Pd/C-H_2-Catalysed Deuterium Exchange Reaction of the Benzylic Site in D_2O

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Received 10 April 2002

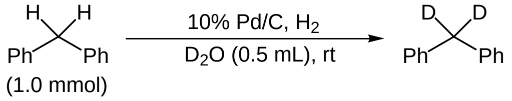
Abstract: Pd/C is found to catalyse efficient and chemoselective exchange of deuterium derived from D_2O with hydrogens on a benzylic carbon in the presence of a catalytic amount of hydrogen at room temperature.

Key words: catalysis, chemoselectivity, deuterium exchange, deuterium labelled compounds, palladium on carbon

Deuterium labelled compounds have been extremely useful in many different branches of science, including analysis of drug metabolism, investigation of reaction mechanisms and kinetics and so on.[1,2] While various methods are available in the literature for the preparation of deuterium labelled compounds,[1] post-synthetic and catalytic displacement of hydrogen bound to the carbon of unlabelled compounds by deuterium is efficient and greatly reduces effort and cost. The catalytic deuterium exchange reaction is an underdeveloped methodology and existing techniques usually utilize acid,[3] base[4] and metal[5–7] catalysed, microwave-enhanced[8] and supercritical[9] exchange reactions. Many such conventional procedures are only applicable to the H-D exchange reactions of the aromatic ring, and few general methods are available for hydrogen bound to the aliphatic carbon.[4,6,7] However, these methods usually require high heat, high pressure, stoichiometric reagents, vast amounts of catalyst, strongly basic or acidic conditions, special apparatus and/or deuterium atmosphere, and some of the reactions achieve only a low degree of deuterium efficiency and selectivity. Hence, the development of new, deuterium-efficient and post-synthetic H-D exchange methods remains a subjects of great interest.

Herein, we describe a distinctly general procedure for the H-D exchange reaction at the benzylic position that operates under mild conditions. Only 10% of the weight of the substrate of 10% Pd/C, which approximately corresponds to 1.6 mol% Pd metal, efficiently catalyses the exchange of the deuterium derived from D_2O as a solvent[10] with a substrate possessing a benzylic position, resulting in chemoselective incorporation of deuterium in the presence of a catalytic amount of hydrogen at room temperature.

Table 1 Assessment of Pd/C-H_2-catalysed Deuterium Exchange Reaction of Diphenylmethane in D_2O[a]



Entry	H_2	Time (d)	D content (%)[b]
1	None[c]	1	0
2 (1st run)	Balloon	1	66
3 (2nd run)[d]	Balloon	1	77
4 (3rd run)[e]	Balloon	1	81
5	Balloon	3	73
6	10 mL	3	95
7	10 mL	5	96

[a] All reactions were carried out under ordinary pressure using 10% Pd/C (10% of the weight of the substrate) in D_2O (99.8% D content, 0.5 mL) at r.t. Unless otherwise noted, commercial diphenylmethane (168 mg, 1.00 mmol) was used as the starting substrate.

[b] Determined by ^{1}H-NMR.

[c] Under atmospheric air.

[d] The 66% deuterated diphenylmethane (the product of entry 2) was used as the starting substrate.

[e] The 77% deuterated diphenylmethane (the product of entry 3) was used as the starting substrate.

The Pd/C-catalysed H-D exchange reaction of diphenylmethane was carried out under several conditions (Table 1). While no exchange was observed in the absence of hydrogen gas (entry 1), hydrogen was found to dramatically activate the reactivity of the Pd/C-catalysed H-D exchange reaction. The initial reaction was carried out using 168 mg (1.00 mmol) of diphenylmethane and 17 mg [10% of the weight of diphenymethane; only 1.7 mg (0.0 16mmol) of Pd metal] of 10% Pd/C in 0.5 mL of D_2O (22.55 mmol) at room temperature under ordinary hydrogen atmosphere using a hydrogen balloon for 1 day. Deuterium incorporation of 66% at the benzylic methylene of diphenylmethane was achieved in one reaction, but the result was less satisfactory (entry 2). With the use of the 66% deuterated product of the first reaction (entry 1) as a substrate for the second H-D exchange reaction, the deuterium content (D content) of the second product was slightly increased to 77% (entry 3) and the third reaction gave 81% deuterated product (entry 4). Furthermore, elongation of the reaction time (3 days) merely leads to minimal increase of the deuterium incorporation (73%,

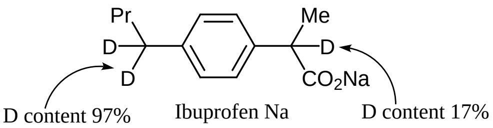
Synlett 2002, No. 7, 01 07 2002. Article Identifier:
1437-2096,E;2002,0,07,1149,1151,ftx,en;Y05502ST.pdf.

ISSN 0936-5214

entry 5). The efficiency of the H-D exchange reaction can be greatly enhanced by reduction in the volume of hydrogen. The exchange reaction proceeded dramatically using only 10 mL of hydrogen (ca. 0.45 mmol; 0.45 equiv vs. diphenylmethane) instead of a hydrogen balloon (ca. 2000 mL) for 3 days at room temperature to provide 1,1-diphenyl-1,1-D$_2$-methane with 95% D content in 88% isolated yield (entry 6). While elongation of the reaction time to 5 days led to no significant change, subsequent experiments were carried out in the presence of 10 mL of hydrogen for 3 days at room temperature.[11]

Table 2 shows the results of H-D exchange reaction of various substrates. The reactions were very clean and no chromatographic separation was required to obtain spectrally pure products. No side products were isolated from any reaction and virtually no competitive deuteration on the aromatic ring was observed. For the substrates in Table 2, methoxy and hydroxy substituents on the aromatic ring or side chain apparently do not have any influence on the course of the H-D exchange reaction (entries 3 and 4). The incorporation of deuterium into the branched benzylic position (methine) also proceeded without any problems (entries 9 and 10). The reaction using 4-ethylbenzoic acid or methyl 4-ethylbenzoate as a substrate gave only moderate D content (entry 5 or 6) while the reaction using 4-ethylbenzoic acid sodium salt gave nearly quantitative D content (entry 7). The failure of 4-ethylbenzoic acid and methyl 4-ethylbenzoate to undergo full labeling may be rationalized by invoking coordination of palladium with the carboxylic acid or ester oxygen leading to a less reactive catalyst (complex).

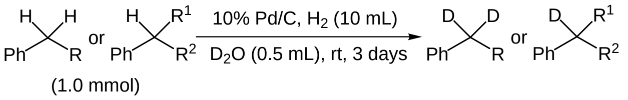
In the same manner, the H-D exchange reaction of Ibuprofen, a nonsteroidal antiinflammatory medicine, was also attempted under the same conditions (Figure). Castell et al. previously reported[12] a base-catalysed deuterium labeling of Ibuprofen using D$_2$O-NaOH under reflux conditions. Although the benzylic methylene of their product was not deuterated, the benzylic methine connected to the carboxylic acid was labelled with ca. 50% D content On the other hand, the benzylic methylene was highly deuterated (97% D content) under our reaction conditions while the deuterium efficiency of the benzylic methine was somehow not attractive (Figure).

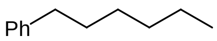
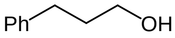
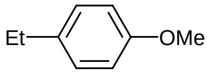
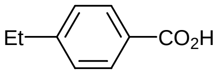
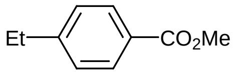
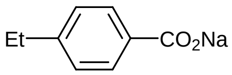
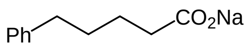
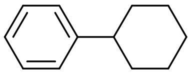


Figure

The reaction mechanism is not clear yet for our specific H-D exchange reaction. It has been proposed that a catalytic amount of hydrogen gas is an obvious activator of the Pd/C-catalysed H-D exchange reaction. Since equilibrium is an apparent state between H-D and D-H exchange, the amount of hydrogen gas is significant for the deuterium efficiency of the product.

Table 2 Results of 10% Pd/C-H$_2$-catalysed Deuterium Exchange Reaction of Benzylic Site in D$_2$O[a]



Entry	Substrate	D content (%)[b]	Yield (%)[c]
1	$\mathrm{PhCH_2Ph}$	95	88
2		97	73[d]
3		92	98
4		96	40[d]
5		61	>99
6		74	74[d]
7		98	>99
8		90	97
9		98	55[d]
10	PhCH(Me)Et	93	20[d]

[a] All reactions were carried out under ordinary hydrogen pressure (10 mL) using 10% Pd/C (10% of the weight of the substrate) in D$_2$O (99.8% D content, 0.5 mL) at r.t. for 3 d.

[b] Determined by ^{1}H-NMR.

[c] Yields refer to those of pure isolated products, fully characterized by spectral and analytical data.

[d] The low isolated yield of the deuterated product is due to low boiling point and the volatile nature.

In summary, we have developed a mild and totally catalytic one-pot method for the chemoselective H-D exchange reaction at the benzylic position in very high D content. Less than 2 mol% of palladium metal in the presence of a catalytic amount of hydrogen can carry out efficient H-D exchange at room temperature under ordinary pressure. The reaction is general for a variety of substrates. The simplicity of this method makes it an attractive new tool for the post-synthetic deuterium labeling to a wide variety of disciplines.

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(10) The reaction in CD_3OD also gave similar result and the detail will be reported in due course.

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