

Tritiated Methylene Diiodide: A New Synthetic Labelling Reagent

Manouchehr Saljoughian,* Hiromi Morimoto, Philip G. Williams and Nicholas DeMello

National Tritium Labeling Facility, Lawrence Berkeley Laboratory 75-123, University of California, Berkeley, CA 94720, USA

A simple synthesis of tritiated or deuteriated methylene diiodide is reported, providing a useful reagent for the incorporation of tritium or deuterium into a cyclopropyl ring through the Simmons–Smith reaction, as illustrated by regiospecific addition to perillyl alcohol.

In the Simmons–Smith reaction^{1,2} methylene diiodide (CH_2I_2) is added across a double bond to prepare a cyclopropyl group in both a regio- and stereo-selective manner.³ The fact that many biologically important compounds contain a cyclopropyl ring, and that a large number of biological pathways have intermediates containing cyclopropyl rings,⁴ encouraged us to investigate a simple procedure for the synthesis of this reagent labelled with tritium. The availability of the isotopically labelled methylene diiodide (TCH_2I_2) allows the facile regio- and stereo-selective tritiation of compounds for which there is currently no established synthetic labelling route.

A single synthesis of a tritiated cyclopropyl group in a steroid has been published. It was produced by cyclization of a labelled methyl group, since the stereochemistry of the cyclization was specifically of interest.⁵ In an exchange procedure, tetramethylcyclopropanecarboxylic acid has been labelled by reflux with tritiated or deuteriated water at 200 °C for several hours.⁶ Syntheses of deuteriated cyclopropyl molecules are well known,⁷ but these methods have not been applied to tritium labelling. Early work on the Simmons–Smith reagent for mechanistic studies reported the synthesis of mono-⁸ and di-deuteriated methylene diiodide,⁹ by the use of exchange reactions of iodoform and methylene diiodide, respectively. To our knowledge, the direct insertion of a tritiated methylene group into a double bond to yield a labelled cyclopropyl compound has not been reported.

We have taken advantage of a simple reduction–oxidation reaction¹⁰ in which iodoform is reduced with sodium arsenite in the presence of tritiated water to generate tritiated methylene diiodide and sodium arsenate. Sodium arsenite is prepared from arsenious oxide and sodium hydroxide (Scheme 1). Exploratory chemistry for the one-pot process was performed with deuterium oxide as the source of hydrogen isotope, and yielded *ca.* 75% of the desired reagent according to GC analyses of several experiments. The deuteriated product was analysed by ²H (46 MHz) and ¹H (300 MHz) NMR spectroscopy, and showed the expected patterns (Fig. 1A–C). The deuterium spectrum in Fig. 1B clearly shows the small proton–deuteron coupling ($J_{\text{HD}} = 0.97 \pm 0.03$ Hz) in the DCH_2I_2 . The proton spectrum (Fig. 1C) has two major features: a singlet from the CH_2I_2 molecules occurs 3.4 Hz downfield from the DCH_2I_2 triplet, with $J_{\text{HD}} = 0.91 \pm 0.02$ Hz. Integration of the two patterns in this proton spectrum confirms the contribution of hydrogen (*ca.* 7.5%) expected from the molar ratios of deuteron and proton sources. If necessary, the protonated molecules could be simply eliminated by the use of NaOD.

The analogous experiment with low-level tritiated water gave tritiated methylene iodide, as proved by 320 MHz ³H NMR analyses. In this experiment, arsenious oxide (0.16 mmol) and sodium hydroxide (0.94 mmol) were placed in a 10 ml flask with a magnetic stirring bar. The solid mixture was

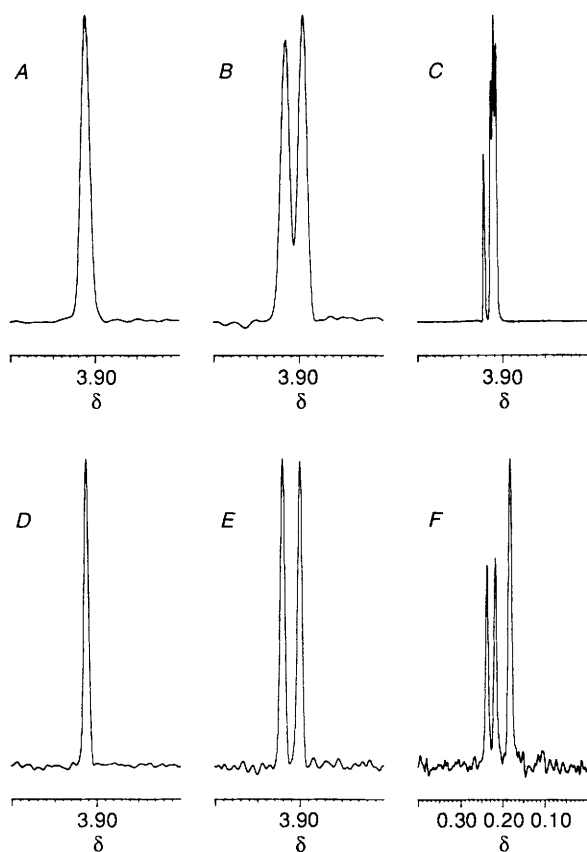
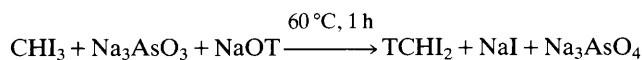
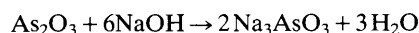


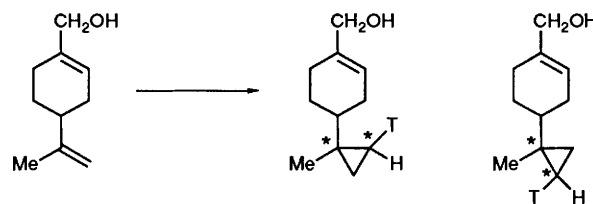
Fig. 1 NMR spectra of methylene diiodide in the δ 4.0–3.8 region. (A) Proton decoupled 46 MHz ^2H NMR spectrum of DCHI_2 in CHCl_3 . (B) Proton coupled ^2H NMR spectrum of DCHI_2 in CHCl_3 . (C) 300 MHz proton NMR spectrum of DCHI_2 in CDCl_3 . (D) Proton decoupled 320 MHz ^3H NMR spectrum of TCHI_2 in CDCl_3 . (E) Proton coupled ^3H NMR spectrum of TCHI_2 in CDCl_3 . (F) Proton decoupled ^3H NMR spectrum of the product of a cyclopropanation reaction, in C_6D_6 (δ 0.4–0 region).

dissolved in HTO (250 μl , 13.9 mmol, 4.4 Ci ml^{-1}). Iodoform (0.31 mmol) was then added and the mixture was stirred at 60 $^\circ\text{C}$ for one hour. The mixture was cooled and extracted with CDCl_3 (0.34 mL), and the extract dried over MgSO_4 . The total radioactivity in the reagent was assayed by liquid scintillation counting (9 mCi, 74% yield). The proton decoupled and proton coupled ^3H NMR spectra are shown in Figs. 1D and 1E respectively, and the observed coupling constant ($J_{\text{HT}} = 6.54 \pm 0.10$ Hz) is that predicted from the proton spectrum of the deuteriated analogue, previously obtained (Fig. 1B).

The utility of the tritiated reagent was demonstrated by adding to the unhindered double bond in perillyl alcohol to form a tritio-cyclopropyl ring regioselectively (Scheme 2), as was previously demonstrated for the non-radioactive reagent.¹¹ The ^3H NMR spectrum of the purified product (Fig. 1F) included three peaks, with integrals in a 1:1:2 ratio. We believe the peaks arise from the structures shown in Scheme 2, with two chiral carbon centres in each form of the molecule. Two of the four tritons in these isomers have similar chemical shifts and the tritium resonances are overlapped (Fig. 1F), hence yielding the observed 1:1:2 ratio. In this modified Simmons–Smith reaction perillyl alcohol (0.6 mmol) was dissolved in dry CHCl_3 (0.5 ml) and TCHI_2 (9 mCi, 0.23 mmol) in CDCl_3 (0.5 ml) was added. The mixture was stirred for 5 min, after which Bu^i_3Al (2 ml; 1 mol l^{-1}) was added and



Scheme 1



Scheme 2 TCHI_2 , Bu^i_3Al , room temp., 3 h

the mixture stirred at room temperature for a further three hours. The reaction was quenched by the addition of CHCl_3 (5 ml) followed by excess of NaF and water (2 ml). The lower (CHCl_3) layer was then withdrawn and dried, and evaporation of the solvent gave the desired tritiated product for ^3H NMR and radio-HPLC analyses. HPLC purification yielded 3 mCi of the cyclopropyl product, which represented a radiochemical yield of 33%.

These experiments demonstrate a simple synthesis of tritiated methylene diiodide at low specific activity, and the use of the reagent in an exemplary regioselective tritiation of perillyl alcohol. Similarly, specifically deuteriated materials may be readily made with a single deuterium atom on one carbon of the cyclopropyl ring. Hence the addition of a labelled methylene species to an unsaturated carbon–carbon bond provides a general approach to producing labelled cyclopropyl substrates.

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