# Organic & Biomolecular Chemistry

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DOI: 10.1039/C7OB00062F

Journal Name

COMMUNICATION

# Facile and General Acid-Catalyzed Deuteration at Methyl Groups of *N*-Heteroarylmethanes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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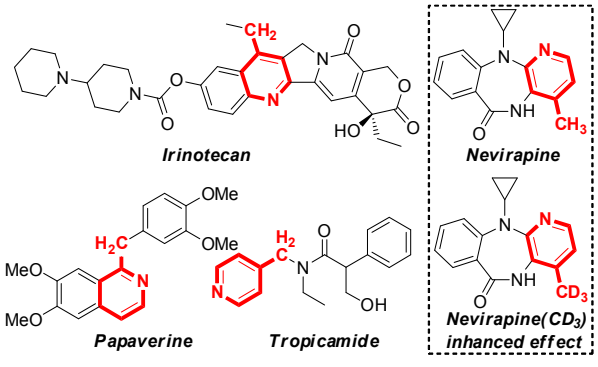
**A facile and general Brønsted acid-catalyzed deuteration at the methyl group of *N*-heteroarylmethanes was achieved through a dearomatic enamine intermediate under a relatively mild reaction condition. Both 2-methyl and 4-methyl groups in quinolones were deuterated with high deuterium incorporation. Pyridines, benzo[*d*]thiazoles, indoles and imines including those clinic drugs were also deuterated efficiently at the methyl groups. This reaction could be conducted at a large scale (500 mmol), showing good potential for large-scale synthesis.**

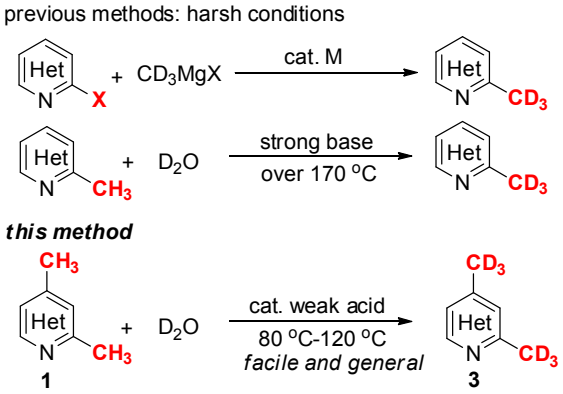
Deuterated compounds are widely applied in mass and NMR spectroscopies.[1] They are also recognized as powerful tools in mechanistic and metabolic studies.[2] Thus, the selective introduction of deuterium into functional molecules has attracted impressive interest.[3] *N*-heteroarylmathanes usually occur as key core units in many natural products and pharmaceutical drugs[4] (Scheme 1).




***Scheme 1.*** examples of pharmaceutical molecules containing *N*-heteroarylmethane unit.

Considering the striking effect of methyl group in clinical medicines,[5] the selective deuteration at the methyl group of such compounds would greatly facilitate the studies on the overall therapeutic and metabolic profile of a related drug. Some deuterated medicines are also recognized to enhance the formation of active metabolites and reduce the formation of toxic metabolites, thus positively impacting their metabolic fate.[6] In addition, numerous efforts have been devoted to the functionalization of methyl group in such compounds,[7] the mechanistic studies also require corresponding deuterated compounds. However, methods for preparing those deuterated compounds are rather limited.[8-10]

Those deuterated compounds are conventionally prepared by cross coupling between aryl halides with $CD_3MgX$ catalyzed by a transition metal complex.[8] Direct deuteration at the methyl group of *N*-heteroarylmethanes would be an attractive step-economic method; however current strategy usually requires a strong base and high reaction temperature (over 170 °C) (Scheme 2).[9,3a] In addition to the issues of safety and manipulation, these protocols also suffer from severe limitations of functional groups tolerance.




***Scheme 2.*** Synthesis of *N*-heteroarylmethanes-$CD_3$

Herein, we report a facile Brønsted acid-catalyzed deuteration at the methyl group of *N*-heteroarylmethanes with $D_2O$ to produce the corresponding deuterated

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Electronic Supplementary Information (ESI) available: General information, experimental procedures, copies of $^1H$ and $^{13}C$ NMR spectra for products. See DOI: 10.1039/b000000x/

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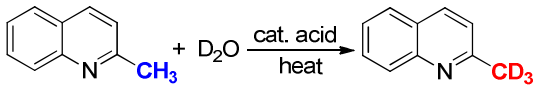
DOI: 10.1039/C7OB00062F




compounds with high ratios of deuterium incorporation (Scheme 2). This reaction is general, both 2-methyl and 4-methyl groups in various *N*-heteroarylmethanes including those with functional groups are deuterated efficiently under the mild reaction conditions. This new transformation can be performed in a large scale and be applicable to some bioactive pharmaceutical molecules, showing good industrial potential.

**Table 1.** Brønsted acid-catalyzed deuteration of 2-methylquinoline[a]



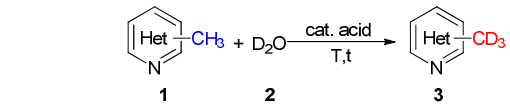

1a 2 3a

| Entry | Cat. [mol%] | Temp. [°C] | Deuterium incorporation[%][b] |
|---|---|---|---|
| 1 | - | 60 | trace |
| 2 | PhCOOH (20) | 60 | 90 |
| 3 | PhCOOH (20) | 80 | 97 |
| 4 | PhCOOH (20) | 100 | 97 |
| 5 | HOAc (20) | 80 | 67 |
| 6 | $Ph_2P(O)OH$ (20) | 80 | 93 |
| 7 | TFA (20) | 80 | 77 |
| 8 | $CF_3SO_3H$ (20) | 80 | 93 |
| 9 | $PhSO_3H$ (20) | 80 | 70 |
| 10 | PhCOOH (10) | 80 | 97 |
| 11 | PhCOOH (7.5) | 80 | 97 |
| 12 | PhCOOH (5) | 80 | 94 |
| 13 | PhCOOH (2.5) | 80 | 89 |
| 14[c] | PhCOOH (7.5) | 80 | 96 |
| 15[d] | PhCOOH (7.5) | 80 | 92 |
| 16[e] | PhCOOH (7.5) | 80 | 89 |

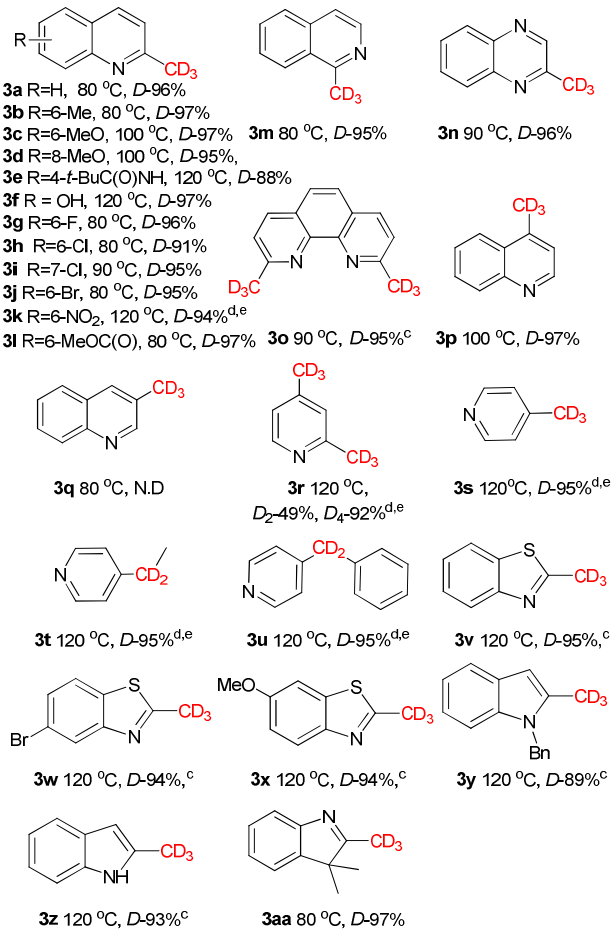
[a] Reaction conditions: **1a** (0.2 mmol), $D_2O$ (0.4 mL), air, 10 mL glass tube, 80 °C, 4 h. The mixture after reaction was neutralized by saturated $NaHCO_3$ aqueous solution. [b] Based on $^1H$ NMR spectroscopy; [c] 0.2 mL $D_2O$ was used. [d] 0.1 mL $D_2O$ was used. [e] 0.05 mL $D_2O$ was used.

Inspired by recent advances of acid-mediated functionalization of methyl groups in *N*-heteroarylmethanes where the methyl groups are proposed to be activated by Brønsted acids through an enamine intermediate (Scheme 2),[7d,7f] we envisioned that the selected deuteration at the methyl groups would be within reach via a similar process.[11] This is indeed. It was found that by heating the mixture of 2-methylquinoline in $D_2O$ at 60 °C for 4 h, a trace amount of deuterated compounds was produced as indicated by $^1H$ NMR spectroscopy (Table 1, entry 1). By addition of 20 mol% benzoic acid, the ratio of deuterium incorporation was dramatically increased to 90% under similar reaction conditions (Table 1, entry 2). When the reaction was performed at 80 °C, 97% ratio of deuterium incorporation was achieved (Table 1, entry 3). Further elevating the reaction temperature to 100 °C, the reaction efficiency was not improved (Table 1, entry 4). Other acids could also mediate this reaction, despite a little low incorporation ratios were afforded (Table 1, entries 5-9). To our delight, this reaction could take place readily with a lower loading of catalyst and only 7.5 mol% benzoic acid enabled this transformation to occur efficiently (Table 1, entries 10-12).[12,13] The amount of $D_2O$ was also screened. 96% ratio of deuterium incorporation was obtained with 0.2 mL $D_2O$ (Table 1, entry 14), whereas further reducing the loading of $D_2O$ would lead to the decrease of deuteration incorporation (Table 1, entries 15 and 16). As for the reaction time, it was found that the ratio of deuterium incorporation was *D*-60% at 0.5 h, *D*-87% at 1 h, *D*-91% at 2h, *D*-94% at 3 h, *D*-96% at 4 h and *D*-96% at 5 h, indicating that the reaction reached equilibrium at 4 h (see SI, Figure 2).[13]

**Table 2.** Brønsted acid-catalyzed deuteration at methyl groups of *N*-heteroarylmethanes.[a,b]




1 2 3




[a] Reaction conditions: **1** (0.2 mmol), $D_2O$ (0.2 mL), benzoic acid (0.015-0.02 mmol), 10 mL glass tube, 4-8 h. The mixture after reaction was neutralized by saturated $NaHCO_3$ aqueous solution. [b] The percent of deuterium incorporation was calculated based on $^1H$ NMR spectroscopy (for details, see SI). [c] 15 mol% benzoic acid was used. [d] 20 mol% benzoic acid was used. [e] 16-24 h.

This acid-catalyzed transformation was general; a variety of *N*-heteroarylmethanes could be deuterated at the methyl groups, producing the expected deuterated products with high percent of deuterium incorporation (Table 2). Thus, 2-

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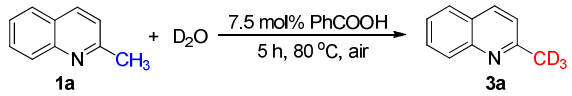
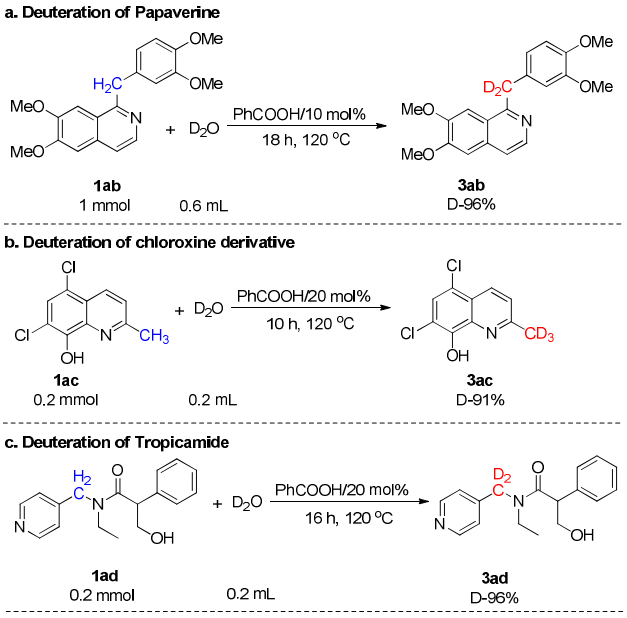
methylquinolines bearing 6-methyl, methoxy, even the easily hydrolytic ester and amide groups all gave the corresponding products efficiently under the current reaction conditions (**3b**-**3e** and **3l**). Substrates with free hydroxyl groups also produced the expected deuterated product (**3f**). The derivatives having halo groups (F, Cl and Br) and electron-withdrawing groups like nitro and carbonyl groups were reactive under the reaction conditions (**3g**-**3l**). 1-Methylisoquinoline and 2-methylquinoxaline were also deuterated at methyl group efficiently (**3m** and **3n**). Neocuproine was also effective for this reaction and both of methyl groups were deuterated readily (**3o**). In addition to methyl group adjacent to nitrogen atom, H/D exchange could also occur readily at the 4-methyl group exemplified as **3p** under the present reaction conditions. However, no deuterium incorporation at the methyl group occurred when 3-methylquinoline was loaded as a substrate (**3q**). Noteworthy, by elevating the reaction temperature to 120 °C, the pyridine derivatives could also be deuterated efficiently at the methyl groups. Worth noting is that 4-methyl group seems to be more active. For example, when 2,4-dimethylpyridine was employed as the substrate, 92% deuterium incorporation was achieved at 4-methyl group, whereas only 49% of 2-methyl group was deuterated. 4-Methylpyridine, 4-ethylpyridine and 4-benzylpyridine were also deuterated selectively at methyl or methylene under similar reaction conditions (**3r**-**3u**). Interestingly, other *N*-heterocyclic methanes also served as good substrates. Benzo[*d*]thiazoles, indoles and imines all were converted to the corresponding deuterated products with high deuterium incorporation (**3v**-**3aa**).

Practically, this reaction could be easily carried out at a large-scale (Scheme 3). Thus, a mixture of 10 mmol 2-methylquinoline in 6 mL $D_2O$ was stirred at 80 °C for 5 h in the presence of 7.5 mol% benzoic acid. The mixture was neutralized with $NaHCO_3$ solution (4 mL) and extracted with ethyl acetate (5×4 mL). After being dried with $Na_2SO_4$ and evaporated under reduced pressure, the corresponding deuterated product **3a** was given in 94% isolated yield (1.37 g) with 95% ratio of deuterium incorporation. A similar result was obtained at 500 mmol scale, showing its potential utility for a large-scale preparation of such compounds (for procedure, see SI).



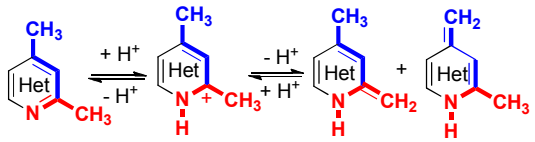

**Scheme 3.** Scale-up experiments.

This Brønsted acid-catalyzed H/D exchange was applicable to deuteration of bioactive molecules, producing the corresponding deuterated products with high deuterium incorporation and thus facilitating metabolic studies on related drugs (Scheme 4). For example, papaverine, an efficient drug for treatment of the tonus of all smooth muscle relaxation, was deuterated with 95% deuterium incorporation. 91% deuterium incorporation was also obtained from the chloroxine derivative 5,7-dichloro-2-methylquinolin-8-ol[4f] under similar reaction conditions. Tropicamide was widely used in pseudomyopia treatment. The corresponding deuterated product was also produced readily via H/D exchange in the current system.




**Scheme 4.** Application on deuteration of bioactive pharmaceutical molecules.

As for the mechanism, the present H/D exchange would take place through an enamie intermediate (Scheme 5). It should be noted that these results described here also provided strong evidence for the proposed mechanism on acid-mediated functionalization of methyl groups in *N*-heteroarylmethanes that the methyl group was activated by Brønsted acid.[7]



**Scheme 5.** Proposed mechanism for the acid-catalyzed deuteration at the methyl groups of *N*-heteroarylmethanes.

In summary, we have developed an efficient Brønsted acid-catalyzed deuteration at the methyl group of *N*-heteroarylmethanes using the simple $D_2O$ as the deuterating reagents. Quinolines, pyridines, benzo[*d*]thiazoles, indoles and imines including those clinic drugs all were deuterated at the methyl groups with high deuterium incorporation under a relatively mild reaction condition. A scale-up experiment also showed the possibility of large-scale synthesis. This deuteration transformation not only provided an efficient deuterating strategy for *N*-heteroarylmethanes, but also provided a strong evidence for the proposed mechanism in the acid-mediated functionalization of methyl groups in *N*-

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heteroarylmethanes. Detailed kinetic studies are underway in our laboratory.

Partial financial supports from NFSC (21403062, 21373080, 21273067), HNNSF 2015JJ3039 and the Fundamental Research Funds for the Central Universities (Hunan University) are gratefully acknowledged. The authors thank Dr. Qing Xu in Wenzhou University for HRMS analysis.

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12 It was deduced that the acids perhaps played dual roles in the H/D exchange reaction: activating the methyl group through a dearomatic enamine intermediate and increasing the solubility of the starting material in $D_2O$ *via* salification.

13 The H/D exchange reaction would be accelerated by increasing the loading of acid. For example, when a stoichiometric amount of benzoic acid was loaded, 93% deuterium incorporation was obtained at 0.5 h.