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ARTICLE

Rapid, Regioselective Deuteration of Dimethyl-2,2'-bipyridines *via* Microwave-Assistance

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Isotopically pure [D₆]-dimethyl-2,2'-bipyridine derivatives were selectively and rapidly formed using microwave-assisted regioselective deuteration of the methyl moieties of the parent bipyridine in a deuterium oxide solution. For instance, [D₆]-4,4'-dimethyl-2,2'-bipyridine was formed in quantitative yield within 15 minutes, in a simple and convenient process.

Introduction

Hydrogen-deuterium (H-D) exchange reactions at carbon are witnessing increasing attention since isotopically labeled compounds are recognized to have cumulative significance in NMR spectroscopy and mass spectrometry.¹ For example, deuterated compounds are widely used as efficient tools for mechanistic investigations of chemical reactions, metabolic pathways, structural elucidations of biological macromolecules, and as internal standards for quantitative analyses of contaminants in foods and the environment.¹⁻² Therefore, efficient regioselective deuterium labeling approaches are of high importance for the preparation of deuterated reagents. For this reason, a range of deuteration methods has been reported, for instance based on transition metal-,³ enzyme-,⁷ acid-,⁴ or base-catalysis;⁵ super- or subcritical conditions;⁶ as well as microwave-enhanced exchange reactions.⁸ Many of these describe reactions performed at high temperature under pressure and/or for long periods of time, and the majority does not lead to chemo- and/or regioselective deuteration. In addition, these methods often require non-commercially available catalysts, strongly acidic or basic additives, and expensive D₂ gas, and can furthermore lead to low deuteration efficiencies and regioselectivities. Consequently, the development of inexpensive, high-yielding, chemo- and/or regioselective deuteration processes under mild conditions is strongly desired. Herein, this objective has been addressed, where a simple and efficient method to deuterated bipyridine structures is reported.

4,4'-Dimethyl-2,2'-bipyridine **1**, 5,5'-dimethyl-2,2'-bipyridine **2**, and 6,6'-dimethyl-2,2'-bipyridine **3** as shown in Figure 1, are well-known and widely used bidentate ligands in applications of transition metal complexes, particularly in the inorganic photochemistry and supramolecular chemistry fields.⁹

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Examples of H-D exchange reactions of this class of compounds have also been reported. For example, Pavlik et al. reported that methyl groups at various positions of pyridine derivatives could be deuterated by a D₂O-Na₂CO₃ solution at 110 °C from methylpyridine *N*-oxide derivatives.¹⁰ However, regioselective deuteration of the methyl groups without the introduction of deuterium on the pyridine ring could not be observed in this synthetic route. Browne and co-workers reported routes to regioselective deuteration of heteroaromatic compounds containing pyrazyl, pyridyl, 1,2,4-triazole, thienyl, methyl, and phenyl moieties based on subcritical aqueous media.^{6b} The main deuterated product was in this case the fully deuterated [D₁₂]-4,4'-dimethyl-2,2'-bipyridine **1-d₁₂**, whereas selective introduction of deuterium atoms on the 4- and 4'-methyl moieties could not be observed. However, although **1-d₁₂** was obtained in good yield, the reactions required lengthy reaction times (4-6 days) as well as a high temperature (200 °C).

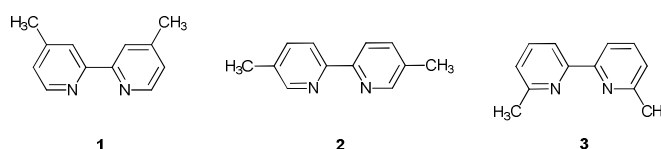


Fig. 1 Bipyridine compounds examined.

During the last decade, microwave-assisted organic synthesis has witnessed rapid growth, and has been widely used to accelerate different reactions.¹¹ Enhanced selectivities have also been reported in some cases.¹¹ For example, several examples of microwave-assisted deuteration in D₂O have been reported,^{2d, 8d} of which some showed noticeable acceleration effects in conjunction to enhanced deuteration selectivities.¹²

The regioselective introduction of deuterium atoms into the 2,2'-bipyridine core, of special interest for spectroscopy applications, has however been limited. Current protocols generally involve time-consuming, multiple steps, can be of unfriendly nature, and may suffer from occasional, imperfect deuteration.^{6c, 13} There is thus a lack of generally applicable,


high-yielding, and low-cost deuteration procedures for this class of compounds. Furthermore, the motivation behind the interest in the deuteration of 2,2'-bipyridine ligands is their prospective applicability in the further investigation of supramolecular systems. Herein, we report a rapid, one-pot, regioselective deuteration method of 4,4'-dimethyl-2,2'-bipyridine (**1**), 5,5'-dimethyl-2,2'-bipyridine (**2**) and 6,6'-dimethyl-2,2'-bipyridine (**3**) in D₂O under microwave irradiation to afford the deuterated products **1-d₆**, **2-d_n** (n=1-6) and **3-d₆**.

Results and discussion

Conventional heating conditions

The investigation of the direct H-D exchange reaction of bipyridine **1** was initiated by optimizing the reaction conditions using conventional heating. The H-D exchange reactions in D₂O solutions were thus studied using various inorganic catalysts at different reaction temperatures for 24 h. The results from these exchange reactions are summarized in Table 1. Of the catalysts, Pd/C,¹⁴ and Na₂CO₃, known H-D exchange reaction catalysts for heterocyclic compounds,^{8d, 10} and bipyridines,^{6c, 13b} did however not give any H-D exchange of compound **1** in D₂O solutions (Entries 1-4). In all cases, increasing the reaction temperature did not yield significant advantages over the reaction conducted at lower temperature (Entries 1-4). Increasing the amount of 10% Pd/C from 10 wt% to 30 wt% had an insignificant effect on the deuterium incorporation, yielding a small amount of **1-d₁** (10%, Entry 5). Less than quantitative recoveries could be obtained in this case, due to difficulties in removing the substrate from the Pd/C catalyst. Increasing the amount of Na₂CO₃ from 10 wt% to >100 wt% failed to improve the deuterium incorporation with no desired **1-d₆** product (Entry 6). However, the use of 1 M NaOD/D₂O provided slight H-D exchange at the methyl moieties of compound **1** (Entry 7), while no H-D exchange was observed at the bipyridine ring.

Table 1 Direct H-D exchange of bipyridine **1** using conventional heating



Entry	Catalyst ^{a)}	Temperature (°C)	Recoveries ^{b)} (%)	% D ^{c)}
1	Pd/C	rt	quant	-
2	Na ₂ CO ₃	90	quant	-
3	Na ₂ CO ₃	reflux	quant	-
4	Pd/C	reflux	quant	-
5 ^{d)}	Pd/C	reflux	87	(10 1-d₁)
6 ^{d)}	Na ₂ CO ₃	reflux	quant	-
7	NaOD	reflux	quant	9

^{a)} 10% Pd/C (10 wt%) or Na₂CO₃ (10 wt%), and 1 M of NaOD/D₂O (>100 wt%) were used. ^{b)} Based on recovered yield. ^{c)} Deuterium incorporation was determined by ¹H NMR spectroscopy and ESI-MS. ^{d)} 10% Pd/C (30 wt%) or Na₂CO₃ (>100 wt%) were used.

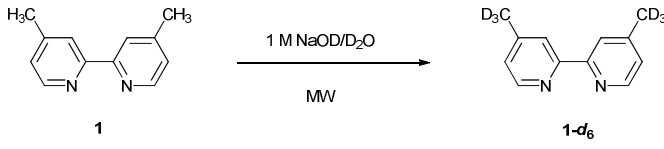
Regioselectivities and yields/conversions of the deuterated products could therefore be estimated using the unchanged bipyridine signal as internal reference in the ¹H NMR spectrum,

and the peak intensity of the initial substance **1** as internal reference in the ESI-MS spectrum, respectively. Although the H-D exchange reactions of compound **1** were unsuccessful under the reaction conditions listed in Table 1, these results suggested further investigation of the H-D exchange reaction in 1 M of NaOD/D₂O as catalyst.

Microwave heating conditions

The H-D exchange reaction of bipyridine **1** in the presence of NaOD/D₂O was next evaluated under microwave heating conditions (Table 2). The results were in this case very clear, and the exchange reaction proceeded more efficiently. Similar results as under conventional heating conditions were obtained until the temperature reached at 150 °C, yielding low amounts of deuterated product, but increasing the temperature resulted in higher product yields. At 160 °C, up to 93% conversion could be recorded after 3 hours, but microwave irradiation at 170 °C for 15 min yielded excellent H-D exchange of all methyl protons (Entry 7). In addition, no H-D exchange of the bipyridine ring protons could be observed under these conditions. Decreasing the amount of NaOD clearly showed reduced deuterium incorporation and **1-d₆** product, accompanied by slightly decreased regioselectivity providing some **1-d₄** and **1-d₅**. On the other hand, increasing the concentration of NaOD to 2 M caused explosion of the MW reaction vessel with the present setup and 1 M was therefore chosen as the optimal concentration.

Table 2 Optimization of direct H-D exchange reaction of compound **1**^{a)}



Entry	Time (min)	Temperature (°C)	Pressure (Bar)	Yield ^{b)} (%)	% D ^{c)}
1	15	130	5	quant	-
2	15	140	7	quant	3
3	15	150	8	quant	7
4	15	160	11	quant	87
5	60	160	11	quant	91
6	180	160	12	quant	93
7	15	170	15	quant	97
8 ^{d)}	15	170	14	quant	78
9 ^{e)}	15	170	14	quant	82

^{a)} Reactions were performed in microwave reactor. ^{b)} Based on recovered yield. ^{c)} Deuterium incorporation was determined by ¹H NMR spectroscopy and ESI-MS. ^{d)} 0.1 M of NaOD/D₂O was used. ^{e)} 0.5 M of NaOD/D₂O was used.

The ¹H and ¹³C NMR spectra of deuterated product **1-d₆** are displayed in Figure 2 together with those of compound **1** for comparison. Upon H-D exchange, the singlet corresponding to the 4- and 4'-methyl moieties of compound **1** disappeared. Moreover, the two additional carbon satellite peaks of the methyl carbons in the ¹³C NMR spectrum revealed the characteristic C-D correlation pattern.

To further confirm the identity of compound **1-d₆** as deuterated, a crude reaction of compound **1** in methanol solution was analyzed by ESI-MS (Figure 3a). The distribution is in this case very clear, with a significant signal of [**1-d₆**+Na]⁺ at 213.1267. Accordingly, compound **1-d₆** was thus clearly obtained.

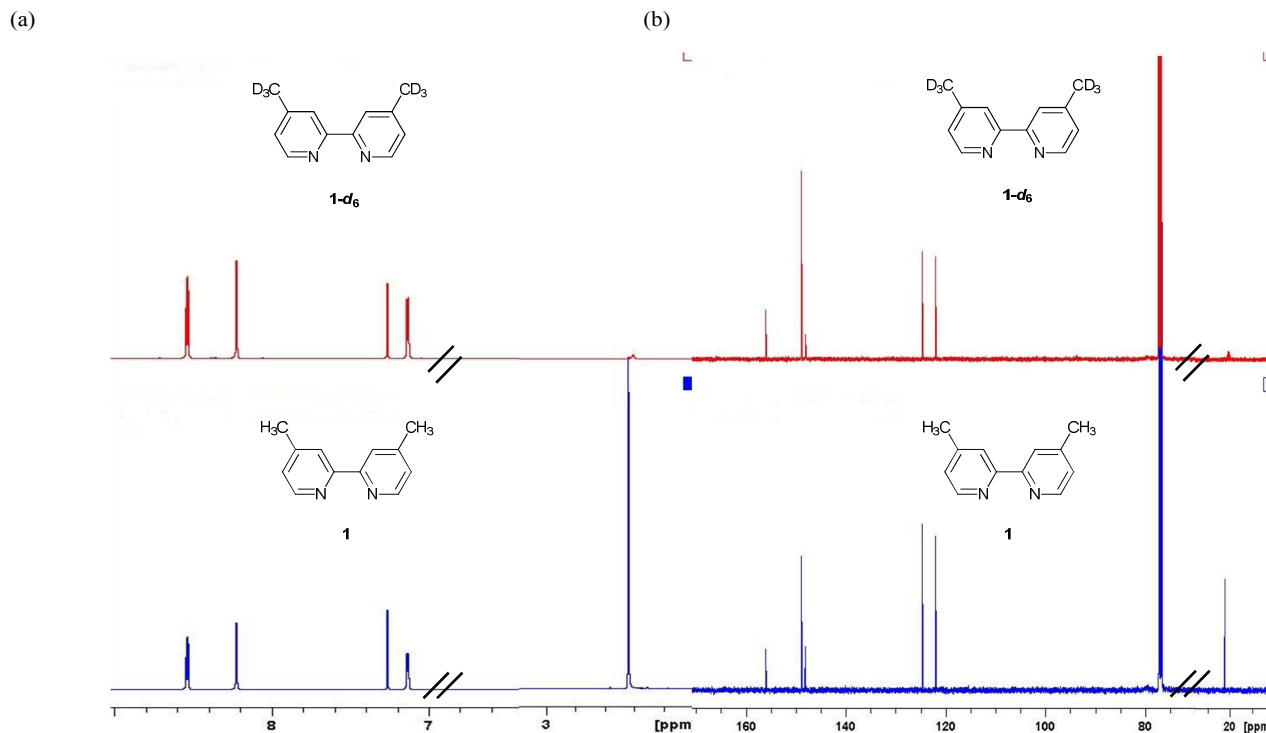


Fig. 2 (a) ^1H NMR of compounds **1** and **1- d_6** in CDCl_3 solution. (b) ^{13}C NMR of compounds **1** and **1- d_6** in CDCl_3 solution.

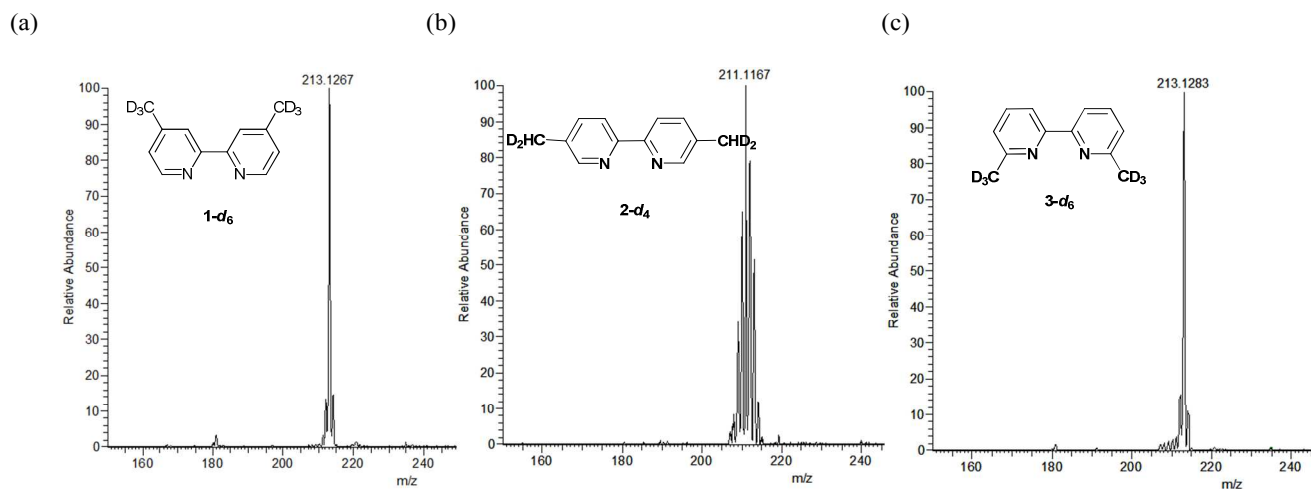
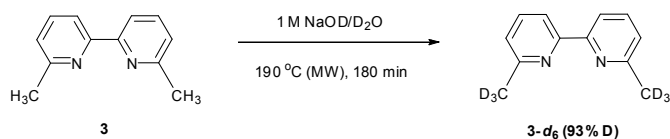


Fig. 3 ESI-MS spectra of H-D exchange reactions of (a) **1**, (b) **2** and (c) **3** in methanol solution.

In addition, the direct H-D exchange reaction of bipyridine **2** and **3** were also evaluated under the optimal reaction conditions for both species using microwave irradiation at 190°C for 3 hours with pressure 21 bar using ESI-MS in methanol solution. Their results are shown in Figure 3b and 3c (^1H and ^{13}C NMR spectra see Supporting Information).

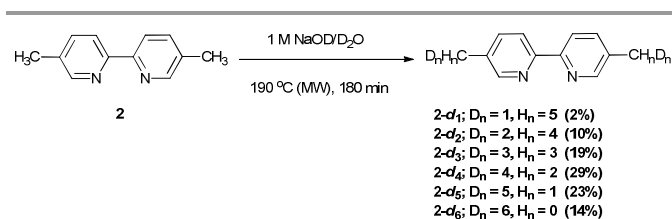


Scheme 1 Optimal H-D exchange reaction of compound **3**.

In the case of compound **3** as shown in Scheme 1 reveals a corresponding significant signal $[\mathbf{3-d}_6+\text{Na}]^+$ at 213.1283 along with a very small peak of compound **3**. The ^1H and ^{13}C NMR spectra of compound **3- d_6** demonstrated good H-D exchange of all methyl protons as quantitative yield with 93% deuterium incorporation (see Supporting Information).

In contrast to bipyridines **1** and **3**, a distribution of deuterated products of bipyridine **2** was obtained with the deuterated compound **2- d_4** as the major product (29%), together with lower amount of further deuterated products **2- d_5** (23%), **2- d_3** (19%), **2- d_6** (14%), **2- d_2** (10%), and **2- d_1** (2%), respectively (Figure 3b and Supporting Information). The results are shown in Scheme 2 as monitored by ESI-MS. Although, several optimized H-D exchange reaction conditions

of compound **2** were considered by the increasing of the temperature and/or time, in which the more deuterium incorporations were obtained in both case. On the other hand, the fully deuterated products as in the case of bipyridine **1** or **3** could not be observed. In analogy to bipyridines **1** and **3**, however, deuteration took place at the methyl moieties of compound **2**, and no H-D exchange of the bipyridine ring protons was found. One of the most important properties of alkylpyridines is the increased acidity of the hydrogens attached to α -carbon of the side-chains *via* electron distribution and the effect is strongest for the alkyl group at position 2 and 4 of the pyridine ring that corresponding with position 6 and 4 in the case of 2,2'-bipyridine ring, respectively. The mobilities of hydrogens in the α -positions of the side-chains were found to decrease as follows: 4-methylpyridine > 2-methylpyridine > 3-methylpyridine (pK_a 30-37).¹⁵ Accordingly, hydrogens on 6,6'- and 4,4'-methyl substituents were more easily exchanged by deuterium than those hydrogens at 5,5'-methyl positions.



Scheme 2 Optimal H-D exchange reaction of compound **2**.

Conclusions

In summary, a synthetic method for the regioselective deuteration of 4,4'-dimethyl-2,2'-bipyridine **1**, 5,5'-dimethyl-2,2'-bipyridine **2**, and 6,6'-dimethyl-2,2'-bipyridine **3** to (*d_n*)-bipyridine under microwave-assisted direct H-D exchange is demonstrated. The process is straightforward, resulting in a high degree of isotopic purity, and untraceable amounts of side-products.

Experimental Section

General Information

The deuterium contents of deuterium oxide was 99.9 atom %. 1 M NaOD/D₂O solution was directly prepared by the dissolving of sodium metal (230 mg) in 99.9 atom % D₂O (10 mL). ¹H and ¹³C NMR spectra were recorded on a Bruker DMX 500 spectrometer at 500 MHz and 125 MHz. All NMR spectra were measured in CDCl₃ (¹H: δ = 7.26, ¹³C = 77.16) using the solvent residual signal as internal standard; chemical shifts (δ) are reported in parts per million (ppm) values and *J* values are given in Hertz (Hz). Microwave irradiation was performed with a Biotage® Initiator classic microwave reactor with a non-invasive sensor pressure control system; temperatures of the reaction mixtures were monitored by a perpendicularly focused IR temperature sensor and not by an internal temperature probe. High-resolution mass spectrometry was performed with an electrospray mass spectrometer (a Finnigan LCQ Advantage Max: LC-MS/MS).

4,4'-bis(methyl-*d*₃)-2,2'-bipyridine (**1-d₆**)

Direct H-D exchange reaction of **1** was converted as follows (Table 2, Entry 7); 4,4'-dimethyl-2,2'-bipyridine (30 mg, 0.163 mmol) and 1 M NaOD/D₂O (1 mL) were put in a 10 mL pressure-resistant glass ampoule. The ampoule was sealed with an aluminium cap and placed into a cavity of microwave irradiation reactor using continuous microwave irradiation applied with stirring to preserve a 170 °C temperature, without cooling, for 15 min. After that, the reaction mixture was allowed to cool to room temperature, followed by filtration of the involved white precipitation of product by vacuum filtration. The separated white precipitation was washed with water several times and dried under vacuum. The desired **1-d₆** was afforded in quantitative yield with 97% deuterium incorporation. ¹H NMR (500 MHz, CDCl₃): δ_{ppm} 8.53 (d, 2H, *J* = 5.0 Hz, bpy-*H*), 8.22 (s, 2H, bpy-*H*), 7.13 (dd, 2H, *J* = 1.6 and 5.0 Hz, bpy-*H*), 2.41 (s, 0.20H, 2 x CH₃). ¹³C NMR (125 MHz, CDCl₃): δ_{ppm} 156.06 (s), 148.94 (s), 148.06 (s), 124.67 (s), 122.03 (s), 20.32 (t, *J* = 20.0 Hz). MS (ESI) *m/z*: calcd for C₁₂H₆D₆N₂ (M+Na)⁺ 213.1275, found 213.1267.

5,5'-bis(methyl-*d*₃)-2,2'-bipyridine (**2-d₆**)

H-D exchanged reaction mixture of 5,5'-dimethyl-2,2'-bipyridine **2** (Scheme 2): ¹H NMR (500 MHz, CDCl₃): δ_{ppm} 8.48 (s, 2H, bpy-*H*), 8.24 (d, 2H, *J* = 8.0 Hz, bpy-*H*), 7.60 (dd, 2H, *J* = 1.4 and 8.0 Hz, bpy-*H*), 2.36-2.33 (m, 2.39H, 2 x CH₃). ¹³C NMR (125 MHz, CDCl₃): δ_{ppm} 153.59 (s), 149.46 (s), 137.56 (s), 133.08 (t, *J* = 5.0 Hz), 120.40 (s), 18.01 (m). MS (ESI) *m/z*: calcd for C₁₂H₁₀D₂N₂ (M+Na)⁺ 209.1024, found 209.1017; C₁₂H₉D₃N₂ (M+Na)⁺ 210.1086, found 210.1080; C₁₂H₈D₄N₂ (M+Na)⁺ 211.1149, found 211.1139; C₁₂H₇D₅N₂ (M+Na)⁺ 212.1212, found 212.1219; C₁₂H₆D₆N₂ (M+Na)⁺ 213.1275, found 213.1263.

6,6'-bis(methyl-*d*₃)-2,2'-bipyridine (**3-d₆**)

[D₆]-6,6'-dimethyl-2,2'-bipyridine **3-d₆** was afforded in quantitative yield with 93% deuterium incorporation (Scheme 1): ¹H NMR (500 MHz, CDCl₃): δ_{ppm} 8.18 (d, 2H, *J* = 7.5 Hz, bpy-*H*), 7.69 (t, 2H, *J* = 8.0 Hz, bpy-*H*), 7.15 (d, 2H, *J* = 8.0 Hz, bpy-*H*), 2.61 (s, 0.41H, 2 x CH₃). ¹³C NMR (125 MHz, CDCl₃): δ_{ppm} 157.81 (s), 155.92 (s), 137.05 (s), 123.10 (s), 118.25 (s), 23.81 (t, *J* = 19.0 Hz). HRMS (ESI) *m/z*: calcd for C₁₂H₆D₆N₂ (M+H)⁺ 191.14499, found 191.14419.

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