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ARTICLE

Highly selective H/D exchange reaction of 1,4-dihydropyridines

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Herein, we report a simple, economical, and effective acid-mediated method for the in situ deuteration of Hantzsch esters and their 4-substituted derivatives, including some drugs that constitute important calcium channel blockers effective for hypertension treatment. Hydrogen isotope exchange occurred selectively at α-alkyl C-H bonds in the 2,6-substituents.

Introduction

Hydrogen isotope incorporation is widely used in numerous fields, such as organic synthesis[1] and tracer[2] and mechanistic studies.[3] Application of hydrogen-isotope-labelled molecules can facilitate absorption, distribution, metabolism, and excretion (ADME) studies.[4] Introducing hydrogen isotopes into active drug molecules may alter their pharmacokinetic and pharmacodynamic properties, and deuterated drugs may even be directly applied in clinical pharmacology.[5] This field has attracted more attention since the first deuterated drug, Austedo, was approved for use in the U.S.A., and thus hydrogen isotope exchange (HIE) can be expected to show greater potential in drug discovery and development.[6]

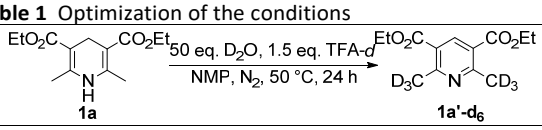
In the past 20 years, numerous methods have been developed to obtain hydrogen-isotope-labelled compounds. Metal catalysts, such as those based on Ir,[7] Co,[8] Fe,[9] Pd,[10] and Ru,[11] have been applied to accomplish HIE with high selectivity and efficiency. Recently, metal-free hydrogen-isotope-labelling processes have also been extensively developed.[12] Acid-mediated labelling processes are the traditional way for achieving HIE, and they are still attractive for incorporating hydrogen isotopes into electronically activated aromatic and unsaturated molecules.[13]

Herein, we describe a simple and cost-effective acid-mediated method for introducing deuterium into 1,4-dihydropyridines and their derivatives in excellent yield and with high incorporation. Compared with the reported method,[14] we did a lot of optimization to reduce the amount of reagents and improve efficiency. Moreover, we expanded the range of substrates, and have explored the mechanism.

Results and discussion

At the beginning of our research, we found that Hantzsch esters were deuterated in an unexpected manner. LC-MS analysis showed products with a distribution of masses. ^{1}H NMR analysis showed that some of the reactant was oxidized and that deuterium was incorporated into the methyl groups at the 2- and 6-positions of the 1,4-dihydropyridine. It should be noted that mainly the substrate **1a** and the corresponding oxidized product **1a'** remained in this reaction system. The remaining unoxidized **1a-d$_6$** had the same D incorporation as the oxidized product **1a'-d$_6$**, as confirmed by NMR spectroscopy. The oxidation of **1a** involved unknown hydrogen transfer under the heating and acidic conditions. More details were discussed in

Table 1 Optimization of the conditions



1a **1a'-d$_6$**

Entry	Variations	D incorporation (%)[b]
1	none[a]	85[c]
2	no TFA-*d*	0
3	TFA	63
4	3 eq. TFA-*d*	82
5	RT	38
6	70 °C	75
7	air	45
8	DMF	74
9	DMA	83
10	MeOH	15
11	MeOD	75

[a] Standard conditions: **1a** (0.2 mmol, 50.7 mg), D_2O (10 mmol, 181 μL), TFA-*d* (0.3 mmol, 23 μL), *N*-methylpyrrolidone (NMP, 2 mL), N_2, 50 °C for 24 h. [b] D incorporation determined by ^{1}H NMR spectroscopy. [c] Average of two parallel reactions.

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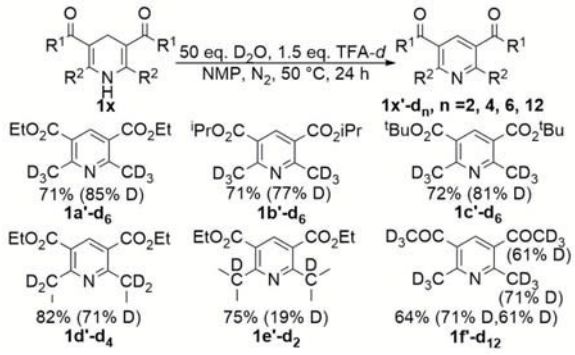
ESI. As shown in Table 1, we performed a series of experiments aimed at optimizing the D incorporation. An oxidized product was obtained with 85% D incorporation at the methyl groups in the 2- and 6-positions under the standard conditions (50 eq. D_2O, 1.5 eq. TFA-*d*, 0.1 M substrate in NMP, N_2, 50 °C, 24 h). Absolutely no deuteration occurred when TFA-*d* was omitted, showing acid to be critical for D incorporation. The D incorporation decreased to 63% when TFA-*d* was replaced by non-deuterated TFA, that is relying on the decreased ratio of D:H in the reaction mixture. D incorporation did not increase when the amount of TFA-*d* increased to 3 equivalents. The effect of temperature on the reaction was also investigated. At room temperature, the D incorporation decreased to 38%, and at 70 °C it was slightly lower at 75%. If the reaction system was not degassed or exposed to air, the D incorporation decreased to 45%. In examining various solvents, we found that non-protic solvents worked much better than protic solvents. D incorporations of 74%, 83%, 15%, and 75% were achieved in media of DMF, DMAc, CH_3OH, and CH_3OD, respectively. To confirm the relationship between oxidation and deuteration, we performed the experiment under standard conditions with **1a'** prepared previously,[15] whereupon 85% D incorporation showed the deuteration and oxidation processes to be independent of one another. During these optimization processes, we also found that the D incorporation did not change when the deuterated product was immersed in chloroform-*d* for 3 days. (see the ESI for more details)

Having optimized the conditions, we applied derivatives of **1a** in the reaction system. As shown in Scheme 1, we first changed the alkyl groups of the 3,5-ester substituents from ethyl to isopropyl and *tert*-butyl, whereupon 77% and 81% D incorporations in the 2,6-methyl groups were obtained, respectively (Scheme 2, **1b'-d$_6$** and **1c'-d$_6$**). Considering the different reactivities of methyl, ethyl, and isopropyl groups, we obtained 71% D incorporation for a 2° carbon centre, whereas for a 3° carbon atom only 18% D incorporation was achieved (Scheme 2, **1d'-d$_4$** and **1e'-d$_2$**). This could be attributed to the greater steric hindrance of the 3° carbon centre, which might hamper the HIE reaction. And this result would contribute to the discussion of mechanism. When the 3,5-ester groups were substituted with acetyl groups, all four methyl groups showed deuterium incorporation (**1f'-d$_{12}$**). The D incorporations were 71% in the 2,6-methyl groups and 61% in the 3,5-substituents. HIE was thus faster at an α-position with respect to nitrogen than at an α-position with respect to carbonyl.

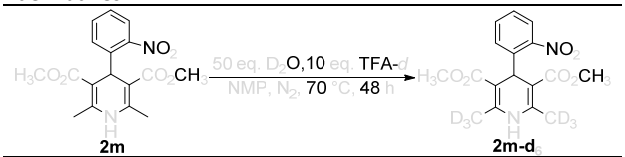


Scheme 1 Substrate scope of Hantzsch ester derivatives.

Following these experiments, we tried to expand the substrate scope to 4-substituted 1,4-dihydropyridines. Numerous 4-substituted 1,4-dihydropyridine pharmaceutical molecules have proved effective as calcium channel blockers and are used for hypertension treatment, such as Nifedipine, Nisodipine, Nimodipine, Lacidipine, and Amlodipine.[16] First, we examined the reaction with Nifedipine under the standard conditions in Scheme 1. To our delight, only little oxidation occurred. However, ^{1}H NMR analysis of the purified product revealed only 24% D incorporation. We then performed a series of experiments to optimize the D incorporation (Table 2). We increased the amount of TFA-*d* and allowed the reaction to proceed for 48 h at 70 °C. The D incorporation reached a peak value of 80% (an average of two parallel reactions) when 10 eq. of TFA-*d* was used. It was confirmed that no D incorporation occurred in the absence of acid. We then varied the number of equivalents of D_2O. Without D_2O, 15% D could still be incorporated. Less D_2O led to lower D content, but more D_2O did not result in a better D incorporation. Considering the amount and the cost of TFA-*d* used in the reaction system, we examined some other cheaper acids. The strong Lewis acid $BF_3{\cdot}OEt_2$ was found to behave well, affording 76% D incorporation. And 68% D was incorporated while TfOH was used. Finally, we investigated the effect of time and extended the deuteration process to about 150 h, but the D content of the product did not rise beyond 80%. (more details are provided in the ESI)

Having optimized the reaction conditions, we then applied them to different 4-substituted 1,4-dihydropyridines (Scheme 2). With a phenyl substituent at the 4-position (**2a-d$_6$**), the D incorporation was 77% under the standard conditions in Table 2. A product with 77% D content (**2b-d$_6$**) was obtained with electron-withdrawing group 2-bromophenyl substituent at the 4-position. With electron-donating groups such as furyl and thienyl at the 4-position (**2d-d$_7$** and **2e-d$_6$**),

Table 2 Optimization of the conditions for 4-substituted DHP derivatives



Entry	Variations	D incorporation (%)[b]
1	1.5 eq. TFA-*d*, 50 °C, 24 h	24
2	6 eq. TFA-*d*	74
3	none[a]	80[c]
4	no TFA-*d*	0
5	no D_2O	15
6	100 eq. D_2O	76
7	TFA	71
8	TfOH	68
9	$BF_3{\cdot}OEt_2$	76
10	150 h	79

[a] Standard conditions: **2m** (0.2 mmol, 69.3 mg), D_2O (10 mmol, 181 μL), TFA-*d* (2 mmol, 154 μL), NMP (2 mL), N_2, 70 °C for 48 h. [b] D incorporation determined by ^{1}H NMR spectroscopy. [c] Average of two parallel reactions.

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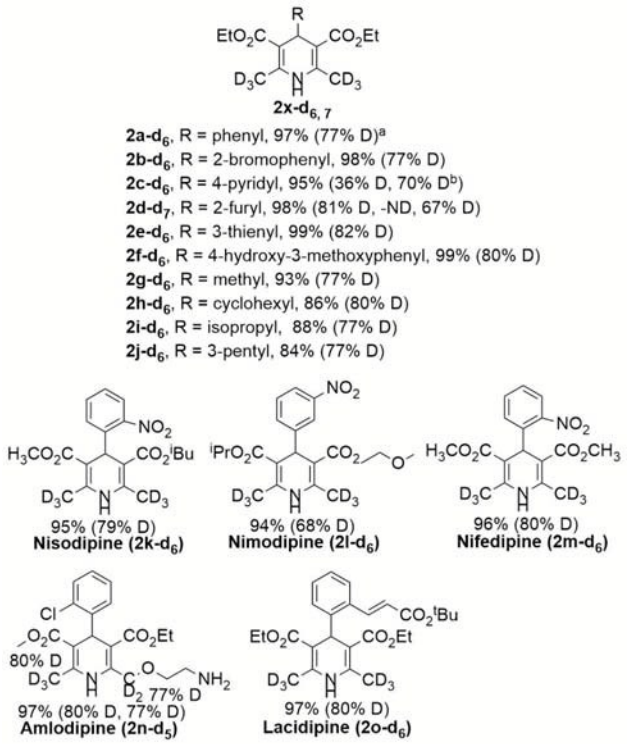
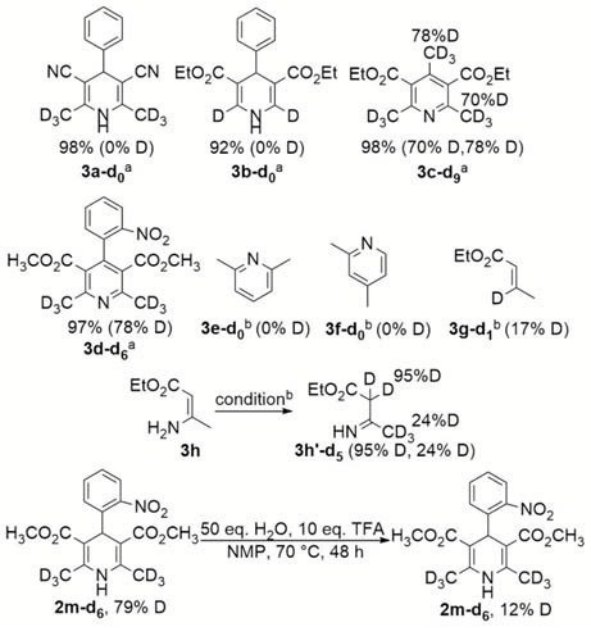


Scheme 2 Deuteration of 4-substituted 1,4-dihydropyridines. [a] 3 eq. TFA-*d* was used. [b] 20 eq. $BF_3{\cdot}OEt_2$ was used.

products with 81% and 82% D incorporation were isolated. With a pyridyl group at the 4-position, however, the D incorporation decreased to 36%. Presumably, the basic pyridyl moiety consumed some active protons or deuterons. Using 20 equivalents of $BF_3{\cdot}OEt_2$ in place of TFA-*d* resulted in 70% D content in the isolated product (**2c- d_6**). With 4-hydroxy3-methoxyphenyl substituents at the 4-position, the isolated products had 80% D incorporation (**2f-d_6**). We then investigated the effects of alkyl substituents. With a methyl group, we obtained a product with 77% D content (**2g-d_6**). Cyclohexyl-, isopropyl-, and 3-pentyl-substituted 1,4-dihydropyridines all served as good radical precursors,[17] and products with 80%, 77%, and 77% D isotope purity were isolated, respectively (**2h-d_6**, **2i-d_6**, and **2j-d_6**). Next, we performed deuteration experiments on the important pharmaceutical molecules Nisodipine, Nimodipine, Amlodipine, and Lacidipine. The first three of these molecules had asymmetric substituent patterns on the pyridine ring. Varying the alkyl groups in the 3,5-positions did not affect the D content, 80% deuterium-labelled Nisodipine (**2k-d_6**) was obtained. With 2-methoxyethyl acetate at the 3-position and a *meta*-nitrophenyl group at the 4-position of Nimodipine (**2l-d_6**), the D incorporation decreased slightly to 68%. For Amlodipine, 80% D incorporation occurred at the methyl group in the 6-position, while 77% D incorporation occurred in the methylene unit at the 2-position (**2n-d_5**). *tert*- Butyl could also be tolerated under these conditions, with 80% D incorporation and very little deprotection after reaction for 48 h (**2o-d_6**). Interestingly, the secondary amino group of most of the 4-substituted 1,4-dihydropyridines was not deuterated after purification, but it was 67% deuterated with a 2-furyl group in the 4-



Scheme 3 Control experiments. [a] Standard conditions as in Table 2. [b] Standard conditions as in Table 1 using CH_2Cl_2 as solvent.

position (**2d-d_7**). As yet, we are unable to explain this phenomenon. All of the deuterated 4-substituted 1,4-dihydropyridines in Scheme 2 were isolated in excellent yields.

We also performed some control experiments with a view to explaining the HIE mechanism in this reaction system (Scheme 3). Replacing the ester groups in the 3,5-positions with cyano groups (**3a-d_0**) or removing the methyl group at the 2,6-positions (**3b-d_0**) led to absolutely no D incorporation. We oxidized **2g** and **2m** to obtain the corresponding pyridines **3c** and **3d** using Pd/C.[15] Under the conditions in Scheme 2, **3d** was deuterated at the same position with a similar D content (**3d-d_6**, 78%). For **3c**, all three methyl groups directly linked to the pyridyl cycle were deuterated simultaneously, although the 78%D content of the methyl group in the 4-position was slightly higher than the 70% D content of the methyl groups in the 2,6-positions (**3c-d_9**). The position between the two ester groups may have been activated for faster HIE. We also tried to deuterate 2,6- and 2,4-lutidines, but without success (**3e-d_0** and **3f-d_0**). No significant deuteration occurred at any methyl group of ethyl (*E*)-but-2-enoate (**3g-d_1**, 17%). However, the situation was very different when an amino group was present at the 3-position (**3h**). Evidently, **3h** underwent enamine exchange and existed in the imine form in the presence of TFA. The α- methylene unit of the imine was 95% deuterated, with 21% D incorporation at the α-methyl group (**3h'-d_5**). Finally, we carried out an experiment using 79% D content **2m-d_6** under the standard conditions in Scheme 2, with non-deuterated reagents (TFA and H_2O). After 48 h, the D content at the 2,6-methyl groups decreased to 12%. A C-D bond is more stable than a C-H bond,[18] but the HIE reaction in this acidic system was evidently reversible. Thus, it is not difficult to understand why deuteration could not be forced to completion.

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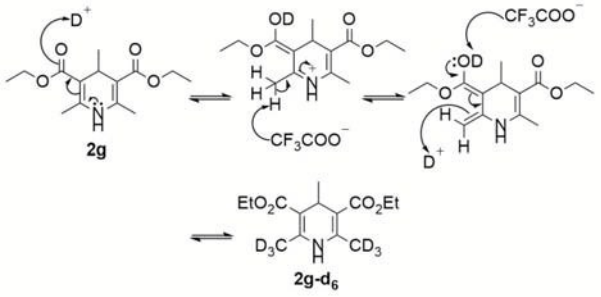

Scheme 4 Proposed mechanism.

From the above experimental results, it was clear that carbonyl or ester groups in the 3,5-positions of 1,4- dihydropyridines directed deuteration towards alkyl groups at the 2,6-positions. Our protocol is also suitable for the corresponding pyridines. Deuteration is not possible without a Brønsted or Lewis acid. The electron-donating or -withdrawing properties of substituents at the 4-position had little effect HIE carbon centres. On the basis of these observations, an acid-promoted enol interconversion and enamine exchange is proposed in Scheme 4. The reaction proceeds to the right under acidic and heating conditions. A study of the detailed reaction mechanism, including how oxygen affected deuteration, is now in progress in our laboratory.

Experimental

Materials and methods

All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was performed using 200-300 mesh silica gels. ^{1}H and ^{13}C NMR spectra were acquired on 400 and 500 MHz Bruker NMR instruments. NMR chemical shifts were reported in ppm and were referenced to TMS (δ = 0.00 ppm, ^{1}H NMR) or the residual solvent peak for $CDCl_3$ (δ = 7.26 ppm, ^{1}H NMR; δ = 77.16 ppm, ^{13}C NMR). Following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are reported in Hertz.

Analytical LC-MS were performed to determine the distribution of hydrogen isotopes of the products on a Shimadzu LC-MS 2020 system equipped with Hedera C18 column (2.1 x 100 mm, 3 μm; heater set on 40 °C) involved a mobile phase of 0.1% formic acid (FA) in water (solvent A) and 0.1% formic acid (FA) in acetonitrile (solvent B) at a flow rate of 0.3 mL/min. All of the samples were performed over the same gredient: from 15 to 55% B in 3 min, then from 55 to 95% B in 7 min, and 95% B for 5 min, 0.1% FA, λ = 254 nm.

General procedure 1 for HIE reactions. To a 10 mL Schlenk tube with a magnetic bar was added 1,4-dihydropyridines (0.2 mmol), D_2O (10 mmol, 181 μL), TFA-*d* (23 μL, 0.3 mmol (or 154 μL, 2 mmol)) and NMP (2 mL). The solution was freezed in liquid nitrogen, then the vessel was evacuated and backfilled with nitrogen following by being warmed to room temperature. The operation was repeated for 3 cycles. The resulting mixture was stirred at 50 °C (or 70 °C) for 24 h (or 48 h), cooled to room temperature, diluted with EA and then washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was further purified by silica gel chromatography. Hydrogen isotope distribution of the products was determined by LC-MS. ^{1}H NMR was performed to determine deuterium incorporation.

Diethyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1a'-d_6). **1a** (50.7 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain **1a'-d_6** as a white solid (36.5 mg, 0.142 mmol, 71%, 85% D). The same result was obtained as **1a'** (50.3 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 4H), 2.82 - 2.76 (m, 0.9H), 1.39 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 162.3, 141.0, 123.2, 61.5, 24.9, 24.8, 24.7, 24.5, 24.4, 24.3, 24.2, 24.1, 14.4.

Diisopropyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1b'-d_6). **1b** (56.3 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain **1b'-d_6** as a white solid (40.4 mg, 0.142mmol, 71%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 5.24 (hept, *J* = 6.3 Hz, 2H), 2.82 - 2.76 (m, 1.4H), 1.37 (d, *J* = 6.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 161.8, 140.9, 123.8, 69.2, 24.9, 24.8, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2, 22.0.

Di-tert-butyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1c'-d_6). **1c** (61.8 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain **1c'-d_6** as a white solid (44.8 mg, 0.144 mmol, 72%, 81% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 2.79 - 2.74 (m, 1.2H), 1.59 (d, *J* = 1.1 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 161.2, 140.9, 124.8, 82.2, 28.3, 25.0, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2.

Diethyl 2,6-bis(ethyl-1,1-d2)pyridine-3,5-dicarboxylate (1d'-d_4). **1d** (28.1 mg, 0.1 mmol) and TFA-*d* (12 μL, 0.150 mmol) were used according to general procedure 1 to obtain **1d'-d_4** as a pale yellow solid (23.2 mg, 0.082 mmol, 82%, 71% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 4H), 3.22-3.13 (m, 1.2H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.29 (d, *J* = 8.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 166.2, 141.4, 122.8, 61.6, 30.5, 30.2, 14.4, 14.0, 14.0, 13.9.

Diethyl 2,6-bis(propan-2-yl-2-d)pyridine-3,5-dicarboxylate (1e'-d_2). **1e** (61.9 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain **1e'-d_2** as a white solid (46.1 mg, 0.150 mmol, 75%, 19% D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 4H), 3.86 (hept, *J* = 6.7 Hz, 1.6H), 1.39 (t, *J* = 7.1 Hz, 6H), 1.28 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 166.7, 140.3, 122.2, 61.5, 32.9, 22.3, 22.2, 14.4.

1,1'-(2,6-bis(methyl-d3)pyridine-3,5-diyl)bis(ethan-1-one-2,2,2-d3) (1f'-d_{12}). **1f** (38.7 mg, 0.2 mmol) and TFA-*d* (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain **1f'-d_{12}** as a pale yellow solid (26.0 mg, 0.128 mmol, 64%, 71% D, 61% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 2.77 – 2.71 (m, 1.7H), 2.62 – 2.57 (m, 2.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 160.4, 138.0, 130.3, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 28.8, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2.

Diethyl 2,6-bis(methyl-d3) -4-phenyl-1,4-dihydropyridine -3,5-dicarboxylate (2a-d_6). **2a** (65.9 mg, 0.2 mmol) and TFA-*d* (46 μL, 0.6

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mmol) were used according to general procedure 1 to obtain **2a-d$_6$** as a white solid (65.1 mg, 0.194 mmol, 97%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.11 (td, *J* = 7.0, 1.4 Hz, 1H), 5.88 (s, 1H), 4.98 (s, 1H), 4.12 – 4.04 (m, 4H), 2.32 – 2.25 (m, 1.4H), 1.21 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 147.9, 144.1, 128.1, 127.9, 126.2, 104.2, 59.8, 39.7, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.7, 14.4.

Diethyl 4-(2-bromophenyl) -2,6-bis(methyl-d3) -1,4-dihydropyridine-3,5-dicarboxylate (2b-d$_6$). **2b** (81.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2b-d$_6$** as a pale yellow solid (81.2 mg, 0.196 mmol, 98%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.15 (td, *J* = 7.5, 1.3 Hz, 1H), 6.93 (ddd, *J* = 7.9, 7.2, 1.7 Hz, 1H), 6.07 (s, 1H), 5.35 (s, 1H), 4.09 (qd, *J* = 7.1, 4.7 Hz, 4H), 2.25 – 2.19 (m, 1.4H), 1.19 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 147.6, 143.9, 143.9, 132.8, 131.7, 127.7, 127.5, 122.7, 104.2, 104.1, 59.8, 39.8, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6, 14.5.

Diethyl 2,6-bis(methyl-d3) -1,4-dihydro-[4,4'-bipyridine] -3,5-dicarboxylate (2c-d$_6$). **2c** (66.1 mg, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (494 µL, 4 mmol) were used according to general procedure 1 to obtain **2c-d$_6$** as a pale yellow solid (63.9 mg, 0.190 mmol, 95%, 70% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.1 Hz, 2H), 7.24 – 7.21 (m, 2H), 6.50 (s, 1H), 5.00 (s, 1H), 4.13 – 4.05 (m, 4H), 2.34 – 2.27 (m, 1.8H), 1.21 (t, *J* = 7.1 Hz,61H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 156.7, 149.1, 145.3, 145.3, 123.6, 102.7, 102.7, 60.1, 39.6, 19.5, 19.4, 19.3, 19.2, 19.1, 19.1, 18.9, 14.4.

Diethyl 4-(furan-2-yl) -2,6-bis(methyl-d3)-1,4-dihydropyridine -3,5-dicarboxylate-1-d (2d-d$_7$). **2d** (63.9 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2d-d$_7$** as a white solid (63.5 mg, 0.196 mmol, 98%, 81% D, -ND, 67% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 1.8, 0.9 Hz, 0.3H), 6.23 – 6.16 (m, 1H), 6.03 (s, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 5.19 (s, 1H), 4.21 – 4.09 (m, 4H), 2.31 – 2.25 (m, 1.1H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 158.8, 158.7, 145.3, 140.9, 110.1, 109.9, 104.5, 100.8, 59.9, 33.5, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.5, 14.4.

Diethyl 2,6-bis(methyl-d3) -4-(thiophen-3-yl)-1,4-dihydropyridine -3,5-dicarboxylate (2e-d$_6$). **2e** (67.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2e-d$_6$** as a pale yellow solid (67.3mg, 0.197 mmol, 99%, 82% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 5.0, 3.1 Hz, 1H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.91 (dd, *J* = 3.3, 1.3 Hz, 1H), 5.96 (s, 1H), 5.13 (s, 1H), 4.19 – 4.07 (m, 4H), 2.30 – 2.24 (m, 1.1H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 148.0, 144.6, 144.6, 127.7, 124.7, 120.4, 103.5, 103.5, 77.4, 77.2, 76.9, 59.9, 34.7, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6, 14.4.

Diethyl 4-(4-hydroxy-3-methoxyphenyl) -2,6-bis(methyl-d3) -1,4-dihydropyridine-3,5-dicarboxylate (2f-d$_6$). **2f** (75.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2f-d$_6$** as a white solid (75.4 mg, 0.198 mmol, 99%, 80% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 1.6 Hz, 1H), 6.75 – 6.70 (m, 2H), 5.88 (s, 1H), 5.63 – 5.52 (m, 1H), 4.91 (s, 1H), 4.13 – 4.05 (m, 4H), 3.81 (s, 3H), 2.31 – 2.24 (m, 1.2H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 145.9, 144.0, 143.9, 143.8, 140.2, 120.5, 114.0, 111.0, 104.3, 104.3, 59.8, 55.8, 39.2, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0, 19.0, 18.9, 18.8, 18.7, 14.4.

Diethyl 4-methyl-2,6-bis(methyl-d3) -1,4-dihydropyridine- 3,5-dicarboxylate (2g-d$_6$). **2g** (53.5 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2g-d$_6$** as a pale yellow solid (50.8 mg, 0.186 mmol, 93%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 4.27 – 4.13 (m, 4H), 3.84 (q, *J* = 6.5 Hz, 1H), 2.28 – 2.21 (m, 1.4H), 1.30 (t, *J* = 7.1 Hz, 6H), 0.98 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 144.4, 104.8, 104.8, 59.7, 28.6, 22.4, 19.5, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 14.6.

Diethyl 4-cyclohexyl-2,6-bis(methyl-d3) -1,4-dihydropyridine -3,5-dicarboxylate (2h-d$_6$). **2h** (67.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2h-d$_6$** as a pale yellow solid (58.7 mg, 0.172 mmol, 86%, 80% D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.24 – 4.05 (m, 4H), 3.89 (d, *J* = 5.7 Hz, 1H), 2.28 – 2.20 (m, 1.2H), 1.65 – 1.58 (m, 2H), 1.57 – 1.46 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.17 (dq, *J* = 6.0, 3.0 Hz, 1H), 1.09 – 0.98 (m, 3H), 0.88 (qd, *J* = 13.6, 12.6, 5.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 144.7, 101.9, 59.6, 45.9, 38.4, 28.9, 26.8, 26.7, 19.4, 19.2, 19.0, 18.8, 18.6, 14.5.

Diethyl 4-isopropyl -2,6-bis(methyl-d3) -1,4-dihydropyridine -3,5-dicarboxylate (2i-d$_6$). **2i** (59.1 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2i-d$_6$** as a white solid (53.0 mg, 0.176 mmol, 88%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.15 (ddq, *J* = 39.2, 10.8, 7.1 Hz, 4H), 3.89 (d, *J* = 5.5 Hz, 1H), 2.28-2.22 (m, 1.4H), 1.56 (pd, *J* = 6.9, 5.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H), 0.72 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 144.8, 101.8, 59.7, 38.9, 35.6, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.5.

Diethyl 2,6-bis(methyl-d3) -4-(pentan-3-yl)-1,4- dihydropyridine-3,5-dicarboxylate (2j-d$_6$). **2j** (64.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2j-d$_6$** as a white solid (55.4 mg, 0.168 mmol, 84%, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.21 – 4.09 (m, 5H), 2.27 – 2.21 (m, 1.4H), 1.29 (t, *J* = 7.1 Hz, 6H), 1.14 (ddq, *J* = 20.9, 13.8, 7.1 Hz, 4H), 1.03 (qd, *J* = 6.5, 4.5 Hz, 1H), 0.85 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 144.7, 102.3, 59.7, 50.0, 34.6, 21.3, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.8, 18.7, 18.6, 14.4, 11.9.

3-isobutyl 5-methyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2k-d$_6$). **2k** (77.7 mg, 0.2 mmol) and TFA-*d* (154 µL, 2 mmol) were used according to general procedure 1 to obtain **2k-d$_6$** as a yellow solid (74.9 mg, 0.190mmol, 95%, 79% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 3.83 – 3.75 (m, 2H), 3.56 (s, 3H), 2.34 – 2.27 (m, 0.6H), 2.27 – 2.20 (m, 0.6H), 1.87 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.76 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 167.5, 147.9, 145.1, 145.0, 142.5, 132.9, 131.2, 127.1, 124.1, 103.9, 103.5, 70.5, 51.1, 34.7, 27.6, 19.1.

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3-isopropyl 5-(2-methoxyethyl) 2,6-bis(methyl-d3)-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2l-d_6). **2l** (83.7 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **2l-d_6** as a pale yellow solid (79.8 mg, 0.188 mmol, 94%, 68% D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, *J* = 2.0 Hz, 1H), 7.98 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.65 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 6.04 (s, 1H), 5.08 (s, 1H), 4.93 (p, *J* = 6.2 Hz, 1H), 4.22 – 4.10 (m, 2H), 3.59 – 3.47 (m, 2H), 3.33 (s, 3H), 2.35 – 2.28 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 166.7, 150.1, 148.2, 145.3, 144.5, 134.8, 128.7, 123.4, 121.4, 104.0, 103.1, 70.6, 67.4, 63.1, 59.0, 40.1, 22.2, 21.9, 19.6, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0.

Dimethyl 2,6-bis(methyl-d3) -4-(2-nitrophenyl) -1,4-dihydropyridine- 3,5-dicarboxylate (2m-d_6). **2m** (69.3 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **2m-d_6** as a yellow solid (67.7 mg, 0.192 mmol, 96%, 79% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.23 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.15 (s, 1H), 5.70 (s, 1H), 3.57 (s, 6H), 2.32 – 2.23 (m, 1.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 147.9, 145.2, 145.2, 142.3, 132.9, 131.1, 127.1, 124.0, 103.6, 103.6, 51.1, 34.6, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6.

3-ethyl 5-methyl 2-((2-aminoethoxy)methyl -d2)-4-(2-chlorophenyl) -6-(methyl-d3) -1,4-dihydropyridine -3,5-dicarboxylate (2n-d_5). Amlodipine besylate (113.4 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **2n-d_5** as a wite solid (79.9 mg, 0.194 mmol, 97%, 80% D, 77% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.37 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.11 (td, *J* = 7.5, 1.4 Hz, 1H), 7.01 (td, *J* = 7.5, 1.7 Hz, 1H), 5.38 (s, 1H), 5.07 (s, 2H), 4.81 – 4.67 (m, 0.5H), 4.07 – 3.96 (m, 2H), 3.68 (hept, *J* = 5.2 Hz, 2H), 3.58 (s, 3H), 3.09 (t, *J* = 4.7 Hz, 2H), 2.33 (d, *J* = 11.0 Hz, 0.6H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.4, 145.9, 145.2, 145.1, 145.1, 144.8, 132.4, 131.6, 129.3, 127.5, 127.0, 103.8, 102.2, 102.2, 102.1, 70.0, 68.2, 60.0, 50.9, 40.5, 37.3, 18.7, 14.3.

Diethyl (E)-4-(2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)phenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2o-d_6). **2o** (91.1 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **2o-d_6** as a white solid (89.5 mg, 0.194 mmol, 97%, 80% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 15.8 Hz, 1H), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.10 (td, *J* = 7.6, 1.4 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 5.99 (s, 1H), 5.32 (s, 1H), 4.05 (dq, *J* = 10.8, 7.2 Hz, 2H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 2H), 2.31 – 2.24 (m, 1.2H), 1.53 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 166.8, 148.5, 144.3, 144.3, 143.9, 132.0, 130.6, 130.1, 126.5, 125.5, 120.2, 104.7, 104.6, 80.2, 59.8, 35.8, 28.4, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.4.

Diethyl 2,4,6-tris(methyl-d3)pyridine-3,5-dicarboxylate (3c-d_9). **3c** (53.1 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **3c-d_9** as a colorless oil (53.8 mg, 0.196 mmol, 98%, 70% D, 78% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (q, *J* = 7.1 Hz, 4H), 2.50 – 2.44 (m, 1.8H), 2.24 – 2.20 (m, 0.7H), 1.36 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 155.0, 142.2, 127.7, 61.7, 23.0, 22.9, 22.8, 22.7, 22.6, 22.6, 22.5, 22.4, 22.3, 22.2, 22.2, 17.0, 16.9, 16.8, 16.7, 16.7, 16.6, 16.4, 16.3, 16.3, 16.2, 14.3.

Dimethyl 2,6-bis(methyl-d3) -4-(2-nitrophenyl)pyridine -3,5-dicarboxylate (3d-d_6). **3d** (68.9 mg, 0.2 mmol) and TFA-*d* (154 μL, 2 mmol) were used according to general procedure 1 to obtain **3d-d_6** as a white solid (68.0 mg, 0.194 mmol, 97%, 78% D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.9, 7.6, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.48 (s, 6H), 2.64 – 2.59 (m, 1.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 157.1, 147.7, 145.3, 133.0, 132.1, 130.7, 129.7, 124.9, 124.4, 52.3, 23.6, 23.5, 23.5, 23.4, 23.3, 23.2, 23.1, 23.1, 23.0, 22.9, 22.8.

Conclusions

In summary, we have found a simple, effective, economical, and functional group compatible method for deuteration of 1,4-dihydropyridines and the corresponding pyridines, which occurred selectively at the alkyl groups in the 2,6-positions. 4-Substituted 1,4-dihydropyridines were deuterated more slowly than their unsubstituted counterparts. This protocol complemented existing acid-mediated labelling processes.

Conflicts of interest

There are no conflicts to declare.

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