Short Note

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A convenient method for palladium-catalyzed reductive deuteration of organic substrates using deuterated hypophosphite in D_2O

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A convenient method for the deuteration of organic substrates using deuterated hypophosphite as the deuterium source was investigated. Transfer deuteration of organic substrates, such as aromatic halides, alkenes, alkynes, epoxides, and *O*-benzyl derivatives, in the presence of palladium on carbon in deuterium oxide proceeded efficiently to give the corresponding deuterated products in excellent yields with high deuterium contents.

Keywords: deuterated hypophosphite; transfer deuteration; palladium catalyst; deuterium oxide

Introduction

The synthesis of deuterium-labeled compounds has gained importance in recent years because of their increasing applications, such as mechanistic probes for chemical[1] and biological[2] reactions, in structural analyses using NMR spectroscopy,[3] as internal standards for mass spectrometry,[4] and for improving the metabolic stability of drugs.[5] Catalytic hydrogenation or hydrogenolysis using deuterium gas is one of the most widely used methods for introducing deuterium atoms into organic molecules.[6] However, deuterium gas is very expensive, and its availability is often restricted by export controls. Therefore, *in situ* generation of deuterium gas or transfer deuteration using readily available deuterated compounds is preferable. In this context, Sajiki and coworkers developed an excellent deuteration protocol based on a Pd/C-catalyzed H_2–D_2 exchange reaction.[7]

On the other hand, we previously reported the palladium-catalyzed transfer hydrogenation of organic substrates using hypophosphite in water containing a nonionic surfactant.[8] In this work, we investigated a convenient method for the deuteration of organic substrates using deuterated hypophosphite as a deuterium source. There have been limited examples of the use of deuterated hypophosphorous acid and its salts for this application. Oshima and coworkers reported the D_3PO_2-mediated deuteration of organic halides via a radical chain process,[9] which was applied to the radical deuteration of a dithiocarbonate group by Grainger and coworkers.[10] Reductive deuteration using deuterium iodide catalytically generated from D_3PO_2 and a small amount of I_2 in AcOD was also reported by Fry and coworkers.[11]

Results and discussion

Although a deuterated hypophosphorous acid solution is commercially available, the reagent is very expensive. Therefore, the preparation of deuterated hypophosphite (D_2PO_2) via an H–D exchange reaction of unlabeled hypophosphite was examined. It was reported that the direct H–D exchange of NaH_2PO_2 in D_2O is impossible[12a] and can be achieved only after acidification with DCl.[9] In the present study, we performed the direct H–D exchange of a commercially available aqueous 50% H_3PO_2 by mixing the solution with excess D_2O.[12] H–D exchange at the phosphorous atom was monitored using ^{31}P NMR spectroscopy and was found not to instantaneously reach equilibrium. Consequently, the mixture was left to stand for 1 h, concentrated, and a new solution was prepared with fresh D_2O. Three cycles of solvent evaporation and treatment with fresh D_2O were required to increase the deuterium content of the D_3PO_2 to a level sufficient for deuteration reactions.

When a solution of 4-chlorobenzoic acid in D_2O was treated with D_3PO_2 in the presence of Na_2CO_3 and a catalytic amount of 10% Pd/C (approximately 10 wt %) at 50 °C for 1.5 h, complete conversion to [4-D]benzoic acid was observed. After a typical workup, the product was isolated in pure form in 94% yield with a 95% deuterium content, which was ascertained by ^1H NMR spectroscopy (Table 1, Entry 1). The reaction at room temperature was not complete within 1.5 h and resulted in 74% conversion (data not shown). The addition of Na_2CO_3 was necessary to neutralize the D_3PO_2 and liberated hydrogen chloride. In this case, the base also assisted the dissolution of the weakly acidic substrate in the reaction media, leading to efficient conversion. When the amount of Na_2CO_3 was decreased, a higher reaction temperature or longer reaction time was required to complete the dechlorination.

The reductive deuteration of other aromatic halides was similarly performed, and the results are compiled in Table 1. Deuterogenolysis of 4-bromobenzoic acid efficiently produced [4-D]benzoic acid in 93% yield (Entry 2); however, the reaction

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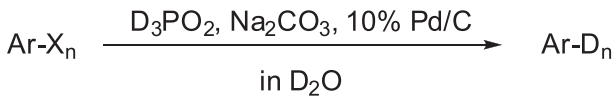
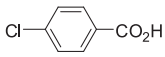
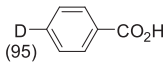
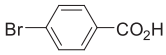
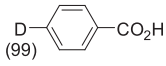
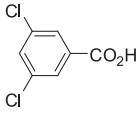
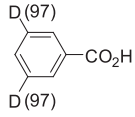
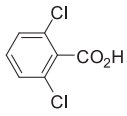
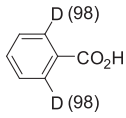
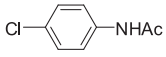
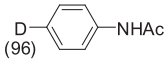
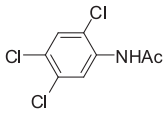
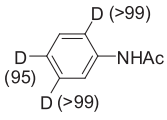
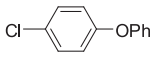
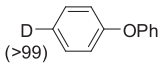
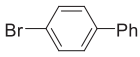
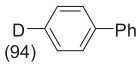
Table 1. Deuterogenolysis of aromatic halides



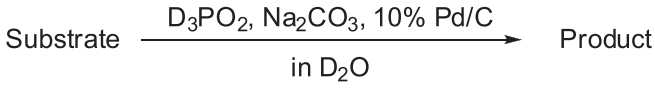
Entry	Substrate	D_3PO_2 (equiv.)	Na_2CO_3 (equiv.)	Temp (°C)	Time (h)	Product (%D[a])	Yield (%[b])
1		1	2	50	1.5		94
2		1	2	50	1.5		93
3		2	3	50	Overnight		94
4		2	3	50	Overnight		98
5		1	2	50	Overnight		93
6		3	4	Reflux	1.5		94
7		3	3	50	Overnight		99
8		2	2	Reflux	Overnight		93

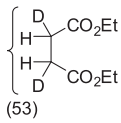
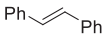
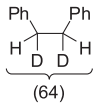
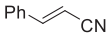
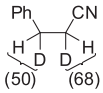
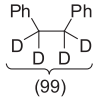
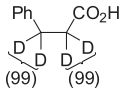
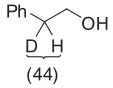
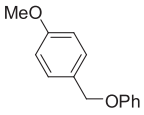
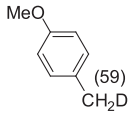
[a]Data in parentheses are deuterium contents determined by ^{1}H NMR spectroscopy. While the main labeling sites are as indicated, smaller amounts of deuterium could be present in other molecular sites.
[b]Isolated yield.

did not proceed with 4-iodobenzoic acid. Similar treatment of 3,5-dichlorobenzoic acid and sterically hindered 2,6-dichloro derivative gave [3,5-D_2]benzoic acid and [2,6-D_2]benzoic acid in 94% and 98% yields, respectively (Entries 3 and 4). Reactions of 4-chloroacetanilide and 2,4,5-trichloroacetanilide also proceeded smoothly to afford [4-D]acetanilide and [2,4,5-D_3]acetanilide in 93% and 94% yields, respectively (Entries 5 and 6); however, the latter required a higher reaction temperature. Deuteration of lipophilic haloaromatics, such as 4-chlorodiphenyl ether and 4-bromobiphenyl, could be achieved using an excess of the reagents or at an elevated reaction temperature, giving [4-D]-diphenyl ether and [4-D]biphenyl in 99% and 93% yields, respectively (Entries 7 and 8). In all cases, efficient and regioselective deuterium incorporation was observed.

To extend the substrate scope, deuteration of alkenes, alkynes, epoxides, and *O*-benzyl derivatives was investigated, and the results are listed in Table 2. Transfer deuterogenation of diethyl maleate proceeded efficiently at room temperature to give dideuterated succinate in 93% yield (Entry 1), whereas the reaction of stilbene and cinnamonitrile required refluxing overnight to obtain satisfactory results (99% yield for both 1,2-diphenyl[1,2-D_2]ethane and 3-phenyl[2,3-D_2]propionitrile) (Entries

Table 2. Reductive deuteration of various substrates



Entry	Substrate	D_3PO_2 (equiv.)	Na_2CO_3 (equiv.)	Temp (°C)	Time (h)	Product (%D[a])	Yield (%[b])
1		2	2	Room temperature	Overnight	 (53)	93
2		1	1	Reflux	Overnight	 (64)	99
3		2	2	Reflux	Overnight	 (50) (68)	99
4		5	5	50	Overnight	 (99)	quant
5		3	3	50	Overnight	 (99) (99)	99
6		3	3	50	Overnight	 (44)	quant
7		2	2	Reflux	1.5	 (59)	quant

[a]Data in parentheses are deuterium contents determined by ^1H NMR spectroscopy. While the main labeling sites are as indicated, smaller amounts of deuterium could be present in other molecular sites.
[b]Isolated yield.

2 and 3, respectively). However, in these cases, it should be noted that over-deuteration occurred to some extent. The H–D exchange reaction at the benzylic position in the presence of activated palladium was well studied.[13]

The deuterogenation of acetylenic compounds, such as diphenylacetylene and phenylpropiolic acid at 50 °C, afforded the corresponding tetradeuterated products in nearly quantitative yields with sufficient deuterium contents (Entries 4 and 5, respectively), although the former water-insoluble substrate required the use of a large excess of the reagents.

Upon exposure to the established reaction conditions, styrene oxide underwent reductive ring opening to furnish 2-phenylethanol with one deuterium atom at the benzylic position in quantitative yield (Entry 6). The treatment of the *O*-benzyl derivative, 4-methoxybenzyl phenyl ether, under the same reaction conditions gave 4-[D]methylanisole in 99% yield (Entry 7), although a considerable amount of over-deuteration at the benzylic position was observed.[13]

Conclusions

We have established a convenient and cost-effective method for the preparation of deuterium-labeled organic compounds without the use of expensive deuterium gas. We describe the

simple and direct preparation of a D_3PO_2 solution from commercially available aqueous 50% H_3PO_2 and the reductive deuteration of various aromatic halides, alkenes, alkynes, epoxides, and *O*-benzyl derivatives. The deuteration reaction is catalyzed by Pd/C and performed in D_2O in the presence of Na_2CO_3 as a neutralization agent. The products are obtained in high yields with high deuterium contents; and functional groups such as amides, esters, and nitriles are tolerated.

Experimental section

Melting points were determined using a Yamato MP-21 melting point apparatus (Yamato Scientific Co., Tokyo, Japan) in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury plus 400 spectrometer (Agilent technologies, Santa Clara, USA) at 400 and 100 MHz, respectively. All of the chemical shifts are reported as δ values (ppm) relative to the residual solvent signal ($\delta_H = 7.26$ for $CDCl_3$ and $\delta_H = 2.50$ for DMSO-d_6) or the central line of $CDCl_3$ ($\delta_C = 77.0$) and DMSO-d_6 ($\delta_C = 39.5$); *J* values are expressed in hertz.

All reagents and solvents were purchased from commercial suppliers and used as received.

Preparation of 1-M D_3PO_2 in D_2O

A commercially available 50% aqueous H_3PO_2 solution (2.67 g, 20.2 mmol) was diluted with D_2O (10 ml), and the mixture was left to stand for 1 h at room temperature. The solvent was then removed by evaporation, and fresh D_2O (10 ml) was added. The cycle of solvent evaporation and treatment with D_2O (10 ml) was repeated for a total of three times. The obtained 1-M D_2O solution of D_3PO_2 was directly used for deuteration reactions or stored for several days after neutralization with Na_2CO_3 (1 equiv.).

General procedure for reductive deuteration

A solution of D_3PO_2 (1 mmol) in D_2O (4 ml) was added dropwise to a mixture of 4-chlorobenzoic acid (157 mg, 1.00 mmol), Na_2CO_3 (214 mg, 2.02 mmol), and 10% Pd/C (17.7 mg) in D_2O (6 ml) over a period of 30 min at 50 °C. After stirring for an additional 1 h, the reaction mixture was cooled and acidified with 1-M HCl, and $CHCl_3$ was added as the extraction solvent. The mixture was then filtered through Hyflo Super Cel to remove the catalyst, and the organic phase was separated, dried over $MgSO_4$, and concentrated to give [4-D]benzoic acid (116 mg, 0.942 mmol) in 94% yield as a white solid, mp 119–121 °C (lit,[14] mp 122.4 °C). ^{1}H NMR ($CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 128.4, 129.3, 130.2, 133.5 (t, *J* = 24.1 Hz), 172.0.

[3,5-D_2]benzoic acid

Isolated in 94% yield as a white solid, mp 119–121 °C (lit,[14] mp 122.4 °C). ^{1}H NMR ($CDCl_3$) δ 7.62 (br s, 1H), 8.13 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 128.2 (t, *J* = 24.8 Hz), 129.2, 130.1, 133.6, 171.9.

[2,6-D_2]benzoic acid

Isolated in 98% yield as a white solid, mp 120–121 °C (lit,[14] mp 122.4 °C). ^{1}H NMR ($CDCl_3$) δ 7.49 (br d, *J* = 7.4 Hz, 2H), 7.63 (br t, *J* = 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 128.4, 129.1, 129.9 (t, *J* = 25.5 Hz), 133.8, 172.3.

[4-D]acetanilide

Isolated in 93% yield as a white solid, mp 110–112 °C (lit,[15] mp 113–115 °C). ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 3H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 9.93 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.1, 119.2, 122.9 (t, *J* = 23.6 Hz), 128.7, 139.4, 168.6.

[2,4,5-D_3]acetanilide

Isolated in 94% yield as a white solid, mp 109–111 °C (lit,[15] mp 113–115 °C). ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 7.27 (s, 1H), 7.53 (s, 1H), 9.92 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.0, 118.6 (t, *J* = 24.4 Hz), 118.8, 122.5 (t, *J* = 24.9 Hz), 128.2 (t, *J* = 24.0 Hz), 128.4, 139.2, 168.2.

[4-D]diphenyl ether

Isolated in 99% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.03 (d, *J* = 7.8 Hz, 4H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.33–7.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 118.9, 122.9 (t, *J* = 24.7 Hz), 123.2, 129.6, 129.7, 157.2.

[4-D]biphenyl

Isolated in 93% yield as a white solid, mp 67–68 °C (lit,[16] mp 69–71 °C). ^{1}H NMR ($CDCl_3$) δ 7.36 (t, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 127.1, 127.2, 128.6, 128.7, 141.2. The deuterated carbon signal was not observed because of signal overlap.

Diethyl [2,3-D_2]succinate

Isolated in 93% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 6H), 2.57 (br s, 1.88H), 4.12 (q, *J* = 7.1 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 14.1, 28.8 (t, *J* = 19.7 Hz), 60.6, 172.3.

1,2-Diphenyl[1,2-D_2]ethane

Isolated in 93% yield as a white solid, mp 48–49 °C (lit,[17] mp 52.0–52.5 °C). ^{1}H NMR ($CDCl_3$) δ 7.20–7.23 (m, 6H), 7.28–7.32 (m, 4H), 2.92 (br s, 1.44H). ^{13}C NMR ($CDCl_3$) δ 37.5 (t, *J* = 19.5 Hz), 125.9, 128.3, 128.4, 141.7.

3-Phenyl[2,3-D_2]propionitrile

Isolated in 99% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.60 (br s, 0.64 H), 2.93 (br s, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.9 (t, *J* = 20.8 Hz), 31.0 (t, *J* = 19.9 Hz), 119.1, 127.1, 128.1, 128.7, 137.9.

1,2-Diphenyl[1,1,2,2-D_4]ethane

Isolated in 93% yield as a white solid, mp 51–52 °C (lit,[17] mp 52.0–52.5 °C). ^{1}H NMR ($CDCl_3$) δ 7.19–7.23 (m, 6H), 7.27–7.32 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 37.0 (quint, *J* = 19.7 Hz), 125.9, 128.3, 128.4, 141.6.

3-Phenyl[2,2,3,3-D_4]propanoic acid

Isolated in 93% yield as a white solid, mp 46–47 °C (lit,[18] mp 47–48 °C). ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 3H), 7.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 29.7 (quint, *J* = 19.6 Hz), 34.9 (quint, *J* = 19.6 Hz), 126.3, 128.2, 128.5, 140.0, 179.5.

2-Phenyl[2-D]ethanol

Isolated in quantitative yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.86 (m, 1.12H), 3.85 (br d, *J* = 6.2 Hz, 2H), 7.24 (m, 3H), 7.32 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 38.7 (t, *J* = 19.7 Hz), 63.4, 126.3, 128.4, 128.9, 138.4.

4-[D]methylanisole

Isolated in quantitative yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.28 (m, 1.23H), 3.79 (s, 3H), 6.81 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.1 (t, *J* = 19.1 Hz), 55.2, 113.6, 129.7, 129.8, 157.4.

Conflict of Interest

The authors do not report any conflict of interest.

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