JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 421–427.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.936

Research Article

Convenient methods for the synthesis of d_4, d_2 and d_6 isotopomers of 4-(4-fluorobenzyl)piperidine

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Summary

Pure 4-(4-fluoro-[2,3,5,6-$^2H_4$]benzyl)piperidine was prepared via the Grignard reaction of 4-fluoro-[2,3,5,6-$^2H_4$]bromobenzene and pyridine-4-aldehyde followed by consecutive deoxygenation and heteroatomic ring saturation in the presence of palladium on carbon catalyst. An improved method for the catalytic H/D exchange in benzylic positions of 4-(4-fluorobenzyl)piperidine and its d_4 derivative has also been described. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: deuterium-labelled compounds; Grignard reaction; catalytic hydrogenation; palladium on carbon; benzylpiperidines

Introduction

The efficacy of NR2B selective NMDA receptor antagonists in neuroprotection, anti-hyperalgesic and anti-Parkinson animal models have attracted significant recent interest.[1,2] Typical antagonists contain basic nitrogen which, in most cases, is contained within a 1,4-diaralkylpiperidine ring, such as in (*1R,2S*)-3-[4-benzylpiperidin-1-yl)-1-(4-hydroxyphenyl)-2-methyl-1-propanol (Ro 25,6981)[3] or in 6-[2-[4-(4-fluorobenzyl)-piperidyl]-ethanesulfinyl]-3H-benzoxazol-2-one (CI-1041, besonprodil, Scheme 1).[4]

Stable isotopically labelled derivatives of these compounds are necessary for pharmacological research.[5,6] The substituted benzylpiperine moiety is an essential part of the above-mentioned NMDA receptor antagonists in many

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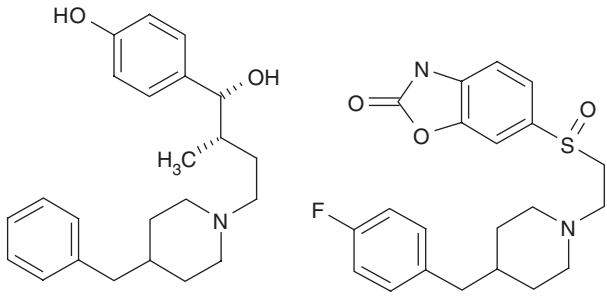
Contract/grant sponsor: Gedeon Richter Ltd.

Received 8 December 2003
Revised 4 February 2005
Accepted 7 February 2005



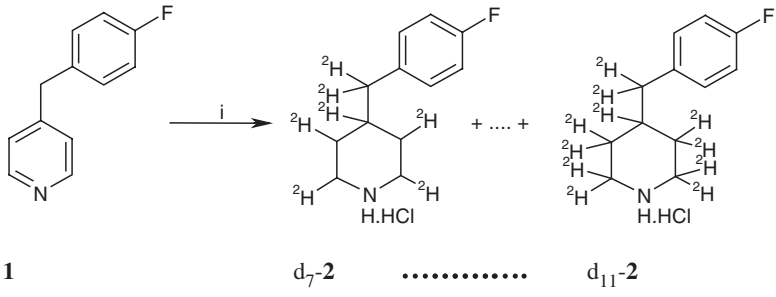
Scheme 1. Examples of biologically active benzylpiperidine derivatives

cases, therefore, development of efficient methods for the preparation of deuterium-labelled 4-benzylpiperidine derivatives would be of significant practical importance. Sajiki *et al.*[7] have reported a process for the H/D exchange at the benzylic positions of alkylbenzenes and diphenylmethane using a palladium on carbon catalyst at room temperature.[7] Recently, Franklin *et al.*[8] have published the synthesis of a d_1–d_8 isotopomeric mixture of an *N*-alkylated 4-(4-fluorobenzyl)piperidine derivative.[8] Such mixtures can create trouble during the evaluation of pharmaceutical investigations. Synthesis of isotopomerically pure deuterium-labelled benzylpipieridines would be a solution of these problems. In order to identify such a method, systematic investigations of the synthesis of deuterium-labelled derivatives of 4-(4-fluorobenzyl)piperidine have been carried out in our laboratory.

Results and discussion

In the first attempt, the application of Sajiki's catalytic method[7] has been attempted for the H/D exchange of the benzylic hydrogens in 4-(4-fluorobenzyl)piperidine. According to the GC-MS analysis, 93.4% of the starting material remained unchanged following prolonged reaction times whilst 6.6% of the starting material was found to have lost fluorine.

In a second attempt, 4-(4-fluorobenzyl)pyridine (**1**) was dissolved in a methanolic hydrogen chloride solution and the solution treated with deuterium gas in the presence of a palladium on carbon catalyst. These reaction conditions were identical to those developed for the piperidine synthesis in our laboratory.[9,10] After consumption of the calculated amount of deuterium gas, the product, 4-(4-fluorobenzyl)piperidine (**2**), was found to contain no deuterium. When the same experiments were repeated in deuterated alcohol in the presence of deuterium chloride, a mixture of d_7-**2**–d_{11}-**2** isotopomers of the product were obtained in high yield (Scheme 2). On the basis of the GC-MS and ^{1}H-NMR investigations, it can be stated that the hydrogen atoms in the benzylic position have been completely exchanged and



Scheme 2. Synthesis of the d_7–d_{11} isotopomers of 4-(4-fluorobenzyl)piperidine (2, i: $^2H_2$, Pd/C, $C^2H_3O^2H$, ^2H_2O, ^2HCl)

some of the original hydrogens from pyridine were also exchanged (d_9-**2**–d_{11}-**2** isotopomers). In other words, the deuterated protic solvent acts as the deuterium source for these reactions rather than the direct introduction of deuterium occuring from deuterium gas. It is in accordance with the literature data on the competitive H/D exchange of the acidic hydrogens from the protic solvents on the surface of palladium catalyst.[11]

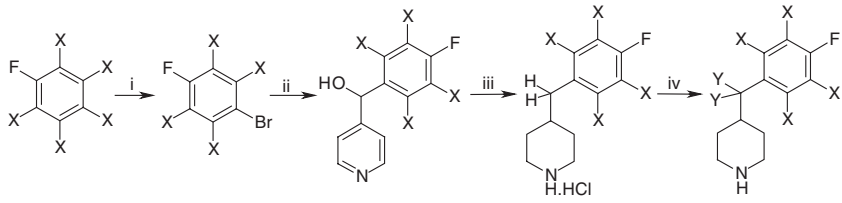
*Preparation of 4-(4-fluorophenyl-[$^2H_2$]methyl)piperidine (d_2-**2**) and 4-(4-fluoro-[2,3,5,6-$^2H_4$]phenyl-[$^2H_2$]methyl)piperidine (d_6-**2**)*

The saturated heterocyclic ring of 4-(4-fluorobenzyl)piperidine remained intact when treated with deuterium gas in deuterated alcoholic solution of deuterium chloride in the presence of a palladium on carbon catalyst at 60°C[9,10] whilst, under the same conditions, the H/D exchange reaction was almost complete for the benzylic position. Thus d_2-**2** was synthetised in 90% isotopomeric purity calculated on the basis of the benzylic hydrogens (Scheme 3).

Deuterium incorporation in benzylic position could be increased close to 95% when the exchange reaction was repeated in fresh deuterated solvent when starting from the 80% d_2-**2** isotopomer-containing product. In the same way, 4-(4-fluoro-[2,3,5,6-$^2H_4$]benzylpiperidine (d_4-**2**) could also be deuterated in the benzylic position and thus d_6-**2** was prepared in 90% isotopomeric and chemical purity. It has to be mentioned that prolonged reaction time and elevated temperature (higher that 60°C, 6 h) resulted in contamination of d_2-**2** and d_6-**2** with 5–7% of the defluorinated derivatives (calculated from the GC-MS data). Purification of these crude products was carried out by repeated recrystallization of the hydrochloride salts followed by distillation of the liberated base in vacuum (the free base is air sensitive).

*Preparation of 4-(4-fluoro-[2,3,5,6-$^2H_4$]benzyl)piperidine (d_4-**2** isotopomer)*

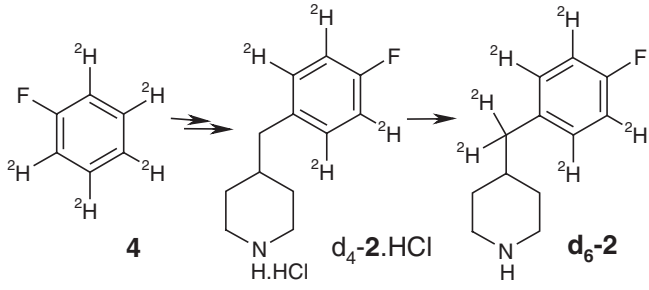
Synthesis of the titled compound was accomplished using our newly developed synthesis of substituted benzylpiperidines.[9,10] The starting material



4 X=H **3** X=H **5** X=H **2**X=H d_2-**2** X=H, Y=^{2}H

d_5-**4** X=^{2}H d_4-**3** X=^{2}H d_4-**5** X=^{2}H d_4-**2** X=^{2}H d_6-**2** X=^{2}H, Y=^{2}H

Scheme 3. Preparation of the d_4-, d_2-2 and d_6-2 isotopomers (i: Br_2, $FeCl_3$, CH_2Cl_2; ii: Mg, THF then pyridine-4-aldehyde; iii: H_2, Pd/C CH_3OH; iv: $^2H_2$, Pd/C, $C^2H_3O^2H$, ^2HCl)



Scheme 4.

1-bromo-4-fluoro-[2,3,5,6-$^2H_4$]benzene (d_4-**3**) could be obtained from 1-bromo-4-fluorobenzene with $AlCl_3$-catalyzed H–D exchange,[12] or by bromination of the commercially available [2,3,4,5,6-$^2H_5$]fluorobenzene (d_5-**4**). We used a modified version of the second, simpler method for gaining access to the pure 1-bromo-4-fluoro-[2,3,5,6-$^2H_4$]benzene (d^4-**3**) in good yield (Scheme 4). 4-Fluoro-[2,3,5,6-$^2H_4$]phenyl-hydroxymethyl)pyridine (d_4-**5**) was obtained from d_4-**3** and pyridine-4-aldehyde by Grignard reaction. Deoxygenation and heteroaromatic ring saturation was accomplished using our method[10] yielding the hydrochloric acid salt of 4-(4-fluoro-[2,3,5,6-$^2H_4$]benzyl)piperidine (d_4-**2**.HCl) in more than 98% chemical and isotopomeric purities (Scheme 3). The abundance of deuterobromobenzene derivatives to be found in the literature,[13–17] makes our method for preparation of 4-(4-fluoro-[2,3,5,6-$^2H_4$] benzyl)piperidine (d_4-**2**) one which can be generally applied to the synthesis of a wide range of deuterium-labelled benzylpiperidine derivatives.

Experimental

Materials and methods

All commercial starting materials were purchased from Aldrich and Merck-Schuchardt and were used without further purification. Anhydrous

terahydrofuran was obtained by distillation from sodium wire after the characteristic blue colour of *in situ*-generated sodium diphenylketyl had been found to persist. All Grignard-reactions were carried out under dry argon atmosphere.

^{1}H-NMR spectra were recorded in hexadeuteriodimethylsufoxide or deuteriochloroform solution at 300 and 500 MHz (Varian Innova Spectrometers). Chemical shifts refer to tetramethylsilane ($\delta = 0$ ppm), coupling constants are given in Hz. Melting point were determined using Büchi capillary melting point apparatus. IR spectra were recorded as KBr pellets with a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. GC-MS analyses were recorded on a Finnigan Mat/Automass II GC/MS. Gas chromatography was performed using a DB-5 capillary column (30 m × 0.25 mm ID, 0.25 μm film). The temperature program: 45°C (hold 3 min) heating to 300°C at 10°C/min, hold 15 min.

*4-(4-Fluoro-[α,α-$^2H_2$]benzyl)piperidine (d_2-**2**)*

4-(4-Fluorobenzyl)piperidine (**2**, 0.022 mol, 0.42 g) was dissolved in a mixture of [$^2H_4$]-methanol (5 ml) and deuterium chloride solution (0.005 mol/ml D_2O, 0.49 ml). Catalyst (10% Pd/C, 0.20 g) was added and the solution was stirred with deuterium gas under 3 bar pressure at 60°C for 6 h. At 25°C the catalyst was filtered and the solution was concentrated *in vacuo*. The residue was recrystallized 3 times from ethanol (5.5 ml)/ diethyl ether (130 ml) mixture then treated with a 5% aqueous sodium hydroxide solution (2.5 ml) in the presence of dichloromethane (10 ml). The aqueous phase was extracted with dichloromethane (3 × 5 ml), the organic solutions combined and washed with brine (5 ml), dried over sodium sulfate and concentrated *in vacuo*. Final purification was carried out by distillation of the residue oil (0.24 g) *in vacuo* to yield 4-(4-fluoro-[α,α-$^2H_2$]benzyl)piperidine (d_2-**2**), deuterium content in benzylic position: 90%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.10–1.19 (m, 2H), 1.57–1.62 (m, 3H), 2.52 (t, $J = 11.4$, 2.2H (0.2H, residue of the benzylic hydrogens)), 3.04 (d, $J = 12.0$, 2H), 6.91–6.98 (m, 2H), 7.05–7.09 (m, 2H). Ms (M/Z): 42, 55, 56, 69, 84, 195.

*4-(4-Fluoro-[α,α,2,3,5,6-$^2H_6$]benzyl)piperidine (d_6-**2**)*

This compound was prepared from d_4-**2**.HCl using the above-described method. Deuterium content of the product was $<90\%$ calculated on the basis of the six labelled positions. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.10–1.19 (m, 2H), 1.57–1.62 (m, 3H), 2.52 (t, $J = 11.4$, 2.2H (0.2H residue of the benzylic hydrogens)), 3.04 (d, $J = 12.0$, 2H). GC-MS (M/Z): 42, 55, 56, 69, 84, 199.

*1-Bromo-4-fluoro-[2,3,5,6-$^2H_4$]benzene (d_4-**3**)*

Bromine (34.84 g, 0.218 mol) in dichloromethane (40 ml) was added dropwise at 18°C to a solution (40 ml) of [2,3,4,5,6-$^2H_5$]fluorobenzene (d_5-**4**, 20 g, 0.2 mol) and 0.6 g $FeCl_3$ over a 60 min period. The mixture was stirred for a further 30 min after which chilled water (60 ml) was added. The organic layer was separated and washed with water (2 × 60 ml), aqueous sodium bisulfite (2 g in 40 ml) and again with water (40 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by atmospheric distillation to yield compound d_4-**3**, 29.87 g (83.4%); colorless oil, b.p. 150–152°C; GC-MS: M/Z 40, 52, 72, 76, 78, 99, 178, 180.

*(4-Fluoro-[2,3,5,6-$^2H_4$]phenyl)pyridin-4-ylmethanol (d_4-**5**)*

A solution of pyridine-4-aldehyde (0.161 mol, 17.19 g) in tetrahydrofuran (50 ml) was added to the Grignard-reagent prepared from d_4-**3** (0.167 mol, 29.87 g) and magnesium turnings (0.164 mol, 3.93 g) in tetrahydrofuran (200 ml) at 20°C. After 10 h stirring, saturated ammonium chloride solution (65 ml) and brine (60 ml) were poured into the reaction mixture, the phases were separated and the tetrahydrofuran solution was dried and concentrated *in vacuo*. The crude product was recrystallized from toluene (80 ml) to give a white solid (d_4-**5**); m.p. 132–134°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.75 (d, $J = 2.7$, 1H), 6.19 (d, $J = 2.7$, 1H), 7.36–7.47 (m, 2H), 8.47–8.52 (m, 2H); IR (KBr pellets, cm^{-1}) ν_{max} 1604, 1420, 1192, 1052, 792, 648.

*4-(4-Fluoro-[2,3,5,6-$^2H_4$]benzyl)piperidine hydrochloride (d_4-**2**.HCl)*

A mixture of 10% Pd/C catalyst (5 g), c. HCl (5 ml) and methanol solution (100 ml) of d_4-**5** (10.35 g, 0.05 mol) was hydrogenated at atmospheric pressure at ambident temperature until equivalent amount of hydrogen gas was consumed. The reaction mixture was warmed up to 60–65°C and, after the consumption of further three equivalents of hydrogen gas, allowed to cool and the catalyst was filtered and the solution concentrated *in vacuo*. Treatment of the residue with diethyl ether (50 ml) gave compound d_4-**2**.HCl in pure form; m.p. 162–164°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.31–1.49 (m, 2H), 1.62–1.86 (m, 3H), 2.52 (d, $J = 7.1$, 2H), 2.70–2.84 (m, 2H), 3.14–3.24 (m, 2H), 9.14 (br. s, 2H); IR (KBr pellets, cm^{-1}) ν_{max} 2920, 1576, 1428, 1312, 1204, 1120. GC-MS of the base d_4-**2**: M/Z 56, 84, 98, 113, 197.

Conclusion

Convenient and generally applicable methods have been developed for the preparation of d_2, d_4 and d_6 isotopomers of 4-(4-fluorobenzyl)piperidines. On the basis of the experimental results, we concluded that the use of both a deuterated acid and alcohol-type solvent are essential in these protocols as

these components are the primer source of deuterium in the H/D exchange reaction.

Acknowledgements

The authors are indebted to Gedeon Richter Ltd. for the financial support.

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