Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXVII, No. 4

Synthesis of Deuterium-Labelled Alkenes

G. Sirokmán, Á. Molnár and M. Bartók*

Department of Organic Chemistry, József Attila University, Dóm tér 8, H-6720 Szeged, Hungary

SUMMARY

Novel or improved synthesis of six deuterated 1-alkenes (1-hexene-[3,3-$^2H_2$], 5-methyl-1-hexene-[3,3-$^2H_2$], 1-pentene-[1,1,2-$^2H_3$], 1-hexene-[2-^2H], 1-hexene-[1,1,3,3-$^2H_4$] and 1-hexene-[1,1,2,3,3-$^2H_5$]) are reported. The isotopic purities of these labelled alkenes were 99, 99, 92, 99, 76 and 86%, respectively.

Key words: Deuterium, Isomeric alkenes

INTRODUCTION

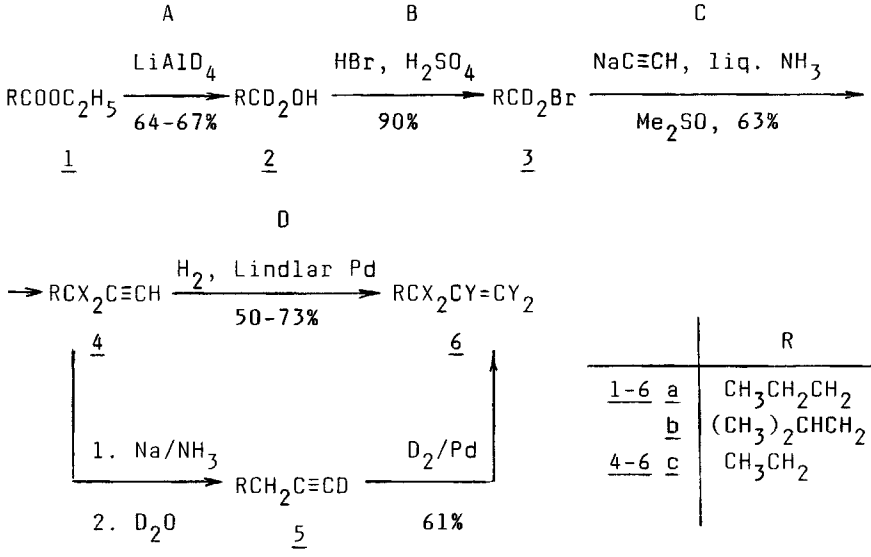
The systematic variation of deuterium labels in alkenes is useful for the determination of structure (1), reaction mechanism (2) and general isotopic effects (3). The synthesis of such molecules is difficult due to the tendency of the reactive intermediates to undergo double bond isomerization and nonselective exchange reactions (2, 4). For this reason, it is preferable to form the double bond after the deuterium is introduced into the required position (5).

*Author to whom correspondence should be addresssed

0362–4803/89/040439–10$05.00

Received June 7, 1988
Revised August 29, 1988

To elucidate the mechanism of catalytic double bond isomerization (6), 1-hexene and 1-pentene were labelled with deuterium at C-1, C-2 and C-3, at C-1 and C-2, at C-1 and C-3, at C-2 and at C-3. C-3 labelled 1-alkenes, 6, were obtained as shown in Scheme A. The reduction of heptanoic acid ester with sodium and O-deuterioacetic acid in diethyl ether was earlier reported (7), but a similar reduction of valeric acid ester proved unsatisfactory (8): only 70% deuterium incorporation was achieved at C-1. On performing the same reaction, we obtained 2a (step A) in a yield lower than 30% due to side reactions. Furthermore, the use of liquid ammonia in the coupling reaction (step C) and in the Birch reduction (9), which was proposed for step D (8), causes substantial losses on evaporation of the solvent if small amounts of volatile compounds are to be prepared. This reduces the overall yield to 10% or less.



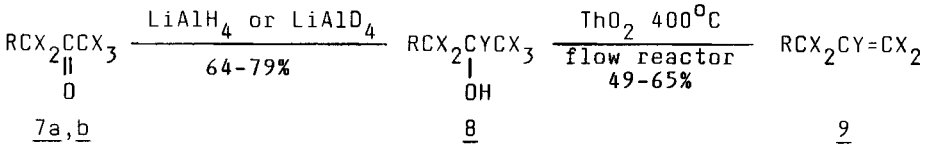
		R	X	Y
1-6	a	$CH_3CH_2CH_2$	D	H
	b	$(CH_3)_2CHCH_2$	D	H
4-6	c	CH_3CH_2	H	D

SCHEME A

The use of simple procedures permits considerable improvements in the yields of the labelled alkenes. The reduction of 1a with lithium aluminum deuteride gave 65% pure 2a. 4a was prepared in 63% yield by using a mixture of dimethyl sulphoxide, liquid ammonia and

dibutyl ether as solvent (10) instead of liquid ammonia. 4a was hydrogenated over Lindlar palladium catalyst (11), to produce 6a, in 73% yield. 6b was synthesized by a similar reaction sequence. 5c was synthesized by a known method (12), though another synthesis may be adapted (13), and it was reduced to 6c without any difficulty over the Lindlar catalyst with gaseous deuterium.

Due to its ElcB (14) mechanism, that involves the primary abstraction of a proton from the less hindered terminal methyl group on the action of basic surface sites followed by the elimination of a hydroxide ion (15), the strictly Hofmann-oriented elimination reaction of 2-alkanols (8) over thoria catalyst (16) offers an appealing way to obtain three different labelled compounds from 7a as starting material (Scheme B).



7a,b 8 9

7-9	X	Y
a	H	D
b	D	H
c	D	D
R	$CH_3CH_2CH_2$	

SCHEME B

The exchange reaction of 7a with deuterium oxide incorporates five deuterium atoms at C-1 and C-3. Selective deuteration of ketones is also possible (17). If desired, deuterium can be introduced at C-2 by reduction of the ketone with lithium aluminum deuteride. Subsequent dehydration over thoria caytalyst produces the labelled alkenes with 76-81% selectivity and in 49-56% yield. The pure 1-alkenes were produced free of isomeric alkenes by fractional distilla-

tion, in the following yields based on 7a: 9a 44%, 9b 25% and 9c 28%. To the best of our knowledge, the syntheses of 9b and 9c have now been reported for the first time, while 9a can be prepared otherwise, too (18).

The average deuterium content at the labelled positions (D) are listed in the Table. 6a, 6b and 9a were isotopically 99% pure, which is a higher value than reported earlier (8). In the case of 6c an exchange reaction is probably responsible of a slight loss of deuterium. The purity was 92%.

While dehydration over thoria did not affect the deuterium content at C-2, 24% and 14% losses of the deuterium at C-1 and C-3 were observed for 9b and 9c. This moderate exchange is, very probably, a consequence of both the ElcB mechanism of dehydration (15) and isomerization of the products.

These labelled alkenes were succesfully used to investigate the mechanism of alkene isomerization over heterogeneous catalysts (6). The main features of our syntheses are the following:
(a) high isotopic purity is achieved, (b) five different labellings of 1-alkenes are possible, and (c) three products can be synthesized from an alkanone via a common labelled intermediate in a sequence of two or three simple reactions. The method proposed for labelling 1-alkenes in allylic position is generally applicable; however, the scope of the procedure involving dehydration is limited to simple alkenes because of the severe reaction conditions.

EXPERIMENTAL

α-Deuterated 1-alkanols 2a, 2b

To a stirred suspension of lithium aluminum deuteride (11.6 g, 0.275 mole) in dry diethyl ether (400 ml), 1a (58 g, 0.5 mole) in diethyl ether (400 ml) was added during one hour. The mixture was then stirred at room temperature for 12 hours. First water (20 ml)

TABLE

DEUTERIUM LABELLED 1-ALKENES 6 AND 9 PREPARED

PRODUCT	CONVERSION[a] (%)	SELECTIVITY[b] (%)	YIELD[c] (%)	B. p. (°C)	MS(70eV)[d] D[e] (%)	MS(70eV)[d] M[f] (%)	IR (film)[g] (cm^{-1})	1H NMR (CCl_4, TMS_{int})[h] (δ ppm)
6a	-	-	73	64-66	99	M+2(100)	2090m,2190m(νCD) 1635s(νC=CH_2)	0.85(t,3H),1.30(m,4H),4.70(d,1H) 4.90(q,1H),5.65(q,1H)
6b	-	-	50	83-85	99	M+2(100)	2105m,2195m(νCD) 1645s(νC=CH_2)	0.93(d,6H),1.40(m,3H),5.50(d,1H) 5.80(q,1H), 6.70(q,1H)
6c	-	-	61	29.5-30	92	M+3(100) M+2(33)	2330m,2200m(νCD) 1585s(νC=CH_2)	0.95(t,3H),1.40(m,2H),2.05(t,2H)
9a	92	81	56	65-66	99	M+1(100)	2215m(νCD), 1595m(νC=CH_2)	0.93(t,3H),1.30(m,6H),4.83(s,2H)
9b	80	76	49	65-66	76	M+4(100),M+3(74) M+2(43),M+1(19) M(5)	2335m,2180m(νCD) 1590m(νC=CH_2)	0.94(t,3H), 1.35(m,4H), 2.00(s,~0.2H,3-H) 4.90(s,~0.2H,1-H),5.45(s,1H)
9c	87	79	55	65-66	86	M+5(100),M+4(49) M+3(26),M+2(12) M+1(7)	2340m,2220m(νCD) 1585m(νC=CH_2)	0.95(t,3H), 1.35(m,4H), 2.00(s,~0.2H,3-H) 4.91(s,~0.2H,1-H)

[a]Determined by GC on a PEG 20M column. [b]Ratio of 1-hexene in the product, determined by GC on a 4 m 10% LAC-296 on Chromosorb P column at 45 °C. [c]Yield of isolated pure product. [d]Recorded on an MM-12F spectrometer. [e]Average deuterium content at the labelled positions determined from the distribution of the molecules with different number of incorporated deuterium atoms. [f]M= molecular mass of the unlabelled compound. In brackets the relative intensities of the molecular peaks are given. [g]Recorded on a Pye Unicam SP 1000 spectrophotometer; m=medium, s=strong. [h]Recorded on a 60 MHz JEOL JNM-C-60 HL specrometer; t=triplet, m=multiplet, d=doublet, q=quadruplet, s=singlet.

was added and the mixture was stirred till the complete decomposition of the reducing agent. Then sodium hydroxide (14.6 g) dissolved in water (20 ml) was added slowly with continuous stirring, so that aluminum hydroxide would precipitate as small, spherical particles, easy to filter. The precipitate was filtered off, and the etheral solution was dried over magnesium sulphate and fractionated. The yield of 2a was 25.4 g (67%), b.p. 116-118 °C. 2b was prepared from methyl isovalerate (93.5 g, 0.81 mole). The yield was 51.1 g (64%), b.p. 128-130 °C.

α-Deuterated 1-bromoalkanes 3a, 3b

3a and 3b were prepared from the corresponding alkanols by refluxing them with azeotropic HBr and sulphuric acid. Starting from 2a (63.1 g, 0.83 mole) 3a (110 g, 95%) was prepared, b.p. 99-100.5 °C. 2b (33.7 g, 0.37 mole) was converted into 3b. The yield was 51.5 g (90%), b.p. 129-132 °C.

Coupling of bromoalkanes with sodium acetylide (4a, 4b)

In a 2 l three-necked round-bottomed flask equipped with a gas inlet tube, a mechanical stirrer and a reflux condenser, sodium acetylide (1 mole) was prepared as a suspension in liquid ammonia (800 ml) (10). To this, dimethyl sulphoxide (140 ml), purified by distillation before use, was added and the temperature was adjusted to -35 °C. Then 3a (109 g, 0.78 mole) was introduced during 45 minutes, while a slow acetylene stream was maintained. The mixture was stirred for 2 hours, after which dibutyl ether (80 ml) was added. The mixture was poured onto ice (800 g), the phases were separated and the water phase was extracted with dibutyl ether (30 ml). The solution of 4a was dried over magnesium sulphate and fractionated on a Vigreux column. The collected fraction at 69-72 °C was pure 6a. The yield was 41.8 g (63%). IR (film) 2090m (C-D), 2110m (νC≡C + νCD), 2190m (νCD) cm^{-1}. ^1H NMR (CCl_4) δ 0.93 (t, 3 H), 1.50 (m, 4H), 1.76 (s, 1 H). Starting from 3b (43 g, 0.28 mole) 4b (7.2 g,

26%) was obtained. B.p. 88-90 °C. The low yield was due to losses caused by the evaporation of ammonia.

Hydrogenation of alkynes over Lindlar palladium; Typical Procedure

1-hexene-[3,3-$^2H_2$] (6a)

4a (41.6 g, 0.48 mole) was dissolved in pure decalin (370 ml) in a simple hydrogenation apparatus (11), then Lindlar catalyst (3 g, Fluka) and additive (0.03 g, Cat. No.: 62150, Fluka) were added. The reaction was stopped after the calculated amount of hydrogen had reacted. The solution was filtered to remove the catalyst and 6a was recovered by fractional distillation.

1-Pentene-[1,1,2-$^2H_3$] (6c)

1-Pentyne-[1-^2H] (34.5 g, 0.51 mole, b.p. 40.5-52.5 °C, prepared according to (12)) was dissolved in pure decalin (300 ml) and deuterated in the presence of Lindlar catalyst according to the Typical Procedure. Deuterium gas was produced from deuterium oxide (isotopic purity: 99.5%) in a hydrogen generator (General Electric 15 EHG 2B4).

2-Hexanone-[1,1,1,3,3-$^2H_5$] (7b)

The multiple stepwise exchange reaction of 7a (100 g, 1 mole) with deuterium oxide (a total of 132 ml, 99.5%) was carried out as described (19). The yield of 7b was 82.3 g (78.3%), b.p. 126-128 °C.

Reduction of 2-alkanones with lithium aluminum hydride or deuteride; Typical Procedure. 2-Hexanol-2-^2H (8a)

Lithium aluminum deuteride (1.72 g, 0.041 mole) was suspended in dry diethyl ether (70 ml), and 2-hexanone (13.7 g, 0.137 mole) dissolved in dry diethyl ether (100 ml) was added. The mixture was refluxed for 1 hour, then ice-cooled water (7 ml) and diluted hydrochloric acid (1:1, 35 ml) were added. The water phase was extracted with three portions of diethyl ether. The combined organic extract was washed with 5% sodium bicarbonate solution and dried over magne-

sium sulphate. The solvent was evaporated off, and the product was fractionated on a 20 cm Vigreux column. The yield of 8a was 11.1 g (79%), b.p. 139-140 °C. ^{1}H NMR (CCl_4) δ 0.93 (t, 3 H), 1.15 (s, 3 H), 1.37 (m, 6 H), 2.50 (s, 1 H).

2-Hexanol-[1,1,1,3,3-$^2H_5$] (8b)

7b (41.2 g, 0.47 mole) was reduced with lithium aluminum hydride (5.24 g, 0.138 mole). The yield of pure 8b was 32 g (64%), b.p. 138-140 °C. ^{1}H NMR (CCl_4) δ 0.95 (t, 3 H), 1.33 (m, 4 H), 2.92 (s, 1 H), 3.63 (s, 1 H).

2-Hexanol-[1,1,1,2,3,3-$^2H_6$] (8c)

7b (41.2 g, 0.47 mole) was reduced with lithium aluminum deuteride (5.78 g, 0.318 mole). The yield of 8c was 33.3 g (66%), b.p. 139-140 °C. ^{1}H NMR (CCl_4) δ 0.94 (t, 3 H), 1.31 (m, 4 H), 2.35 (s, 1 H).

Thoria catalyst (16)

Freshly precipitated, thoroughly washed and dried thorium oxalate (prepared by adding the calculated amount of ammonium oxalate solution to a stirred solution of thorium nitrate) was heated at 400 °C in a slow flow of nitrogen for 16 hours. 10 g of glass rods 5 mm long and 0.5 mm in diameter were wetted with 0.2 ml methanol and mixed with 0.6 g fine powder of thoria. The latter adhered to the support almost completely. This amount of supported catalyst was used in each dehydration experiment without any further treatment.

Dehydration in a flow reactor; General Procedure

The catalyst was placed in a vertical fixed-bed reactor 16 cm long and 2 cm in inner diameter, made from Rasotherm glass. The dead-space of the reactor was filled with 3 mm glass beads. The reactor was heated in an electric oven at controlled temperatures. The reactant was fed into the reactor at a rate of 10 ml/hour.g catalyst by means of a motor-driven syringe. The reaction temperature was 400 °C in each case. The product was collected in a condenser con-

nected to the lower end of the reactor, analysed by gas chromatography and fractionated. The pure 1-alkenes were obtained free from isomers after fractionation on a Fischer Spaltrohrkolonne HMS 500 apparatus (a concentric tube column system) with a capacity of 90 theoretical plates.

REFERENCES

1. Thiem J., Mohm H. and Heesing A. - Synthesis 775 (1985)
   Bazin H. and Chattopadhyaya J. - Synthesis 1108 (1985)
2. Bartók M. et al. - Stereochemistry of Heterogeneous Metal Catalysis, Wiley, Chichester, 1985.
3. Collins C. J. and Bowman V. S. - Isotope Effects in Chemical Reactions, ACS Monograph, Van Nostrand Reinhold, 1970.
4. Murray A. and Williams D. L. - Organic Syntheses with Isotopes, Interscience, New York, 1958
5. Plouzennec-Houe I., Lemberton J.-L., Perot G. and Guisnet M. - Synthesis 659 (1983)
6. Resofszki G., Gáti Gy. and Halász I.- Appl. Catal. 19: 241 (1985)
7. Hill D. G., Judge W. A., Skell P. S., Kantor S. W. and Hauser R. - J. Amer. Chem. Soc. 74: 5599 (1952)
8. Davies N. R. - Aust. J. Chem. 17: 212 (1964)
9. Henne A. L. and Greenlee K. W. - J. Amer. Chem. Soc. 65: 2020 (1943)
10. Brandsma L. - Preparative Acetylenic Chemistry, Elsevier, Amsterdam, 1971, p. 49
11. Lindlar H. - Helv. Chim. Acta 35: 446 (1952)
    Lindlar H. and Dubuis R. - Org. Synth., Coll. Vol. V, p. 880
    Marvell E. N. and Li T. - Synthesis 457 (1973)
12. Rabinovitch B. S. and Looney F. S. - J. Amer. Chem. Soc. 75: 2652 (1953)
13. Lompa-Krzymien L. and Leitch L. C. - Synthesis 124 (1976)

14. Banthorpe D. V. - Elimination Reactions, Elsevier, Amsterdam, 1963, p. 78

15. Noller H. and Kladnig W. - Catal. Rev. Sci.-Eng. 13: 149, 192 (1976)
Thomke K. - 6th Internat. Congr. Catal., London, 1976, paper A21

16. Lundeen A. J. and van Hoozer R. - J. Org. Chem. 32: 3386 (1976)

17. Ono N. and Kaji A. - Synthesis 698 (1986)

18. Barluenga J., Yus M., Concellón J. M. and Bernad P. - J. Org. Chem. 46: 2721 (1981)

19. Shiner V. J. Jr. - J. Amer. Chem. Soc. 74: 5285 (1952)