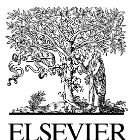

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General method of obtaining deuterium-labeled heterocyclic compounds using neutral D_2O with heterogeneous Pd/C

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Abstract—A protocol of a versatile H–D exchange reaction of heterocyclic compounds catalyzed by heterogeneous Pd/C in D_2O is described. The reaction of various nitrogen-containing heterocycles with 10% Pd/C (10 wt % of the substrate) under hydrogen atmosphere in D_2O as a deuterium source at 110–180 °C for 24 h afforded the corresponding deuterated compounds with satisfactory efficiency of deuteration in moderate to excellent isolated yields. Furthermore, the Pd/C–H_2–D_2O system can be extended to the direct deuteration of biologically active compounds such as sulfamethazine, which is used as a synthetic antibacterial drug for fat stocks and would be applied as a general method for the preparation of the standard materials for the analysis of residual chemicals in foods and so on.
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1. Introduction

Deuterium-labeled compounds have found extensive applications in such research areas as pharmaceutical, bioanalytical, biological, and environmental chemistry to analyze drug metabolism mechanisms, residual agrochemicals in foods using mass spectrometry (MS), structure of biomolecules, and so on.[1,2] Access to the deuterium-labeled compounds has been facilitated by the adoption of the post-synthetic H–D exchange reaction instead of the laborious and costly multi-step synthetic processes starting from originally deuterium-labeled small synthons. Although a huge number of post-synthetic H–D exchange reactions have been reported in the literature, they usually require high temperature and pressure,[3] stoichiometric reagents,[4] expensive or inaccessible reagents,[5] strong bases or acids,[2e,3a–c,3g–j,6] special apparatus,[2e,6f] and/or deuterium atmosphere.[4a–4c,5a,7] Furthermore, some of the methods involve structural transformations[3m,3q,8] or a low degree of deuterium-efficiency.[6c,7g,7m,9] Hence, the development of new, post-synthetic, and deuterium-efficient H–D exchange reactions is still a challenging subject.

We recently developed a regioselective H–D exchange reaction at the benzylic positions using Pd/C as a catalyst in deuterium oxide under hydrogen atmosphere (Pd/C–H_2–D_2O system) at room temperature,[10] and found that the application of heat could promote the H–D exchange reaction not only at the benzylic positions, but also on the non-activated carbons.[11] Since heterocyclic compounds such as indole, pyridine, pyrimidine, and quinoline ring systems are often seen in natural products, pharmaceuticals, veterinary medicines, agrochemicals, and so on, the deuterated heterocycles are of interest as building blocks of such bioactive materials needed as internal standards in GC–MS or LC–MS assays. Taking into consideration the establishment of a general deuteration method of heterocycles as the core nuclei of biologically active compounds using the Pd/C–H_2–D_2O system, we studied the deuteration of a wide range of heterocyclic substrates.

2. Results and discussion

A variety of heterocyclic substrates were heated at 110–180 °C (bath temperature) in the presence of a catalytic amount of 10% Pd/C (10% of the weight of the substrate, Aldrich) in D_2O. The reaction was carried out under ca. 1 atm H_2 pressure and reflux conditions (110–160 °C of the heating head or bath temperature) using ChemiStation™ or reflux condenser (Dimroth type); the inner reaction temperature was at ca. 104 °C (boiling point of D_2O). When a sealed tube was employed as a reaction vessel, the reaction mixture was stirred at 160 or 180 °C under <2.5 atm H_2 pressure (the inner gas pressure was measured by a pressure gauge). The deuterated positions and deuterium-efficiency of the obtained products were determined by ^{1}H NMR (DSS, *p*-anisic acid or dioxane as an internal standard), ^{2}H NMR, and mass spectra. It is noteworthy that water

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Table 1. H–D exchange reaction of pyridine derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

$$\text{Substrate} \xrightarrow[\text{D}_2\text{O, 24 h}]{\text{10\% Pd/C, H}_2} \text{Product-}d_n$$

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1[e,f]	110	97; 81, 81; 99, 99; N	83[k]
2[f]	160	NH_2; 98, 98; 98, 98; N	100
3[g]	180	98; 98, 98; 98; N; NH_2	100
4[g]	180	98; 99, 98; 99; N; NH_2	69
5[g]	180	98, 98; 98; 98; N; NH_2	91
6[g]	180	98; 50, 98; 98; N; NH_2	51
7[g,h]	180	98; 91, 98; 98; N; NH_2	49
8[g]	180	98; 90, 94; 99; N; OH	99
9[f]	160	99; 71, 98; 99; N; OH	100
10	160	97, 31, 5, 26[j]; N, 26[j]; 97, 31, 5, 26[j]	88
11	160	97, 74, 74, 97; N, N; 97, 74, 74, 97	84
12	160	97, 96, 96, 97; 97, 97; 97, N, N, 97	80
13	160	96, 87, 96, 96, 87, 96; 87; N, 87, 87, N; 96, 96	97
14[f]	160	83; 64, 5; 91; N; COOH	99
15[f,i]	160	0; 37, COOH; 98, 69; N	98
16[f]	160	9; 44, $CONH_2$; 99, 97; N	100

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL) for 24 h.
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^{1}H NMR.
[d] Isolated yield, unless otherwise stated.
[e] Substrate (1 mmol) was used in D_2O (4 mL).
[f] The reaction was carried out using the ChemiStation™.
[g] Substrate (500 mg) was used in D_2O (17 mL).
[h] Pd/C [10% (10 wt % of the substrate)] and Pt/C [5% (20 wt % of the substrate)] were used.
[i] Substrate (0.25 mmol) was used in D_2O (1 mL).
[j] Indicated as the average D content.
[k] Determined by GC.

(D_2O)-insoluble substrates are also acceptable for this H–D exchange reaction.

2.1. H–D exchange reaction of pyridine derivatives

As shown in Table 1, the H–D exchange reaction proceeded well on the pyridine nucleus to give the desired multi-deuterated products in satisfactory deuterium-efficiency and isolated yields. In particular, aminopyridine and hydroxypyridine derivatives showed remarkably excellent deuterium-efficiency at 160–180 °C (entries 2–5, 7, and 8). It is noteworthy to mention that the 5-position of 2-amino-6-methylpyridine where the H–D exchange was inefficient only with Pd/C could be deuterated easily by using 5% Pt/C together with 10% Pd/C (entries 6 vs 7). In general, higher efficiency of deuteration at the positions adjacent to the nitrogen atoms on the pyridine rings was observed rather than at other positions. On the other hand, lower incorporation of deuterium at the neighboring positions of a carbon substituent (*ortho*-positions to the substituent) such as CH_2, CO_2H, and $CONH_2$ (entries 10–16) was observed presumably due to steric hindrance. Moreover, as shown in entries 15 and 16, the H–D exchange reaction efficiently proceeded even at the *ortho*-position to the substituent if the position was adjacent to the nitrogen atom in the pyridine ring. It is apparent that the nitrogen atom profoundly influences the deuteration reaction using the Pd/C–H_2–D_2O system. It is expected that the Pd metal can be located in the vicinity of the nitrogen atom of the pyridine ring since Pd metal has a quite high affinity for the nitrogen lone pair. This could be the reason why the 2-position of the pyridine ring was effectively deuterated.

2.2. H–D exchange reaction of indole derivatives

Excellent deuterium incorporation was observed at the methyl substituents as well as at the positions adjacent to the nitrogen atoms on the indole, azaindole, benzimidazole, and quinoline rings, while the efficiency of the deuteration at the neighboring positions of the methyl groups was usually

Table 2. H–D exchange reaction of indole, azaindole, benzimidazole, quinoline derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

$$\text{Substrate} \xrightarrow[\text{D}_2\text{O, 24 h}]{\text{10\% Pd/C, H}_2} \text{Product-}d_n$$

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160	85, 95, 65, 97, 70, 97, N, H	80
2	160	96, 26, 87[h], 87[h], 85, 97, N, H	94
3[e,f]	160	99, 53, 89, 98, 49, 96, N, H	98
4	160	95, 92, 71[i], 96, 71[i], N, H, 96	91
5[f]	140	77, 14, 67, 95, 75, 0, N, 86	95
6	160	HO, 71, 51, 98[j], 97, 98[j], N, H	98
7[f]	160	25, D_3CO, 55, 24, 98, 47, 98, N, H	99
8[e]	160	70, 92, 4, 70[k], 44, 54, 55, 70[k], N, H, 4, 70[k]	96
9	160	97, 81, 65, 98, 98, N, N, H	99
10	160	93, 97, N, 97, 23, 97, N, H	99
11[g]	180	63, 99, 93, 99, 99, 99, 98, N	83

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^{1}H NMR.
[d] Isolated yield.
[e] Substrate (0.25 mmol) was used in D_2O (1 mL).
[f] The reaction was carried out using the ChemiStation™.
[g] Substrate (500 mg) was used in D_2O (17 mL).
[h–k] Indicated as the average D content.

low compared to the position adjacent to the hydroxyl group (Table 2, entries 1–7 and 9–11). In addition, the 7-position of the indole and benzimidazole rings, which are regarded as the *ortho*-positions to the amino groups of the benzene rings, were deuterated efficiently (entries 1–3, 6, 7, and 10). On the other hand, no incorporation was found at the 7-position when 1,2-dimethylindole was used as a substrate (entry 5). The above results also demonstrate that this deuterating method is highly affected by both electronic and steric factors.

2.3. H–D exchange reaction of pyrimidine and imidazole derivatives

When 2-mercaptopyrimidine was used as a substrate, no H–D exchange reaction was observed and dimerization proceeded as a result of the formation of a disulfide linkage (Table 3, entry 1). Probably because the sulfur atom acted as a catalytic poison, the H–D exchange reaction was completely suppressed. On the other hand, when the thiol moiety was replaced with an amino group, the deuteration, especially at the 4- and 6-positions, proceeded smoothly with high efficiency (entry 2). When two methyl groups were introduced to the 4- and 6-positions of 2-aminopyrimidine, no deuterium incorporation at the 5-position was observed, whereas the 5-position, which was adjacent to the hydroxyl group, was deuterated quantitatively when 2-amino-4-hydroxy-6-methylpyrimidine was used as

Table 3. H–D exchange reaction of pyrimidine, pyrazole derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

$$\text{Substrate} \xrightarrow[\text{D}_2\text{O, 24 h}]{\text{10\% Pd/C, H}_2} \text{Product-}d_n$$

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160	0, 0, N, 0, N, SH	NA[h]
2	160	99, 56, N, 99, N, NH_2	99
3[e]	110	CD_3 95, 0, N, 95, D_3C, N, NH_2	100
4[e]	110	OH, 96, N, 96, D_3C, N, NH_2	100
5[f]	160	97, CD_3 97[g], 97[g], D_3C, N, N, H	81

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out using the ChemiStation™ under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^{1}H NMR.
[d] Isolated yield.
[e] The mixture was heated under reflux for 24 h.
[f] The reaction was carried out in a sealed tube.
[g] Indicated as the average D content.
[h] Disulfide of 2-mercaptopyrimidine was formed as a product.

a substrate (entries 3 vs 4). Furthermore, the use of 3,5-dimethylpyrazole led to almost quantitative deuterium incorporation at the 4-position (entry 5). These results suggest that introduction of an appropriate substituent into the substrate may enable us to establish a regioselective H–D exchange reaction by taking advantage of the steric hindrance and/or neighboring effect of the substituent.

2.4. H–D exchange reaction of biologically active compounds

The applications of stable isotope (SI)-labeled compounds for clinical pharmacokinetic studies and the analysis of residual agrochemicals in the environment have rapidly increased in recent years. Since the chemical properties of SI-labeled compounds are similar to those of non-labeled compounds, SI-labeled compounds are the most valuable tracers for these studies and analyses using GC–MS or LC–MS. In spite of the usefulness of SI-labeled isotope tracers, there are often problems incurred in getting a desired labeled tracer because of the difficulties in the synthesis of SI-labeled compounds. Heating a variety of biologically active compounds in the Pd/C–H_2–D_2O system led to efficient introduction of deuterium atoms. The results are summarized in Table 4.

The H–D exchange reactions at the methyl groups in sulfamethazine and nalidixic acid, both of which are antibacterial agents, proceeded effectively (Table 4, entries 1 and 2), but the efficiency of the deuteration at the methyl group of antipirine, an analgesic agent, was seriously reduced (entry 4). Instead, antipirine was regioselectively deuterated on the pyrazolidinone ring (entry 4). When allopurinol, an antiurolithic agent, was used as a substrate, the H–D exchange reaction proceeded effectively (entry 3).

Table 4. H–D exchange reaction of bioactive compounds in D_2O catalyzed by 10% Pd/C–H_2[a]

$$\text{Substrate} \xrightarrow[D_2O,\ 24\ h]{10\%\ Pd/C,\ H_2} \text{Product-}d_n$$

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160	H_2N–C₆H₄–SO_2NH–pyrimidine: 25, 25 / 5, 5 (benzene ring); 96, 96 (methyls); 5 (pyrimidine ring)	97
2	160	93 (methyl); 63, 53 (ring); 0 (N-CH₂), 20 (CH₃); 0 (ring C-H next to COOH)	96
3	160	OH; 97 (pyrazole C-H); 87 (pyrimidine C-H)	99
4[e]	160	Phenyl: 0, 2, 2, 0, 0; N–CH₃: 0; 91 (ring C-H); 9 (C-CH₃)	98

[a] Substrate (0.25 mmol) was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (1 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^1H NMR.
[d] Isolated yield.
[e] The reaction was carried out using the ChemiStation™.

Deuterated drugs often have different actions from the protonated forms in vivo.[12] Some deuterated drugs show different transport processes. Since many deuterated drugs are more resistant to metabolic changes by the isotope effect derived from bulky deuterium, it can be expected that deuterium-labeled drugs demonstrate the feasibility of developing new sustained-release dosage by virtue of the isotope effect. The deuteration method we demonstrated in this paper could be a general method for the preparation of new prolonged drugs as well as the standard materials for the studies of metabolism and the analysis of residual chemicals in the environment.

3. Conclusion

In summary, we have developed an efficient and extensive deuterium incorporation method using a heterogeneous Pd/C–H_2–D_2O system for a wide range of substrates including bioactive substances in moderate to excellent deuterium-efficiency. The results presented here provide a deuterium gas-free, totally catalytic, and post-synthetic deuterium labeling method in D_2O medium. The simplicity of this method makes it an attractive new tool for medicinal, analytical, and organic chemists.

4. Experimental

4.1. General

All the substances examined in this study were obtained commercially and were used without further purification. Pd/C (10%) was purchased from Aldrich Chemical Co. and deuterium oxide (99.9% isotopic purity) was purchased from Cambridge Isotope Laboratories.

ChemiStation™ is a personal organic synthesizer from TOKYO RIKAKIKAI CO., LTD (EYELA). ^1H and ^2H NMR spectra were recorded on a JEOL AL-400 spectrometer or JEOL EX-400 spectrometer (^1H NMR: 400 MHz, ^2H NMR: 61 MHz). Chemical shifts (δ) are given in parts per million relative to residual solvent or internal standard (3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS), *p*-anisic acid, or dioxane). EI and FAB mass spectra were recorded on a JEOL JMS-SX102A spectrometer. GC spectra were recorded on a SHIMADZU GC-17A spectrometer. Preparative thin-layer chromatography was performed using Merk PLC plate (silica gel 60 F254).

4.2. General procedure for H–D exchanges

Method A: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C using the ChemiStation™ under H_2 atmosphere for

24 h. After cooling, the reaction mixture was diluted with methanol (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with methanol (2×10 mL) and the filtrate was concentrated in vacuo.

Method B: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C using the ChemiStation™ under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford deuterated forms.

Method C: A substrate (500 mg, 4.6–5.3 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with methanol (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with methanol (2×5 mL) and the filtrate was concentrated in vacuo.

Method D: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford deuterated forms.

Method E: A substrate (0.5 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL) were heated under reflux for 24 h. After cooling, the reaction mixture was diluted with methanol (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with methanol (2×10 mL) and the filtrate was concentrated in vacuo.

4.2.1. [^{2}H]-Pyridine (Table 1, entry 1). A mixture of pyridine (80 μL, 1.0 mmol) and 10% Pd/C (7.9 mg, 10 wt % of the substrate) in D_2O (4 mL) was refluxed under H_2 atmosphere for 24 h. After cooling, the reaction mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The yield was determined by GC analysis of the crude filtrate (83% yield). Isotope distribution (EIMS): 1% d_1, 2% d_2, 10% d_3, 30% d_4, 53% d_5. ^{1}H NMR (D_2O, DSS as an internal standard) δ 8.51 (s, 0.03H), 7.83 (s, 0.03H), 7.45 (s, 0.38H).

4.2.2. [^{2}H]-4-Aminopyridine (Table 1, entry 2). Method A, 100% yield as a colorless solid. Isotope distribution (EIMS): 4% d_2, 10% d_3, 79% d_4, 7% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 7.97 (s, 0.03H), 6.46 (s, 0.04H), 5.96 (br s, 2H). ^{2}H NMR (DMSO) δ 7.96 (br s), 6.45 (br s).

4.2.3. [^{2}H]-2-Aminopyridine (Table 1, entry 3). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-aminopyridine-d_n as a colorless solid (100% yield). Isotope distribution (EIMS): 1% d_1, 2% d_2, 9% d_3, 82% d_4, 6% d_5. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 8.02 (s, 0.02H), 7.41 (s, 0.02H), 6.61 (s, 0.02H), 6.49 (s, 0.02H), 4.44 (br s, 2H). ^{2}H NMR (CH_2Cl_2) δ 8.06 (br s), 7.45 (br s), 6.66 (br s), 6.54 (br s).

4.2.4. [^{2}H]-2-Amino-4-methylpyridine (Table 1, entry 4). 2-Amino-4-methylpyridine (500 mg, 4.6 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with ethyl acetate (2×5 mL). The combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-4-methylpyridine-d_n as a colorless solid (69% yield). Isotope distribution (EIMS): 1% d_3, 2% d_4, 13% d_5, 76% d_6, 6% d_7, 2% d_8. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 7.93 (s, 0.01H), 6.48 (s, 0.01H), 6.32 (s, 0.02H), 4.35 (br s, 2H), 2.20 (s, 0.07H). ^{2}H NMR ($CHCl_3$) δ 7.94 (br s), 6.53 (br s), 6.37 (br s), 2.20 (br s).

4.2.5. [^{2}H]-2-Amino-5-methylpyridine (Table 1, entry 5). Method C, 91% yield as a pale yellow crystal. Isotope distribution (EIMS): 1% d_2, 3% d_3, 18% d_4, 12% d_5, 61% d_6, 5% d_7. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 7.85 (s, 0.02H), 7.25 (s, 0.02H), 6.43 (s, 0.02H), 4.32 (br s, 2H), 2.12 (s, 0.07H). ^{2}H NMR (CH_2Cl_2) δ 7.89 (br s), 7.30 (br s), 6.48 (br s), 2.14 (br s).

4.2.6. [^{2}H]-2-Amino-6-methylpyridine (Table 1, entry 6). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-6-methylpyridine-d_n as a pale yellow solid (51% yield). Isotope distribution (EIMS): 1% d_3, 7% d_4, 48% d_5, 41% d_6, 3% d_7. ^{1}H NMR (CD_3OD, dioxane as an internal standard) δ 7.33 (s, 0.02H), 6.45 (s, 0.50H), 6.40 (s, 0.02H), 2.26 (s, 0.07H). ^{2}H NMR (CH_3OH) δ 7.35 (br s), 6.47 (br s), 6.40 (br s), 2.25 (br s).

4.2.7. [^{2}H]-2-Amino-6-methylpyridine (Table 1, entry 7). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-6-methylpyridine-d_n as a pale yellow solid (49% yield). Isotope distribution (EIMS): 3% d_4, 17% d_5, 75% d_6, 5% d_7. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 7.31 (s, 0.02H), 6.50 (s, 0.09H), 6.30 (s, 0.02H), 4.39 (br s, 2H), 2.34 (s, 0.06H). ^{2}H NMR ($CHCl_3$) δ 7.35 (br s), 6.53 (br s), 6.34 (br s), 2.34 (br s).

4.2.8. [^{2}H]-2-Hydroxy-4-methylpyridine (Table 1, entry 8). Method C, 99% yield as a colorless solid. Isotope distribution (EIMS): 3% d_4, 19% d_5, 72% d_6, 6% d_7. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 13.03 (br s,

1H), 7.24 (s, 0.01H), 6.31 (s, 0.06H), 6.11 (s, 0.10H), 2.17 (s, 0.06H). ^{2}H NMR (CH_2Cl_2) δ 7.28 (br s), 6.35 (br s), 6.17 (br s), 2.18 (br s).

4.2.9. [^{2}H]-2-Hydroxy-6-methylpyridine (Table 1, entry 9). Method A. Boiling ethanol was used instead of methanol, 100% yield as an off-white solid. Isotope distribution (EIMS): 3% d_4, 35% d_5, 56% d_6, 6% d_7. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.6 (br s, 1H), 7.32 (s, 0.01H), 6.13 (s, 0.02H), 5.97 (s, 0.29H), 2.14 (s, 0.04H). ^{2}H NMR (DMSO) δ 7.32 (br s), 6.12 (br s), 5.97 (br s), 2.09 (br s).

4.2.10. [^{2}H]-4-Phenylpyridine (Table 1, entry 10). Method D, 88% yield as a colorless solid. Isotope distribution (EIMS): 5% d_0, 8% d_1, 24% d_2, 30% d_3, 21% d_4, 9% d_5, 3% d_6. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.67–8.65 (m, 0.07H), 7.84 (d, J=7.24 Hz, 1.91H), 7.74 (s, 1.38H), 7.58–7.51 (m, 2.23H). ^{2}H NMR (DMSO) δ 8.67 (br s), 7.73 (br s), 7.55 (br s).

4.2.11. [^{2}H]-4,4′-Bipyridyl (Table 1, entry 11). Method D. Ethyl acetate was used instead of diethyl ether, 84% yield as a colorless solid. Isotope distribution (EIMS): 1% d_3, 6% d_4, 14% d_5, 25% d_6, 30% d_7, 24% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.76 (s, 0.13H), 7.86 (s, 1.05H). ^{2}H NMR (DMSO) δ 8.74 (br s), 7.86 (br s).

4.2.12. [^{2}H]-2,2′-Bipyridyl (Table 1, entry 12). Method D. Ethyl acetate was used instead of diethyl ether, 80% yield as a colorless solid. Isotope distribution (EIMS): 1% d_4, 6% d_5, 19% d_6, 21% d_7, 53% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.72 (s, 0.07H), 8.42 (s, 0.09H), 7.98 (s, 0.06H), 7.48 (s, 0.06H). ^{2}H NMR (DMSO) δ 8.72 (br s), 8.42 (br s), 7.98 (br s), 7.49 (br s).

4.2.13. [^{2}H]-1,3-Di(4-pyridyl)propane (Table 1, entry 13). Method D. Ethyl acetate was used instead of diethyl ether, 97% yield as a colorless solid. Isotope distribution (EIMS): 3% d_{10}, 8% d_{11}, 23% d_{12}, 36% d_{13}, 30% d_{14}. ^{1}H NMR (DMSO-d_6, p-anisic acid as an internal standard) δ 8.40 (s, 0.15H), 7.29 (s, 0.51H), 2.68 (s, 0.15H), 2.00–1.96 (m, 0.27H). ^{2}H NMR (DMSO) δ 8.42 (br s), 7.31 (br s), 2.65 (br s), 1.93 (br s).

4.2.14. [^{2}H]-Picolinic acid (Table 1, entry 14). Method A, 99% yield as a colorless solid. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.73 (s, 0.09H), 8.07 (s, 0.88H), 8.03–8.01 (m, 0.24H), 7.64 (s, 0.36H). ^{2}H NMR (DMSO) δ 8.72 (br s), 8.00 (br s), 7.64 (br s).

4.2.15. [^{2}H]-Nicotinic acid (Table 1, entry 15). Method A. Boiling water was used instead of methanol, 98% yield as a colorless solid. Isotope distribution (EIMS): 1% d_0, 15% d_1, 46% d_2, 34% d_3, 4% d_4. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 13.4 (br, 1H), 9.10 (s, 0.31H), 8.79 (s, 0.02H), 8.30–8.28 (m, 1H), 7.57 (d, J=7.82 Hz, 0.63H). ^{2}H NMR (DMSO) δ 9.08 (br s), 8.81 (br s), 7.57 (br s).

4.2.16. [^{2}H]-Nicotinamide (Table 1, entry 16). Method A. Boiling ethanol was used instead of methanol, 100% yield as a colorless solid. Isotope distribution (EIMS): 2% d_1, 38% d_2, 50% d_3, 9% d_4, 1% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 9.05 (s, 0.03H), 8.72 (s, 0.01H), 8.24–8.22 (m, 0.91H), 8.19 (br s, 1H), 7.62 (br s, 1H), 7.52 (d, J=7.81 Hz, 0.56H). ^{2}H NMR (DMSO) δ 9.05 (br s), 8.72 (br s), 8.23 (br s), 7.53 (br s).

4.2.17. [^{2}H]-Indole (Table 2, entry 1). Method D, 80% yield as a pale red solid. Isotope distribution (EIMS): 1% d_2, 3% d_3, 10% d_4, 27% d_5, 36% d_6, 23% d_7. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.52–7.50 (m, 0.15H), 7.36–7.32 (m, 0.03H), 7.19 (s, 0.03H), 7.05 (s, 0.30H), 6.96 (s, 0.35H), 6.40 (s, 0.05H). ^{2}H NMR (CH_3OH) δ 7.56 (br s), 7.39 (br s), 7.23 (br s), 7.10 (br s), 7.01 (br s), 6.46 (br s).

4.2.18. [^{2}H]-3-Methylindole (Table 2, entry 2). Method D, 94% yield as a pale red solid. Isotope distribution (EIMS): 1% d_1, 1% d_2, 5% d_3, 16% d_4, 29% d_5, 23% d_6, 16% d_7, 7% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.46 (s, 0.74H), 7.30 (s, 0.03H), 7.06 (s, 0.15H), 6.97 (s, 0.26H), 2.26 (s, 0.11H). ^{2}H NMR (CH_3OH) δ 7.31 (br s), 7.07 (br s), 6.98 (br s), 2.23 (br s).

4.2.19. [^{2}H]-5-Methylindole (Table 2, entry 3). Method B, 98% yield as a pale red solid. Isotope distribution (EIMS): 1% d_1, 1% d_2, 4% d_3, 14% d_4, 30% d_5, 24% d_6, 23% d_7, 3% d_8. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.29 (s, 0.45H), 7.22–7.20 (m, 0.04H), 7.14 (s, 0.02H), 6.89 (s, 0.51H), 6.30 (s, 0.11H), 2.33 (s, 0.04H). ^{2}H NMR (CH_3OH) δ 7.27 (br s), 7.18 (br s), 6.35 (br s), 2.33 (br s).

4.2.20. [^{2}H]-7-Methylindole (Table 2, entry 4). Method D, 91% yield as an off-white solid. Isotope distribution (EIMS): 1% d_2, 2% d_3, 9% d_4, 26% d_5, 25% d_6, 23% d_7, 11% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.35 (s, 0.05H), 7.19 (s, 0.04H), 6.86 (s, 0.58H), 6.40 (s, 0.08H), 2.48–2.42 (m, 0.12H). ^{2}H NMR (CH_3OH) δ 7.39 (br s), 7.22 (br s), 6.92 (br s), 6.45 (br s), 2.43 (br s).

4.2.21. [^{2}H]-1,2-Dimethylindole (Table 2, entry 5). Method B, 95% yield as a wine-red solid. Isotope distribution (EIMS): 6% d_4, 9% d_5, 14% d_6, 21% d_7, 23% d_8, 16% d_9, 11% d_{10}. ^{1}H NMR (DMSO-d_6, p-anisic acid as an internal standard) δ 7.40–7.39 (m, 0.23H), 7.33 (s, 1H), 7.05–7.02 (m, 0.25H), 6.94 (s, 0.33H), 6.17 (s, 0.86H), 3.64–3.59 (m, 0.43H), 2.35 (s, 0.14H). ^{2}H NMR (DMSO) δ 7.43 (br s), 7.07 (br s), 6.98 (br s), 6.22 (br s), 3.60 (br s), 2.34 (br s).

4.2.22. [^{2}H]-5-Hydroxyindole (Table 2, entry 6). Method D, 98% yield as a brown solid. Isotope distribution (EIMS): 3% d_2, 18% d_3, 38% d_4, 33% d_5, 7% d_6, 1% d_7. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 10.8 (br s, 1H), 8.60 (s, 1H), 7.22 (s, 0.02H), 7.19 (s, 0.02H), 6.86 (s, 0.29H), 6.61 (s, 0.03H), 6.23 (s, 0.49H). ^{2}H NMR (DMSO) δ 7.21 (br s), 6.87 (br s), 6.62 (br s), 6.26 (br s).

4.2.23. [^{2}H]-5-Methoxylindole (Table 2, entry 7). Method B, 99% yield as a brown solid. Isotope distribution (EIMS): 12% d_3, 34% d_4, 27% d_5, 17% d_6, 7% d_7, 2% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.23 (s, 0.02H), 7.16 (s, 0.02H), 7.03 (s, 0.45H), 6.73 (s, 0.53H), 6.33 (s, 0.76H), 3.78 (s, 2.26H). ^{2}H NMR (CH_3OH) δ 7.26 (br s), 7.18 (br s), 7.06 (br s), 6.76 (br s), 6.37 (br s), 3.89–3.67 (m).

4.2.24. [^{2}H]-2-Phenylindole (Table 2, entry 8). Method D, 96% yield as a yellow solid. Isotope distribution (EIMS): 2% d_0, 5% d_1, 9% d_2, 11% d_3, 12% d_4, 13% d_5, 16% d_6, 16% d_7, 12% d_8, 3% d_9, 1% d_{10}. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.5 (br s, 1H), 7.89 (s, 1.93H), 7.56–7.54 (m, 0.31H), 7.50–7.41 (m, 0.92H), 7.33 (s, 0.46H), 7.12–7.10 (m, 0.45H), 7.04–7.00 (m, 0.57H), 6.92 (s, 0.08H). ^{2}H NMR (DMSO) δ 7.48 (br s), 6.98 (br).

4.2.25. [^{2}H]-7-Azaindole (Table 2, entry 9). Method A. The reaction was carried out in a sealed tube, 99% yield as a pale yellow solid. Isotope distribution (EIMS): 1% d_1, 2% d_2, 12% d_3, 41% d_4, 39% d_5, 5% d_6. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.6 (br s, 1H), 8.24–8.20 (m, 0.02H), 7.98–7.96 (m, 0.03H), 7.47 (s, 0.08H), 7.06 (s, 0.35H), 6.46 (s, 0.19H). ^{2}H NMR (CH_3OH) δ 8.20 (br s), 7.95 (br s), 7.46 (br s), 7.05 (br s), 6.44 (br s).

4.2.26. [^{2}H]-5-Methylbenzimidazole (Table 2, entry 10). Method A. The reaction was carried out in a sealed tube, 99% yield as a colorless solid. Isotope distribution (EIMS): 2% d_2, 11% d_3, 28% d_4, 24% d_5, 27% d_6, 7% d_7, 1% d_8. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 8.06 (s, 0.03H), 7.48–7.46 (m, 0.03H), 7.38 (s, 0.03H), 7.08–7.07 (m, 0.77H), 2.44–2.40 (m, 0.22H). ^{2}H NMR (CH_3OH) δ 8.07 (br s), 7.47 (br s), 7.40 (br s), 7.09 (br s), 2.38 (br s).

4.2.27. [^{2}H]-Quinoline (Table 2, entry 11). Quinoline (500 mg, 3.9 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with ethyl acetate (2×5 mL). The combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate–hexane, 1:4 v/v) gave quinoline-d_n as pale yellow oil (83% yield). Isotope distribution (EIMS): 1% d_2, 1% d_3, 5% d_4, 12% d_5, 39% d_6, 42% d_7. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 8.93 (s, 0.01H), 8.17 (s, 0.02H), 8.12 (s, 0.01H), 7.83 (s, 0.37H), 7.73 (s, 0.01H), 7.58–7.52 (m, 0.07H), 7.40 (s, 0.01H). ^{2}H NMR ($CHCl_3$) δ 9.01 (br s), 8.26 (br s), 7.92 (br s), 7.82 (br s), 7.65 (br s), 7.47 (br s).

4.2.28. [^{2}H]-2-Aminopyrimidine (Table 3, entry 2). Method A, 99% yield as a colorless solid. Isotope distribution (EIMS): 4% d_1, 31% d_2, 52% d_3, 13% d_4. ^{1}H NMR (CD_3OD, *p*-anisic acid as an internal standard) δ 8.16 (s, 0.03H), 6.54 (s, 0.42H). ^{2}H NMR (CH_3OH) δ 8.26 (br s), 6.67 (br s).

4.2.29. [^{2}H]-2-Amino-4,6-dimethylpyrimidine (Table 3, entry 3). Method E, 100% yield as a colorless solid. Isotope distribution (EIMS): 3% d_4, 16% d_5, 72% d_6, 8% d_7, 1% d_8. ^{1}H NMR (CD_3OD, *p*-anisic acid as an internal standard) δ 6.37 (s, 1H), 2.17–2.13 (m, 0.28H). ^{2}H NMR (CH_3OH) δ 2.22 (br s).

4.2.30. [^{2}H]-2-Amino-4-hydroxy-6-methylpyrimidine (Table 3, entry 4). Method E, 100% yield as a colorless solid. Isotope distribution (EIMS): 1% d_2, 14% d_3, 77% d_4, 8% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 10.7 (br s, 1H), 6.49 (br s, 2H), 5.40 (s, 0.04H), 1.97 (s, 0.11H). ^{2}H NMR (DMSO) δ 5.40 (br s), 1.92 (br s).

4.2.31. [^{2}H]-3,5-Dimethylpyrazole (Table 3, entry 5). Method D, 81% yield as a yellow solid. Isotope distribution (EIMS): 1% d_1, 1% d_3, 7% d_4, 34% d_5, 13% d_6, 41% d_7, 3% d_8. ^{1}H NMR (DMSO-d_6, *p*-anisic acid as an internal standard) δ 12.3 (br s, 1H), 5.72 (s, 0.03H), 2.07 (s, 0.17H). ^{2}H NMR (DMSO) δ 5.75 (br s), 2.06 (br s).

4.2.32. [^{2}H]-Sulfamethazine (Table 4, entry 1). Method A. The reaction was carried out in a sealed tube, 97% yield as a colorless solid. Isotope distribution (FABMS, Gly): 1% d_2, 1% d_3, 2% d_4, 9% d_5, 29% d_6, 33% d_7, 17% d_8, 6% d_9, 2% d_{10}. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.74–7.71 (m, 1.89H), 6.67 (s, 0.95H), 6.61 (d, J=9.28 Hz, 1.51H), 2.25 (s, 0.22H). ^{2}H NMR (CH_3OH) δ 6.66 (br s), 2.24 (br s).

4.2.33. [^{2}H]-Nalidixic acid (Table 4, entry 2). Method D. Chloroform was used instead of diethyl ether, 96% yield as a colorless solid. Isotope distribution (EIMS): 4% d_0, 3% d_1, 7% d_2, 12% d_3, 18% d_4, 28% d_5, 16% d_6, 8% d_7, 4% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 9.23 (s, 1H), 8.66–8.64 (m, 0.47H), 7.64–7.63 (m, 0.37H), 4.67 (q, J=7.08 Hz, 2H), 2.71 (s, 0.22H), 1.45 (t, J=7.08 Hz, 2.40H). ^{2}H NMR (DMSO) δ 8.62 (br s), 7.63 (br s), 2.65 (br s), 1.36 (br s).

4.2.34. [^{2}H]-Allopurinol (Table 4, entry 3). Allopurinol (68.1 mg, 0.5 mmol) and 10% Pd/C (6.8 mg, 10 wt % of the substrate) in D_2O (2 mL) were stirred at 160 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with boiling water (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with boiling water (2×10 mL) and the filtrate was concentrated in vacuo, 99% yield as an off-white solid. Isotope distribution (EIMS): 8% d_0, 19% d_1, 65% d_2, 8% d_3. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 13.7 (br, 1H), 12.1 (br, 1H), 8.15 (br s, 0.13H), 8.03 (s, 0.03H). ^{2}H NMR (DMSO-d_6) δ 8.11 (br s), 8.00 (br s).

4.2.35. [^{2}H]-Antipirine (Table 4, entry 4). Method A, 98% yield as a pale yellow solid. Isotope distribution (EIMS): 17% d_0, 65% d_1, 15% d_2, 5% d_3. ^{1}H NMR (DMSO-d_6, *p*-anisic acid as an internal standard) δ 7.48–7.44 (m, 1.97H), 7.31–7.24 (m, 3H), 5.27 (s, 0.09H), 3.03 (s, 3H), 2.22 (s, 2.73H). ^{2}H NMR (DMSO-d_6) δ 5.31 (br s), 2.17 (br s).

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