Preparation of 4-Iodo-2-methyl-1-butene-1,1-$\underline{d}_2$

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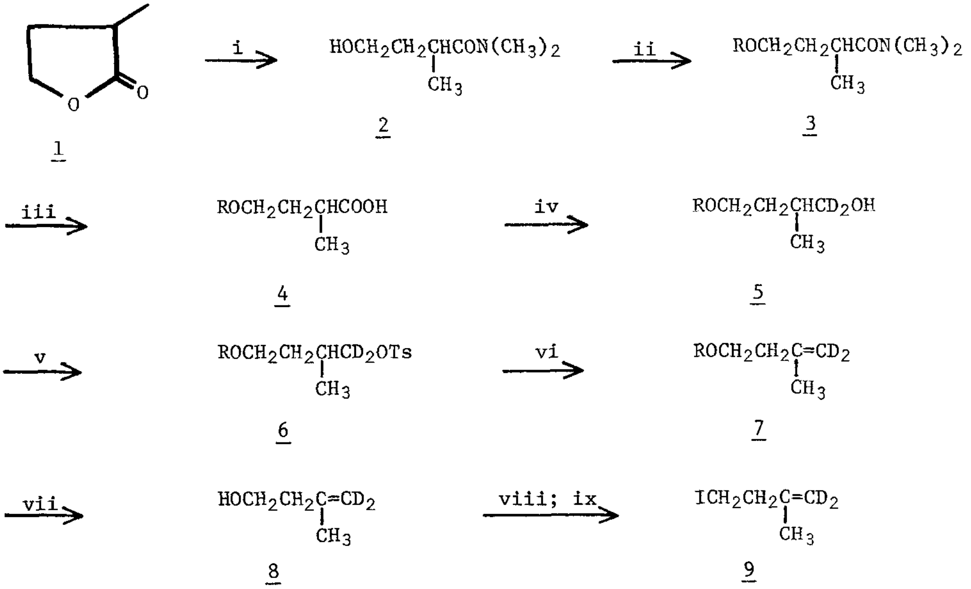
SUMMARY

A nine-step preparation of 4-iodo-2-methyl-1-butene-1,1-$\underline{d}_2$ (9) from 2-methylbutyrolactone (1) is described.

Key words: Isopentenyl group, isoprene unit

For preparation of labelled substrates to be used in a study of photochemical reactions we required 4-iodo-2-methyl-1-butene-1,1-$\underline{d}_2$ (9) as a synthetic intermediate. This compound represents a versatile source of a deuterium-labelled isopentenyl group that may well find application elsewhere. The previously recorded synthesis (1) of the unlabelled material begins with lithiation of isobutylene, a step that would unavoidably scramble the desired deuterium label if isobutylene-$\underline{d}_2$ were used. In devising a suitable alternative approach we specifically avoided the reaction of methylenetriphenylphosphorane with



R = 2-tetrahydropyranyl

i: $(CH_3)_2NH$, neat, 50-60°; ii: DHP, TsOH, THF, rt; iii: aq. KOH, reflux; iv: $LiAlD_4$, Et_2O; v: TsCl, Py; vi: (1) 2.5 equiv. NaI, 0.1 equiv. $\underline{i}$-Pr_2EtN, DMF, 6 h, 50°, (2) 1.5 equiv. DBU added, 3.5 h, 80°; vii: Py·HOTs, MeOH; viii: TsCl, Py; ix: NaI, DMF, 4.5 h, 50°.

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4-iodo-2-butanone or related compounds in view of the possibility of competing β-elimination from the ketone during the Wittig reaction. The synthesis we did develop proceeds conveniently from commercially available material, and we describe it below.

Reaction of 2-methylbutyrolactone (1) with dimethylamine in a bomb at 50-60° furnished the hydroxybutyramide 2 (2) in quantitative yield. Acid-catalyzed addition of dihydropyran (4) to 2 then gave 3, which was hydrolyzed to 4 in aqueous potassium hydroxide. Reduction of acid 4 with lithium aluminum deuteride introduced the required label in the product 5. We converted 5 to its tosylate 6 and, following a method recently developed for mild elimination in such systems (5), treated 6 with sodium iodide in dimethylformamide and then added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This procedure resulted in smooth elimination by way of the primary iodide and formation of alkene 7. Deprotection in methanol, using pyridinium tosylate (6) as catalyst, and subsequent tosylation and reaction with iodide ion gave the desired labelled isopentenyl iodide 9. Spectroscopic properties of 9 and various precursors were compatible with their structures and, apart from differences attributable to the deuterium atoms, identical with those of compounds of the unlabelled series (1). These spectra indicated that 9 contained $\sim$98% of two deuterium atoms at C(1).

EXPERIMENTAL

Materials and Equipment. These have been previously described (7). All gas chromatography was carried out with a Varian Aerograph Model 920 gas chromatograph with a 3 ft x 0.25 in. aluminum column packed with 25% QF-1 on 45/60 Chromosorb W. NMR spectra were recorded on a Varian Model T-60 (60 MHz) spectrometer.

N,N-Dimethyl-4-hydroxy-2-methylbutyramide (2). A mixture of 2-methylbutyrolactone (22.0 g, 0.22 mol) and anhydrous dimethylamine ($\sim$25 ml, 0.38 mol) was heated at 60 °C for 36 h in a bomb reactor. The amide 2 (31.9 g, 100%) was obtained after removal of excess amine; IR 3450 (br), 1632 (s) cm^{-1}; NMR (60 MHz) δ 3.90 (s, 1 H), 3.43 (t, *J* = 6 Hz, 2 H), 3.08 (s, 3 H), 2.88 (s, 3 H), 1.05 (d, *J* = 6 Hz, 3 H). These properties are in agreement with those recorded for 2 (2).

N,N-Dimethyl-4-hydroxy-2-methylbutyramide Tetrahydropyranyl Ether (3). To a solution of the hydroxy amide 2 (14.78 g, 101.8 mmol) in tetrahydrofuran (150 ml) was added *p*-toluenesulfonic acid monohydrate (1.936 g, 10.2 mmol) and, immediately thereafter, dihydropyran (25.7 g, 305.5 mmol). The mixture became warm and was stirred for 45 min. After the addition of solid NaHCO$_3$, the mixture was washed with saturated NaHCO$_3$ soln and brine, and was dried. The remainder of crude hydroxy amide 2 (17.12 g) was similarly processed. The two batches were combined and distilled to give 3 (37.39 g, 74%) bp 108-112° (0.1 mm); IR 1647 (s) cm^{-1}; NMR δ 4.43 (br s, 1 H), 4.00-2.48 (m, 11 H), 2.33-1.22 (m, 8 H), 1.05 (d, *J* = 6 Hz, 3 H).

4-Hydroxy-2-methylbutyric acid Tetrahydropyranyl Ether (4). A mixture of amide 3 (22.8 g, 99.4 mmol), KOH (26.8 g, 477.6 mmol), and water (200 ml) was heated to reflux under a argon atmosphere for 32 h. The mixture was cooled, extracted with ether (2x), and acidified to pH 2.5 with concentrated HCl. After extraction with ether (4x), removal of solvent gave 4 (18.45 g, 92%); IR 3500-2400 (br), 1706 (s) cm^{-1}; NMR δ 11.3 (br s, 1 H), 4.52 (br s, 1 H), 4.00-3.1 (m, 4 H), 2.6 (q, *J* = 7 Hz, 1 H), 1.21 (d, *J* = 7 Hz, 3 H).

2-Methyl-4-(2-tetrahydropyranyloxy)-1-butanol-1,1-d_2 (5). An ethereal solution (10 ml) of acid 4 (1.00 g, 4.95 mmol) was added to a suspension of $LiAlH_4$ (∿200 mg) in ether (20 ml) at a rate sufficient to cause gentle refluxing. Excess hydride was destroyed by the dropwise addition of a soln of saturated Na_2SO_4. The mixture was filtered and dried. Removal of the ether *in vacuo* gave the unlabelled alcohol (0.908 g, 93%).

Large scale reduction with $LiAlD_4$ was carried out similarly and gave comparable yields of 5; IR 3675 (w), 3500 (br), 2190 (br) 2080 (br) cm^{-1}; NMR δ 4.47 (br s, 1 H), 4.00-3.07 (m, 4 H), 2.43 (s, 1 H), 0.91 (d, *J* = 7 Hz, 3 H).

2-Methyl-4-(2-tetrahydropyranyloxy)-1-butene-1,1-d_2 (7). The alcohol 5 (12.0 g, 63.2 mmol) was converted to the tosylate in standard fashion by treatment with tosyl chloride (15.05 g, 78.9 mmol) in pyridine (120 ml) for 16 h at 4 °C. Extractive workup yielded 6 (20.5 g, 94%); IR 1600 (m), 1372 (s) cm^{-1}. A mixture of the tosylate 6 (20.5 g, 59.5 mmol), NaI (22.3 g, 148.8 mmol), diisopropylethylamine (0.769 g, 5.95 mmol) and dimethylformamide (100 ml) was heated at 50° for 6 h under an argon atmosphere. The mixture was cooled, treated with DBU (13.6 g, 89.3 mmol), then heated at 80° for 3.5 h. The mixture was poured onto ice and extracted with ether (3x). The combined extracts were washed with cold, dilute oxalic acid, H_2O, $NaHCO_3$ soln, and brine, and were dried. After removal of ether, crude acetal 7 (8.18 g, 80%) was obtained. Analysis by NMR indicated no remaining tosylate or iodide and essentially pure 7. Analysis by VPC on column A (95 °C) indicated only one component; a small amount of 7 was purified further by preparative VPC; IR 2965 (s) 2325 (w) 1616 (w), 862 (w) cm^{-1}; NMR δ 4.50 (br, s, 1 H), 3.93-3.17 (m, 4 H), 2.23 (t, *J* = 6 Hz, 2 H), 2.00-1.23 (m, with s at 1.73, 8 H).

3-Methyl-3-buten-1-ol-4,4-d_2 (8). The acetal 7 (8.15 g, 47.3 mmol) was treated with pyridinium *p*-toluenesulfonate (1.19 g, 4.75 mmol) in MeOH (125 ml) at 55 °C for 3 h. Most of the MeOH was removed by distillation through a Vigreux column; the residue was diluted with ether, washed with brine (2 x 20 ml), and was dried. Distillation (bp 90-130 °C) afforded the alcohol 8 (4.295 g) contaminated with 2-methoxytetrahydropyran.

4-Iodo-2-methyl-1-butene-1,1-d_2 (9). Treatment of crude alcohol 8 (4.295 g) with tosyl chloride (10.3 g) in pyridine (50 ml) in the usual fashion gave the tosylate (8.062 g); IR 1600 (w), 1370 (s), 1182 (s), 1175 (s), 890 (m) cm^{-1}; NMR δ 7.70 (d, J = 8 Hz, 2 H), 7.27 (d, J = 8 Hz, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 2.43 (s, 3 H), 2.30 (t, J = 6.5 Hz, 2 H), 1.67 (s, 3 H). The tosylate (8.062 g, 33.3 mmol) was taken up in DMF (70 ml) and was treated with NaI (12.0 g, 80 mmol) for 4.5 h at 50 °C. The reaction was worked up in the usual way with pentane. After removal of pentane by distillation, the residue was distilled to afford 9 (4.96 g, 75%) bp 65-69 °C (42 mm); IR 2320 (w), 1620 (br, w), 1435 (s), 1375 (s), 1165 (s), 710 (m) cm^{-1}; NMR δ 3.18 (t, J = 7 Hz, 2 H), 2.54 (t, J = 7 Hz, 2 H), 1.73 (s, 3 H).

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