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One-Pot Synthesis of Deuterated Aldehydes from Arylmethyl Halides

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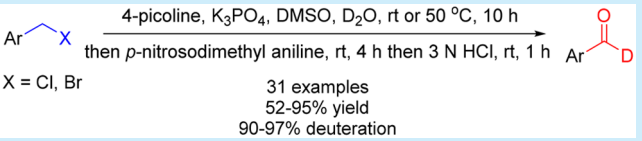
Supporting Information

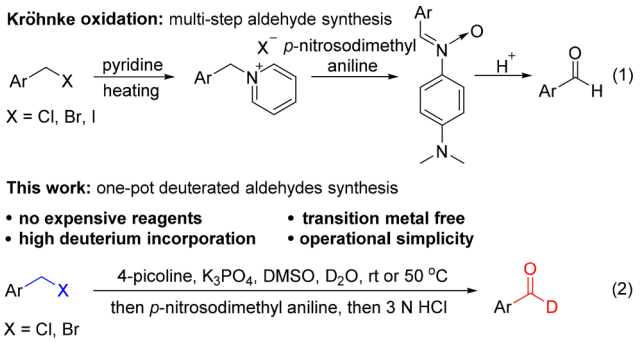
ABSTRACT: A facile, one-pot approach for synthesizing deuterated aldehydes from arylmethyl halides was developed using D_2O as the deuterium source. The efficient process is realized by a sequence of formation, H/D exchange, and oxidation of pyridinium salt intermediates. The mild and air-compatible reaction conditions enable efficient synthesis of diverse deuterated aldehydes with high deuterium incorporation.



The importance of aldehydes is well demonstrated by their irreplaceable roles in numerous transformations.[1] Deuterated aldehydes and their derivatives have a variety of practical applications, such as metabolic pathway probing[2] and reaction mechanism study.[3] Although synthesis of aldehydes has been extensively investigated, efficient synthesis of 1-deuterioaldehydes is still highly challenging. A number of efforts have been devoted to expand the approaches of deuterated aldehydes synthesis.[4−11] Traditional access to deuterioaldehydes mainly includes deuteride reduction of corresponding ester followed by oxidation,[4] Rosenmund reduction of acid chlorides with D_2 gas,[5] H/D exchange of dithiol protected aldehydes,[6] reduction of dihydro-1,3-oxazines,[7] and hydrolysis of benzal-bispyridinium dibromide.[8] However, most of these methods require cumbersome multistep procedures,[6−8] costly deuterated reagents,[4] or harsh conditions.[6,7] More recently, new synthetic approaches have been developed for deuterioaldehydes, such as treatment of tertiary amides with Cp2ZrDCl,[9] decarboxylation of α-oxocarboxylic acids,[10] and ruthenium-, rhodium-, or iridium-catalyzed H/D exchange.[11] Despite these impressive studies, significant synthetic challenges remain to be tackled. In particular, high temperature,[10,11] limited substrate scope,[9] low reagent availability,[9,10] and poor deuterium incorporation[11] of current approaches limited their practical applications. Herein, a novel one-pot process was designed for convenient and economical synthesis of deuterated aldehydes from readily available arylmethyl halides under mild conditions (Scheme 1, eq 3).

Arylmethyl halides are important synthetic intermediates that are used for various transformations.[12] Considering the active nature and wide availability of arylmethyl halides, we investigated their potential to be efficiently converted into deuterated aldehydes. To probe the feasibility, we initiated the study by the reaction of 2-naphthylmethyl bromide (**1a**) using K_2CO_3 (2 equiv) as a base and D_2O as the deuterium source. DMSO was used as both oxidant and solvent, and the mixture was heated to 80 °C for 8 h. However, only a trace amount of aldehyde was detected, and most substrates converted to 2-naphthalenemethanol (Scheme S1). Therefore, we envisioned that the arylmethyl halides should be first stabilized to prevent the formation of alcohol and accelerate the H/D exchange on the benzyl position before further oxidation to an aldehyde.

Scheme 1. Conversions of Arylmethyl Halides to Aldehydes



Pyridinium salts formed by condensation of arylmethyl halides and pyridine can be oxidized to aldehydes by nitrosobenzene, which is known as Kröhnke oxidation (Scheme 1, eqs 2).[13] However, this transformation was rarely used due to the cumbersome multistep operation. With an aim of developing an efficient method for 1-deuterioaldehyde synthesis, we proposed that pyridinium salts could serve as the stabilized intermediates of arylmethyl halides (Scheme 2). In the serach for a feasible synthesis, widely used pyridine was chosen as the auxiliary reagent and readily available *p*-nitrosodimethyl aniline as the oxidant.

To validate the feasibility, we tested the reaction of 2-naphthylmethyl bromide (**1a**) in the presence of pyridine (**I**, 2 equiv), D_2O, and K_2CO_3 (4 equiv) in DMSO (Table 1). The mixture was stirred at room temperature for 10 h before *p*-

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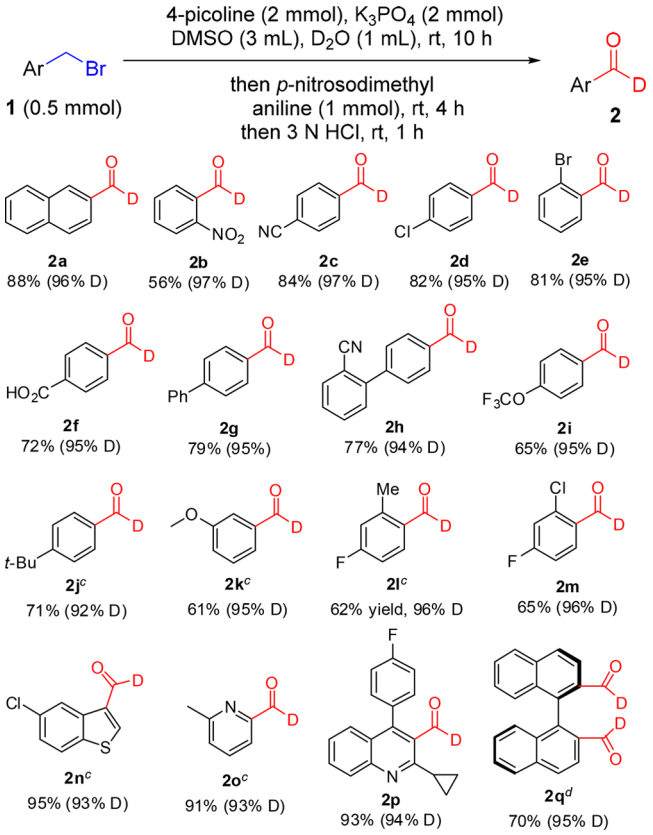
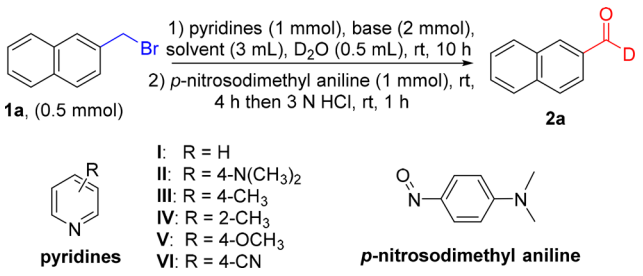
Scheme 2. Scope of the Deuterated Aldehyde Synthesis with Arylmethyl Bromides Standard*



*Reaction conditions: a mixture of DMSO (3 mL), D_2O (1 mL), **1** (0.5 mmol), 4-picoline (2 mmol), and K_3PO_4 (2 mmol) was stirred at room temperature for 10 h before *p*-nitrosodimethyl aniline (1 mmol) was added. After being stirred for 4 h, the mixture was acidified with 3 N HCl (see the SI for details). [a]Yields are for the isolated product. [b]D in brackets represents deuteration, as determined by ^{1}H NMR. [c]Step 1 was conducted at 50 °C. [d]0.25 mmol of substrate **1q** was used.

Table 1. Optimization of the Reaction Conditions[a]



entry	pyridine derivative	solvent, base	yield[b] (%)	deuteration[c] (%)
1	I	DMSO, K_2CO_3	41	65
2	I	MeCN, K_2CO_3	trace	ND[d]
3	I	dioxane, K_2CO_3	28	12
4	I	DMF, K_2CO_3	39	62
5	I	DMSO, Na_2CO_3	41	<10
6	I	DMSO, Cs_2CO_3	trace	ND[d]
7	I	DMSO, K_3PO_4	48	85
8	II	DMSO, K_3PO_4	<10	<10
9	III	DMSO, K_3PO_4	67	82
10	IV	DMSO, K_3PO_4	22	44
11	V	DMSO, K_3PO_4	trace	ND[d]
12	VI	DMSO, K_3PO_4	trace	ND[d]
13[e]	III	DMSO, K_3PO_4	72	92
14[e,f]	III	DMSO, K_3PO_4	90 (88)[g]	95
15[h]	III	DMSO, K_3PO_4	88[g]	98

[a]Standard reaction conditions: a mixture of **1a** (0.5 mmol), pyridine derivative (1 mmol), solvent (3 mL), D_2O (0.5 mL), and base (2 mmol) was stirred at room temperature for 10 h before *p*-nitrosodimethyl aniline (1 mmol) was added. The resulting mixture was stirred for 4 h before being acidified with 3 N HCl (see the SI for details). [b]Yields based on ^{1}H NMR. [c]Deuterium incorporation determined by ^{1}H NMR. [d]Not determined. [e]1 mL of D_2O was used. [f]2 mmol of 4-picoline was used. [g]Yield of the isolated product. [h]0.25 mmol of **1a** was used.

nitrosodimethyl aniline (1 mmol) was added. The resulting mixture was stirred for a further 4 h and then acidified with 3 N HCl. To our delight, the expected product 2-naphthaldehyde (**2a**) was obtained in 41% yield and 65% deuteration (entry 1). Encouraged by the result, we attempted to optimize the reaction conditions to improve the yields and deuterium incorporations. Under the same reaction conditions, solvent screening indicated that the use of DMSO gave the best results both in yield and deuterium incorporation (entry 1), and DMF achieved a similar performance (entry 4), whereas 1,4-dioxane and CH_3CN led to poor results (entries 2 and 3). It was found that the bases were important for the process (entries 1, 5−7). K_3PO_4 with a little higher basicity favors the process (48% yield and 85% deuteration, entry 7). Na_2CO_3 offered the same yield to K_2CO_3 but much lower deuterium incorporation (entry 5). Only a trace amount of product was found with Cs_2CO_3 (entry 6). Consequently, DMSO and K_3PO_4 were chosen as the best solvent and base for further investigation of different pyridines to seek the optimal reaction conditions. Substituents of pyridines had a great effect on the reaction (entries 7−12). For instance, 4-picoline (**III**) gave the best results (67% yield and 82% deuteration, entry 9), while 2-picoline (**IV**) offered a much lower yield and deuterium incorporation, presumably due to steric reasons. Furthermore, pyridines with strong electron-donating (**II**, **V**) or -withdrawing groups (**VI**) had negative effects on the reaction (entries 8, 11−12). When a double amount of D_2O was used, the deuterium incorporation was improved to 92% (entry 13). A further increase of the amount of 4-picoline (**III**) to 4 equiv achieved the optimal result (entry 14). A higher deuterium incorporation (98%) could be obtained by reducing the amount of **1a** to 0.25 mmol (entry 15).

With the optimized reaction conditions in hand (Table 1, entry 14), we first probed the scope of the one-pot process using arylmethyl bromides as substrates. The results revealed that the protocol was suitable for the synthesis of structurally diverse deuterated aldehydes (Scheme 2). A broad range of substituted arylmethyl bromides were tested and were compatible with the process. Electron-deficient substrates (**1a**−**ah**) reacted smoothly to give the corresponding products (**2a**−**h**) in moderate to good yields (56−88%) and excellent deuterations (94−97%). Bromobenzyls with electron-donating groups (**1j**−**l**) also worked well, although a higher temperature (50 °C) was required for the formation of pyridinium salts. It was found that higher temperature promoted the formation of pyridinium salts and accelerated the H/D exchange process. Moreover, fluorine-containing and disubstituted bromobenzyls (**1i,l,m**) also reacted to obtain the corresponding deuterated aldehydes (**2i,l,m**) in moderate yields. Significantly, the 1-deuterioaldehyde synthesis method could be employed to

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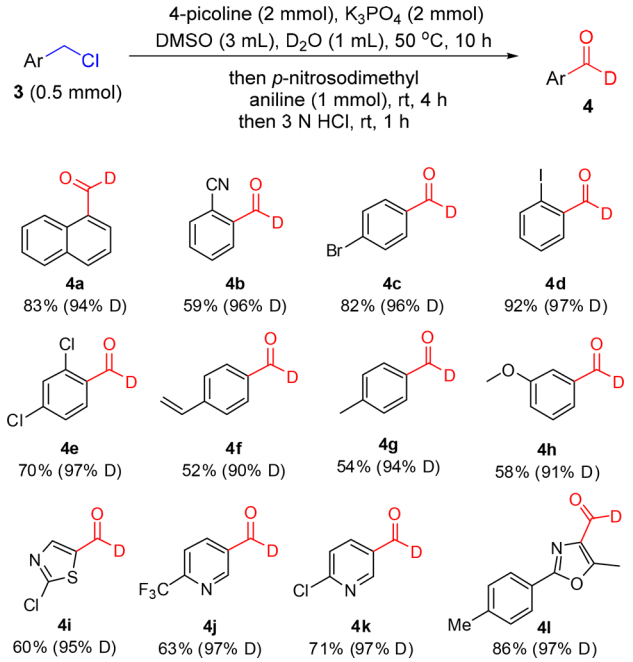
transform various pharmaceutically relevant heterocyclic arylmethyl bromides, such as those containing benzothiophene and pyridine rings, into the corresponding aldehydes **2n–p** in excellent yields (91–95%) and excellent deuterium incorporation (>93%). Bis(bromomethyl) binaphthalene **1q** also served as an effective substrate in this reaction, affording the corresponding aldehyde **2q** in good yield and excellent deuteration. However, aliphatic bromide substrates failed to form the pyridinium salt and the corresponding aldehydes cannot be obtained.

The scope of the transformation with respect to the arylmethyl chlorides was also explored under the optimized reaction conditions (Scheme 3). A series of structurally diverse

Scheme 3. Scope of the Deuterated Aldehyde Synthesis with Arylmethyl Chlorides*

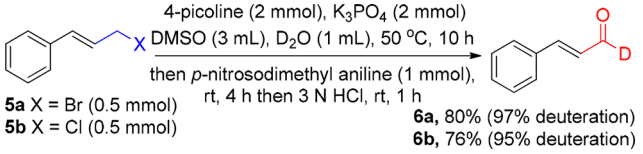


*Reaction conditions: see Scheme 2 and the SI. [a]Yields are for the isolated product. [b]D in brackets represent deuteration, as determined by ^{1}H NMR.

of arylmethyl chlorides were found to undergo the highly efficient one-pot process to form the corresponding 1-deuterioaldehyde products in high yields and excellent deuterium incorporations. The process tolerated a variety of functionalities, including naphthyl (product **4a**), cyano (product **4b**), halides (products **4c–e**) and vinyl (product **4f**). Electron-donating groups on benzyl chloride resulted in slightly decreased yields (product **4g,h**). Similarly, the reaction can be applied to generate deuterated aldehydes from arylmethyl chlorides containing pharmaceutically relevant hetereoaromatic moieties, such as thiazole (product **4i**), pyridines (products **4j** and **4k**), and oxazole (product **4l**). Similar to the aliphatic bromide substrates, the aliphatic chloride substrates also failed to form the pyridinium salt and the corresponding aldehydes.

Furthermore, the protocol was used to transform cinnamyl halides (**5a-5b**) into deuterated cinnamaldehydes (**6a-6b**) in good yields and excellent deuterations (Scheme 4). Notably, only the *trans* products **6a** and **6b** were formed, when *trans*

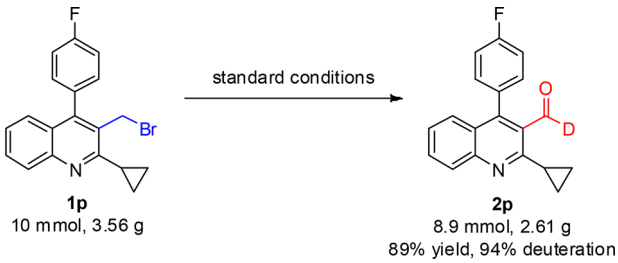
Scheme 4. Deuterated Cinnamaldehyde Synthesis from Cinnamyl Halides



cinnamyl halides were used. To the best of our knowledge, these reactions are the first examples of the formylation of deuterated cinnamaldehydes without applying deuterium-containing reductants.[14]

Finally, to highlight the practical nature of this new synthetic approach, a large-scale (10 mmol) reactions using pitavastatin (a cholesterol lowering drug) intermediate **1p** was performed (Scheme 5). We found that the new methodology is compatible

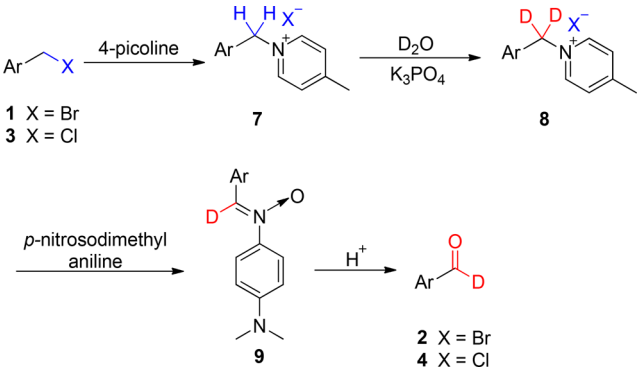
Scheme 5. Gram-Scale Synthesis of Aldehyde-Deuterated Pitavastatin Intermediate 2p



with gram-scale application. Under the standard conditions, aldehyde-deuterated pitavastatin intermediate **2p** was obtained in 89% isolated yield and 94% isotope purity (see the SI for details).

Similar to the Kröhnke oxidation (Scheme 1, eqs 2),[13] a plausible reaction mechanism is proposed for the one-pot synthesis of deuterated aldehyde from arylmethyl halides (Scheme 6). Condensation of arylmethyl halide (**1**, **3**) and 4-

Scheme 6. Proposed Mechanism for One-Pot Synthesis of Deuterated Aldehydes



picoline (**III**) produces pyridinium salt **7**. Then the benzyl hydrogens are exchanged to deuterium in the presence of D_2O and K_3PO_4 to give deuterated pyridinium salt **8**. Oxidation of intermediate **8** by *p*-nitrosodimethyl aniline affords **9**. Finally, acidification of **9** gives corresponding deuterated aldehyde. To support the proposed mechanism, we synthesized and isolated pyridinium salt **7a** (Ar = 2-naphthalene) by mixing 4-picoline

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(III) and 2-(bromomethyl)naphthalene (**1a**) in toluene. Pyridinium salt **7a** could transformed to **2a** in high yield under the standard conditions (Scheme S2). Moreover, deuterated pyridinium salt **8a** (Ar = 2-naphthalene) was detected by LC−MS. These results can support the proposed mechanism.

In conclusion, an efficient one-pot approach was developed to synthesize deuterated aldehydes from arylmethyl halides. The process was realized by formation, H/D exchange, and oxidation of pyridinium salt intermediates, in which inexpensive 4-picoline, readily available nitrosobenzene and D_2O, was used to facilitate the transformations. Moderate to excellent yields and excellent deuterium incorporation can be achieved under mild conditions. Significantly, this protocol can be applied to the synthesis of aldehyde-deuterated pharmaceutical intermediates and deuterated cinnamaldehydes. The results of this study expand the access to 1-deuterioaldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00016.

Experimental details and analytical data PDF)

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Author Contributions

§X.L., S.W., and S.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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