Synthesis of Regio- and Stereospecifically Deuterium Labelled 2-Benzylindanes

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2-Benzylindenes (1, 1a) are hydrogenated to 2-benzylindanes (2) using tris-(triphenylphosphine)-rhodium(I)-chloride in benzene by a strict cis-1,2 addition of hydrogen to the double bond. Thus, stereo- and regio-specific deuterium labelling at the five-membered ring of various 2-benzylindanes has been carried out. The high selectivity of deuterium incorporation is shown independently by \(^1\)H NMR and mass (MIKE*) spectrometry of selected 2-benzylindanes.

Introduction

In the course of our mass spectrometric investigation of the intramolecular hydrogen exchange in gaseous radical cations of \(\alpha,\omega\)-diphenylalkanes [1—3] we required a synthetic access to various stereospecifically deuterium labelled 2-benzylindanes 2.

\[2: X = H, 3', 4'-\text{OCH}_3, -\text{F}, -\text{CH}_3, -\text{OH}, -\text{N(CH}_3)_2; 3',5'-\text{(OCH}_3)_2\]

It is well known that in heterogeneous catalytic hydrogenation of alkenes partial isomerization and/or migration of the double bond occurs [5, 6]. In the case of olefins labelled with deuterium at the \(\text{CH}—\text{CH} = \text{CH}\)-grouping or of using deuterium gas, non-regio-specific and isotopically impure labelling results [6]. As another consequence, the overall hydrogenation of the alkene may generate, in part, the products of trans-addition of \(\text{H}_2 (D_2)\) to the double bond along with that of cis-addition.

Indenes represent a class of alkenes containing a particularly reactive allylic group. Accordingly, heterogeneous catalytic hydrogenation of 2-benzylindenes over various Pt and Pd catalysts in alcoholic solvents, produces 2-benzylindanes with \(\geq 35\%\) incorrect incorporation of the label [7].

We wish to report here on the successful application of tris-(triphenylphosphine)-rhodium(I)-chloride (Wilkinson's catalyst) [8] to the stereo- and regiospecific deuterium labelling of indanes 2 by homogeneous catalytic hydrogenation and deuteration of the corresponding indene precursors 1.

\[\text{Scheme 1.}\]

* MIKE spectrometry: Mass analyzed ion kinetic energy spectrometry.
Results and Discussion

Using RhCl[P(C₆H₅)₃]₃ in ca. 0.2 m benzene solution hydrogenation of 1 takes place slowly (24–36 h) at room temperature with ≥ 99% regio- and stereoselectivity, as shown by ¹H NMR and mass spectrometry (vide infra). Thus, using D₂ gas, [1t,2-D₂]-indanes (2a) are obtained from 1 with ≥ 98% isotopic purity. In the same way, [1c,3,3-D₅]-indanes (2b) and [1,1,2,3,3-D₅]-indanes (2c) are produced from 2-benzyl-[1,1,3-D₃]-indenones (1a), which are synthesized from 1 by basic H/D exchange [8]. The 2-benzylindanes are isolated in nearly quantitative yields, irrespective of the substituent X (Scheme 1).

The stereo- and regiospecificity of the labelling is shown by ¹H NMR spectrometry of, e.g., the unsubstituted 2-benzyl-[1t-2-D₂]-indane (2a) (X = H) (Fig. 1) and by mass spectrometry of 2-(3'-methoxybenzyl)-[1c,3,3-D₃]-indane (2b) (X = 3'-OCH₃) (Fig. 2), respectively. These examples afford complementary structural information and are representative for all of the various substituted and labelled indanes 2.

2a shows an AB-system (δH A = 2.65 ppm, δH B = 2.95 ppm, JAB = −15.8 Hz) due to the C³ methylene group, a singlet at 2.75 ppm due to the benzylic methylene group, and a broad singlet at δ 2.64 ppm, which has to be assigned to the CHD group. Since the shielding of a proton at five-membered rings by a vicinal cis-substituent is well known [10], we have to assume that H³ = H²c and H⁵ = H⁵'. Hence, the resonance at δ 2.64 ppm reflects the cis-position of the CHD-proton (H²'), showing an isotope effect (Δδ = −17 ppm) of reasonable magnitude [11]. There is no resonance within the region of the H⁵ signals (see sinuous arrow in Fig. 1); hence, the trans-C¹ position bears no hydrogen but rather ≥ 99% deuterium atoms (D¹'). In turn, it follows that no deuterium is incorporated in the C³ methylene group.

This interpretation of the ¹H NMR spectrum, showing stereo- and regiospecific deuteration of 1, is corroborated by the mass spectrometric analysis of the complementarily labelled indane 2b (X =

Fig. 1. Partial ¹H NMR spectrum (80 MHz) of 2a (X = H).
3'-OCH₃) (Fig. 1 and Scheme 2). The 3'-methoxy derivative is discussed instead of the unsubstituted 2b (X = H) for the sake of clearness [12].

Fig. 2. Partial mass spectrum (70 eV) (a) and MIKE* spectrum (b) of 2b (X = 3'-OCH₃), showing incomplete (a) and complete (b) exchange of the four hydrogen atoms (◯) at C¹α, C³α, C², and C⁶ prior to fragmentation (cf. Scheme 2).

The major mass spectral fragmentation of ionized 2b (X = 3'-OCH₃) is the formation of C₈H₁₀O⁺' (m/z 122). This McLafferty type fragmentation requires the cleavage of the C²–C⁶ bond, being preceded by the transfer of a hydrogen atom at a γ-position (viz. C¹ or C³) to an ortho-position (viz. C² or C⁶) of the alkyl anisole moiety [3]. This H⁺ transfer has been shown to be reversible, leading to an exchange of the hydrogen atoms at the γ and the ortho positions, the extent of which increases with increasing life-time of the molecular ions [2, 3]. Because of steric reasons the hydrogen atoms trans to the benzyl group (H¹α and H³α) cannot be transferred to the ortho-positions, restricting the exchange to only the four H¹β, H³β, H², and H⁶ atoms.

Whereas the hydrogen exchange is incomplete in the 2b⁺⁺ (X = 3'-OCH₃) molecular ions fragmenting within ca. 1 µs in the ion source of the mass spectrometer (Fig. 2a), it has reached equipartition in the long-lived (ca. 10 µs) metastable 2b⁺⁺ ions [13], fragmenting in the second field-free region of the instrument. This follows from the MIKE* spectrum of 2b⁺⁺ (X = 3'-OCH₃) (Fig. 2b) showing C₈H₁₀DO⁺⁺ (m/z 123) and C₈H₁₁D₂O⁺⁺ (m/z 124) exclusively and with the statistically expected abundance ratio of unity. As a consequence, the cis-positions of 2b (X = 3'-OCH₃) must have been labelled completely (≥ 98% D₂).

In accordance to this result, the reciprocally deuterated 2-(3'-methoxybenzyl)-[1,2-D₂]-indane 2a (X = 3'-OCH₃), bearing no deuterium atom at the cis-positions, shows C₈H₁₀O⁺⁺ (m/z 122) as the only fragment ions formed from the metastable molecular ions (Fig. 3).

Fig. 3. Partial MIKE* spectrum of 2a (X = 3'-OCH₃).
Conclusion

The results of the $^1$H NMR and mass spectrometric analysis of deuterium labelled 2-benzyl-indanes (2) confirm independently that the homogeneous catalytic hydrogenation of 2-benzyl-indenes to 2-benzyl-indanes using RhClP(C$_6$H$_5$)$_3$ in benzene solution occurs with complete (≥ 99%) regio- and stereo-specificity. This warrants the use of this catalyst for deuterium (and tritium) labelling of all kinds of 1H-indenes in general.

Experimental

Melting points were measured with an Electrothermal melting points apparatus and are uncorrected. Boiling points were taken during the distillative purification using a Kugelrohr apparatus, Model GKR-50 (Büchi). All synthetic steps were recontrolled mostly using petroleum ether/ethyl acetate (3/1) as eluent. IR-spectra were recorded with a Model 377 instrument (Perkin Elmer). $^1$H NMR spectra with a WP 80 instrument (80 MHz, Bruker). 70 eV and low energy mass spectra were measured with a MAT 311A instrument (Vacuum Generators) at 6 kV and 100 $\mu$A. Using this technique the magnetic sector selects the metastable ion which is to be investigated by its decompositions which occur after having passed the magnet. The ionic products thus formed are then analysed by scanning the following electrostatic sector field.

2-Benzyl-indene (1) was prepared according to Campbell et al. [14] by dehydration of 2-benzyl-1-indanol in 90% formic acid. This method cannot be applied to, e.g., 2-(3'-methoxybenzyl)-1-indanol because of partial cyclodehydration to 4b,9,9a,10-tetrahydro-indeno[1,2-a]indene [15] which, however, can be omitted by heating the alcohol in dimethylsulfoxide (DMSO) [16]. The complete synthesis of the various substituted 2-benzyl-indenes and -indanes will be given in another context [15], restricting the present description to the preparation of the indanes discussed above.

2-(3'-Methoxybenzyl)-1-indanol was obtained by reduction of the ketone with LiAlH$_4$ in diethyl ether in 86% yield as an approx. 1:1 mixture of the cis and the trans isomers (white needles of m.p. 44–47 °C). 2-(3'-Methoxybenzyl)-1-indanol was obtained after recrystallisation from ethanol.

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Calcd  C 80.28 H 7.13.

Found  C 80.37 H 6.99.

IR (KBr): $\tilde{\nu}$ (cm$^{-1}$) 3390 (br), 3020 (m), 2940 (s), 2840 (m), 1600 (s), 1585 (s), 1260 (s), 1155 (s), 1050 (s), 780 (m), 755 (s), 720 (s), 705 (m). MS (70 eV) of the mixture: $m/z$ 254 (M$^+$; 5% B), 236 (M$^+$ - H$_2$O, 4%), 133 (M$^+$ - CH$_3$OH, 100%), 122 (C$_7$H$_6$OCH$_3^+$, 100%), 121 (C$_7$H$_6$OCH$_3^+$, 32%). The mass spectrometric identification of the pure stereoisomers will be discussed in a separate paper [15].

The mixture of the stereoisomeric indanols (1.28 g, 5.0 mmol) was heated to 170–175 °C in 4 g (50 mmol) of dry, freshly distilled DMSO under N$_2$ atmosphere for 20 h. After cooling, the reaction mixture was worked up by adding water and extracting the emulsion with petroleum ether (50–70) several times. The organic layer was washed with water and dried over MgSO$_4$. After evaporation of the solvent the mixture of the stereoisomeric indanols was obtained as an oil (b.p. 165–170 °C, 0.07 mbar), yield 0.93 g (78%). Recrystallisation from ethanol gave white crystals, m.p. 30–31 °C.

Calcd  C 86.41 H 6.82.

Found  C 86.71 H 6.66.

IR (neat): $\tilde{\nu}$ (cm$^{-1}$) 3055 (m), 2910 (m), 1600 (s), 1585 (s), 1260 (s), 1155 (s), 1050 (s), 780 (m), 755 (s), 720 (s), 705 (m). $^1$H NMR (CDCl$_3$/TMS): $\delta$ (ppm) 3.28 (br. sing., 2 H$_1$), 3.79 (quasi sing., 2 H$_1$), 6.65–7.45 (mult., 8 H arom). MS (70 eV): $m/z$ 236 (M$^+$, 42% B), 235 (M$^+$ - H, 4%), 128 (M$^+$ - C$_3$H$_6$O, 19%), 121 (C$_7$H$_6$OCH$_3^+$, 100%), 115 (C$_9$H$_7$OCH$_3^+$, 12%), 91 (C$_7$H$_5^-$, 10%).

2-Benzyl-[1.1.3-D$_3$]-indene 1a (X = H) and 2-(3'-methoxybenzyl)-[1.1.3-D$_3$]-indene 1a (X = 3'-OCH$_3$) 5 mmol of the indene are added to a mixture of D$_2$O (99.75%, Merck) (3.0 g, 150 mmol), pyridine (5 g, distilled twice from CaH$_2$), and triethylamine (0.5 g, 5 mmol, freshly distilled, b.p. 87–88 °C). The tightly stoppered bulb was heated to 80 °C.
Homogeneous catalytic hydrogenation and deuteration of 2-benzylindenes 1 and 1a (X = H and 3'-OCH3): 2-Benzyl-[1,2-D2]-indane 2a (X = H)

In a 10 ml cylindrical glass tube 210 mg (10 mmol) of 1 (X = H) are dissolved in 5 ml of dry benzene, and 45 mg (0.05 mmol) of RhCl[P(C6H5)3]3 are added. The tube is shut by a septum cap, connected to a micro-hydrogenation apparatus by a syringe needle adaptor and flushed with nitrogen and then deuterium gas. Under vigorous magnetic stirring the stochiometric amount of D2 is absorbed at ambient temperature in ca. 12-15 h, but stirring is continued another 12-24 h until absorption has ceased. (Towards the end of the deuteration reaction the light-red solution gets deep-red, indicating irreversible reaction of the catalyst). The solution is filtered through kieselgel/benzene, the solvent then evaporated and the residue purified by Kugelrohr distillation (b.p. 145-150 °C, 0.01 mbar), affording 2a (X = H) as a colorless oil in nearly quantitative yield. 1H NMR (CDCl3/TMS): δ (ppm) 2.65 and 2.95 (mult., 2 H), 3.76 (sing., 3 H OCH3), 6.7-6.95 (mult., 9 H arom); deuterium content (MS, 70 eV): 96.9% d3, 2.7% d2, 0.4% d1 ≤ 98.8%. 1H NMR of 2b (X = 3’-OCH3): δ (ppm) 2.6-3.0 (mult., H2, 2 H), 3.78 (sing, 3 H OCH3), 6.7-6.9 (mult., 3 H arom); D content (MS, 70 eV): 94.6% d3, 3.0% d2, 0.5% d1, 0.1% d0 ≤ 98.6%.

2-Benzyl-[1,1,2,3,3-D5]-indane 2c (X = H)

This isotope was obtained from 1a (X = H) using D2 gas. 1H NMR (CDCl3/TMS): δ (ppm) 2.65-2.85 (mult., H2, 2 H), 6.9-7.45 (mult., 9 H arom); deuterium content (MS, 70 eV): 96.4% d3, 3.0% d2, 0.5% d1, 0.1% d0 ≤ 98.8%.

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[7] As a marked example, the deuteration of 2-benzyl-[1,1,3-D3]-indene 1a (X = H, see scheme 1) in ethanol over palladium on charcoal (Merck) affords 19% [D4]-, 68% [D3]-, and 9% [D2]-indane 2 (X = H); use of [D5]-ethanol gives 7% [D4]-, 83% [D3]-, and 10% [D2]-hydrocarbon.
[12] The mass spectrometric fragmentation of 2 (X = H) is preceded by a partial epimerization of the C'H₂ and D'H₂ groups which is suppressed in the presence of a 3'-methoxy substituent [3].