Synthesis of 1,2,3- Trideutero Amines, Alcohols and Hydrocarbons from Tricarbonyliron(0) Complexes of 1-Heterodienes and Homodienes

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ABSTRACT

A simple procedure for the synthesis of 1,2,3-trideutero amines, alcohols and hydrocarbons from the reaction between lithium aluminiumdeuteride and tricarbonyliron(0) complexes of 1-heterodienes and homo-dienes is reported.

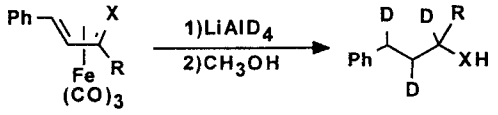
Keywords: (1-heterodiene)tricarbonyliron(0), (homodiene)tricarbonyliron(0), deuteration

INTRODUCTION

The synthesis of isotopically labelled compounds is important to many areas of chemistry, biology and medicine[1]. The need for the development of simple procedures with high efficiency for the incorporation of isotopes into substrates is of particular importance. Such procedures are beneficial since they minimise waste (particularly important in the case of radioactive isotopes) and increase the range of applications to which the compounds can be applied.

In a recent study[2] of the reaction between hydride transfer reducing agents and (1-heterodiene)tricarbonyliron(0) complexes it has been shown that treatment of these complexes with lithium aluminiumhydride leads to formation of saturated amines and alcohols in good to excellent yield. In this paper the use of this procedure for the synthesis of 1,2,3- trideutero 3-carbon fragments is reported.

Treatment of an ether solution of (1-heterodiene)tricarbonyliron(0) complexes **1**, **2** or **3** with lithium aluminiumdeuteride at 0 °C for 3 h followed by a methanol quench and chromatography leads to isolation of the trideutero compounds **4**, **5**, and **6** in good to excellent yield (79 - 90 %). In all cases there was no evidence of the formation of the mono or di deutero compounds.



1 - 3 **4 - 6**

1 X = $PhCH(CH_3)N$	R = H	**4** X = $PhCH(CH_3)N$	R = H
2 X = *p*-$CH_3OC_6H_4N$	R = H	**5** X = *p*-$CH_3OC_6H_4N$	R = H
3 X = O	R = CH_3	**6** X = O	R = CH_3

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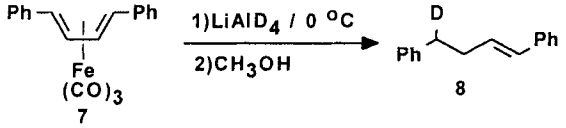
In order to investigate the scope of this novel procedure the reaction between lithium aluminiumdeuteride and a homodiene complex (1,4-diphenylbuta-1,3-diene)tricarbonyliron(0) **7** was investigated. A mixture of the two was stirred at 0 °C for 3 h. After a standard workup and chromatography white crystals identified as 1-deutero-1,4-diphenylbuta-3-ene **8** were obtained. There was no evidence for the isomerisation of **8** under the reaction conditions. The formation of the 1-deutero compound **8** indicates that the first step of the reaction is likely to involve attack by deuteride at a terminal position of the co-ordinated 1,3-diene.



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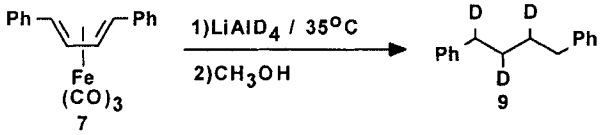
Since only partial saturation of the homodiene was observed at 0 °C the reaction between complex **7** and lithium aluminiumdeuteride was investigated at a higher temperature (35 °C). After standard workup the fully saturated hydrocarbon 1,2,3-trideutero-1,4-diphenylbutane **9** was obtained in good yield.



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It appears therefore that the degree of deuteration may be controlled by the reaction temperature. It is also of note that the formation of the 1,2,3-trideutero hydrocarbon indicates that protonation occurs at the terminal carbon.
This procedure is particularly advantageous since it allows three deuterium atoms to be incorporated into the carbon backbone in a single step. In addition by use of lithium aluminiumtritide the procedure may in principle be adapted for high specific activity tritiation of amines, alcohols and hydrocarbons.

The application of this chemistry for labelling of compounds of biological and pharmaceutical interest is currently in progress and will be reported in a future paper.

EXPERIMENTAL

All reactions were performed under nitrogen using standard Schlenk line techniques[3]. Diethyl ether was dried over lithium aluminiumhydride and was distilled, toluene was dried over sodium metal and was distilled and light petroleum refers to the fraction boiling in the range 30-40 °C. Lithium aluminiumdeuteride was supplied by Aldrich. 1-Heterodiene complexes **1**, **2**, and **3** and homodiene complex **7** were synthesised in accordance with literature procedures[4,5,6]. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected. All ^1H n.m.r. spectra were recorded in $CDCl_3$ (unless otherwise stated) on Perkin-Elmer R34 and Bruker AC 300 instruments at 220 and 300 MHz respectively. ^{13}C n.m.r. spectra were recorded in $CDCl_3$ on Bruker AC 300 or WH 400 instruments at 75.4 and 100.6 MHz respectively. All chemical shifts are quoted in ppm relative to a tetramethylsilane standard. Deuterium spectra were recorded on Bruker WH 400 and AC 300 instruments at 62.42 and 46.00 MHz respectively. Mass spectra were recorded on a Kratos MS80 instrument at 70 ev.

Chromatography was performed on silica (Merck 40-63 μm). Filtrations on alumina were performed using deactivated Brockmann (Grade iv) alumina. Elemental analyses were performed by Butterworth Laboratories and Medac Ltd.

Reaction of (4-Phenyl-1-(-1''-phenylethyl)-1-azabuta-1,3-diene)tricarbonyl)iron(0) 1 with Lithium Aluminiumdeuteride.

To a suspension of lithium aluminiumdeuteride (0.12g, 2.86 mmol) in diethyl ether (10 ml) at 0 ^{o}C was added a solution of complex **1** (0.21 g, 0.57 mmol) in diethyl ether (10 ml) and the resulting mixture was stirred at O ^{o}C for 3 h under an atmosphere of nitrogen. The reaction was quenched with methanol (0.92 g, 28.60 mmol) and was allowed to warm up to room temperature for 1 h to give a dark mixture. This mixture was filtered through a plug of alumina to remove the solid residues and the solvent was removed under reduced pressure to give a dark oil. This oil was chromatographed on silica using light petroleum/diethyl ether (2:1) as the eluent to yield a colourless oil identified as the trideutero amine **3** (0.11 g, 80 %), b.p. 140-142 ^{o}C @ 1mmHg; (Found 242.1857. $C_{17}H_{18}D_3N$ requires 242.1862); δ_H (400 MHz; $CDCl_3$) 1.38 (3H, d, J = 7 Hz CH_3CH), 1.82 (1H, m, NCHDC*H*DCHDPh), 2.60 (2H, m, NC*H*DCHDC*H*DPh), 3.75 (1H, q, J = 7 Hz, C*H*CH_3) and 7.10-7.40 (10H, m, Aryl-*H*); δ^2_H (61.40 MHz; $CHCl_3$) 1.77 (1D, broad, NCHDCH*D*CHDPh) and 3.51 (2D, broad, NCH*D*CHDCH*D*Ph); δ_C (100.62 MHz; $CDCl_3$) 24.16 (CH_3CH), 31.76 (PHCHDCHDCHD), 33.53 (PhCHDCHDCHD, 47.22 (CHDCHDN), 58.19 (CH_3CH), 125.57, 126.43, 126.70, 128.15, 128.21, 128.26, 142.08, 145.67 (aromatic *C*); m/z (e.i.) 242 (M^+, 8.2 %), 227 (M-CH_3) and 105 (100, M-37).

Reaction of (1-(4'-Methoxyphenyl)-4'-phenyl-1-azabuta-1,3-diene)tricarbonyl)iron(0) 2 with Lithium Aluminiumdeuteride.

To a suspension of lithium aluminiumdeuteride (0.14 g, 3.33 mmol) in diethyl ether (5 ml) at 0 ^{o}C was added a solution of complex **2** (0.25 g, 0.67 mmol) in diethyl ether (20 ml) and the resulting mixture was stirred at this temperature for 3 h under an atmosphere of nitrogen. The reaction was quenched using methanol (1.06 g, 32.12 mmol) and was allowed to warm up to room temperature for 1 h. The dark mixture produced was filtered through a plug of alumina to remove the solid residues and the solvent was removed under reduced pressure to yield a dark oil. This oil was chromatographed on silica using light petroleum/diethyl ether (2:1) as the eluent to yield white crystals identified as the trideutero amine **4** (0.12 g, 76 %), m.p. 45-46 ^{o}C; (Found. 244.1701 $C_{16}H_{16}D_3NO$ requires 244.1693) δ_H (400 MHz; $CDCl_3$) 1.90 (1H, m, NCHDC*H*DCHDPh), 2.71 (1H, m, C*H*DPh), 3.09 (1H, m, C*H*DNH), 3.40 (1H, broad, N*H*), 3.74 (3H, s, CH_3O), 6.30-7.40 (9H, m, 2xAryl-*H*); δ^2_H (61.40 MHz; $CHCl_3$) 1.90 (1D, broad, NCHDCH*D*CHDPh), 2.69 (1D, broad, CH*D*Ph) and 3.07 (1D, broad, NCH*D*); δ_C (100.62 MHz; $CDCl_3$) 31.06 (PhCHDCHDCHD), 33.31 PhCHDCHD), 44.31 (CHDCHDCHDN), 55.69 (OCH_3), 113.94, 114.77, 123.78, 128.27, 141.61, 142.50 and 151.90 (aromatic *C*); m/z (e.i.) 244 (M^+, 45 %) and 107 (100 M-CHDCHDPh).

Reaction of (4-Phenyl-1-oxabuta-1,3-diene)tricarbonyliron(0) 3 with Lithium Aluminiumdeuteride.

A solution of complex **3** (0.25 g, 0.90 mmol) in diethyl ether (10 ml) was added to a stirred slurry of lithium aluminiumdeuteride (0.19 g, 4.50 mmol) at 0 ^{o}C. and the resulting mixture was stirred at this temperature for 3 h under an atmosphere of nitrogen. The reaction was quenched using methanol (1.44 g, 45.0 mmol) and the resulting dark mixture was allowed to warm up to room temperature for 1 h. The dark mixture produced was filtered through a plug of alumina to remove the solid residues and the solvent was removed under reduced pressure to yield a dark oil. This oil was chromatographed on silica using light petroleum/diethyl ether (2:1) as the eluent to yield **6** as a colourless oil. (0.12 g, 87 %). (Found 153.1270 $C_{10}H_{14}D_3O$ requires 153.1279); δ_1H (300 MHz; $CHCl_3$) 1.19 (3H, s, CH_3), 1.70 (1H, m, PhCHDC*H*D), 2.65 (1H, m, PhC*H*DCHD) and 7.00-7.70 (5H, m, Aryl-*H*); δ^2_H (46.00 MHz; $CHCl_3$) 1.70 (1D, broad, PhCHDCH*D*), 2.65 (1D, broad, PhCH*D*CHD), and 3.75 (1D, broad, CHDC*D*OHCH_3); δ_C (75.4 MHz; $CDCl_3$) 23.4 (CH_3), 32.0 (PhCHDCHD), 40.7 (PhCHD), 67.2, (CHDCDOH) and 125.7-142.0 (aromatic *C*); m/z (e.i.) 153 (M^+, 80 %).

***Reaction of (1,4-Diphenylbuta-1,3-diene)tricarbonyliron(0) 7 with Lithium Aluminiumdeuteride* at 0 °C.**
A solution of complex **7** (0.20 g, 0.57 mmol) in diethyl ether (10 ml) was added to a suspension of lithium aluminiumdeuteride (0.12 g, 2.90 mmol) at 0 °C and the resulting mixture was stirred at this temperature for 3 h under an atmosphere of nitrogen. The reaction was quenched with methanol (0.46 g, 14.5 mmol) and allowed to warm up to room temperature for 1 h. The resulting dark mixture was filtered through a plug of alumina to remove the solid residues and the solvent was removed under reduced pressure to yield a dark oil. This oil was chromatographed on silica using light petroleum as the eluent to yield *E*-1-deutero-1,4-diphenylbut-3-ene **8** (0.10 g, 80 %) as a white solid. m.p. 38-40 °C; (Found. 209.1325 $C_{16}H_{15}D$ requires 209.1330);. δ^1_H (300 MHz; $CDCl_3$) 2.55 (1H, broad, PhCD*H*), 2.70 (2H, broad, CD*HCH*=CH) , 6.29 (1H, broad, CH=C*H*CH_2) and 6.45. (1H, d, J = 12 Hz, PhC*H*=CH); δ^2_H (46 MHz; $CHCl_3$) 2.55 (1D, broad, PhCD*H*); m/z (e.i.) 209 (M+, 25 %).

***Reaction of (1,4-Diphenylbuta-1,3-diene)tricarbonyliron(0) with Lithium Aluminiumdeuteride* 7 at 35 °C.**
A solution of complex **7** (0.20 g, 0.58 mmol) in diethyl ether (10 ml) was added to a stirred slurry of lithium aluminiumdeuteride (0.12 g, 2.90 mmol) and the resulting mixture heated at 35 °C for 3 h. The reaction mixture was allowed to cool to room temperature and further cooled to 0 °C. The reaction was quenched using methanol (0.46 g, 14.5 mmol) and allowed to warm up to room temperature for 1 h. The resulting dark mixture was filtered through a plug of alumina to remove the solid residues and the solvent was removed under reduced pressure to give a dark oil. This oil was chromatographed on silica using light petroleum as the eluent to yield 1,2,3-trideutero-1,4-diphenylbutane as a white solid. (0.11 g, 89 %). Found 213.1638. $C_{16}H_{15}D_3$ requires 213.1643). δ^1_H 1.31 (2H, broad, 2xPhCHDC*H*D), 2.75 (3H, broad, PhC*H*DCHD and PhCH_2C*H*D), 7.00-7.50 (10 H, m, 2xAryl-*H*); δ^2_H (46 MHz; $CHCl_3$) 1.29 (2D, broad, PhCHDCH*D*CH*D*CH_2) and 2.77 (1D, broad, PhCH*D*CHD); δ_C (MHz; $CDCl_3$) 30.5 (PhCHDCHD), 36.80 (PhCHDCHD), 126.31, 128.80, and 143.21 (aromatic *C*); m/z (e.i) (M^+, 213), 92 (100, PhCHD).

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