85 (2H, ABq, H3) 6.63 (1H, d, H2') 3.83 (3H, s, OCH$_3$) ppm. MS (EI, m/z) 260 (M$^+$, 100%) 133 (M$^+$ - I, 60%).

E 2'-Iodo-4-methoxyphenyl[2'-^{13}C]ethene

The above procedure was repeated, now employing CrCl$_2$ (0.512 g., 4.14 mmol), [^{13}C]CHI$_3$ (0.275 g., 0.7 mmol) and 4-methoxybenzaldehyde (0.085 cm^3, 0.95 mg, 0.7 mmol) in thf (15 cm^3). Work-up proceeded as before. Alternatively, recrystallisation of the crude material from hot methanol gave the title compound as white plates, yield 0.136 g (75%) NMR (^{1}H, CDCl$_3$, inter alia) H2' ^{1}J (^{13}C-^{2}H) = 186 Hz, H1', ^{2}J (^{13}C-^{2}H) = 15 Hz. In repeat runs yields of between 71 and 88% were recorded.

ACKNOWLEDGMENTS

We thank S.E.R.C. for the award of a postdoctoral research fellowship (to NAC) and for a studentship through the CASE scheme to (KVB) in collaboration with ICI Chemical and Polymer Group.

REFERENCES

1. For recent references see Stille, J.K., Angew Chem.Int.Ed., 25, (1986) 508; Negishi E-i, Takahashi. T., Baba, S., Van Horn, D.E and Okukado, N, J.Am.Chem.Soc., 109, (1987) 2393 and refs. therein.
2. Takai, K, Nitta, K, and Utimoto, K. J.Am.Chem.Soc., 108, (1986) 7408.
3. Siegel, H and Seebach, D., J.Labelled Comp. and Radiopharm., 17, (1980) 279.
4. Seebach, D., Hassig, R, and Gabriel, J, Helv.Chim.Acta., 66, (1983) 308.
5. Jones, A.R., J.Labelled Comp., 11, (1975) 77.
6. Soroos, H., and Hinkamp, J.B., J.Am.Chem.Soc., 67, (1945) 1642; Seelye, R.N. and Turney, T. J.Chem.Ed., 367, (1959) 572.