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Deuterated ammonium formate as deuterium source in a mild catalytic deuterium transfer reaction of pyridines, pyrazines and isoquinolines

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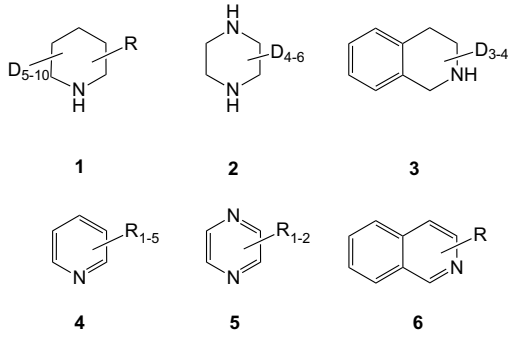
Abstract—The application of deuterated ammonium formate as deuterium source in transfer deuteration reactions of aromatic heterocycles (**4**–**6**) for the synthesis of highly deuterated, substituted piperidines (**1**), piperazines (**2**) and tetrahydroisoquinolines (**3**) has been developed.

1. Introduction

Piperidines **1**, piperazines **2** and tetrahydroisoquinolines **3** are commonly used building blocks in pharmaceutical drugs (Scheme 1).[1] In recent years many methods for the synthesis of these cyclic amines **1**–**3** with a wide variety of substitution patterns or stereoisomers have been developed.[2] One of these methods, the catalytic hydrogenation of substituted pyridines **4**, pyrazines **5** and isoquinolines **6**, is an especially direct approach.[3] However, in most examples hydrogen under high pressure and temperatures have been used wherein sometimes special equipment became necessary. As a practical alternative milder reduction conditions have been established by the catalytic transfer hydrogenation using Pd/C as catalyst and ammonium formate as in situ hydrogen source.[4] However, for the synthesis of isotopically labelled molecules this method has rarely been applied.[5] The deuterated heterocycles **1**–**3** are of interest as building blocks for the preparation of labelled drug candidates needed as internal standards in LC/MS assays. Here we report the development of a catalytic transfer deuteration reaction using deuterated ammonium formate as deuterium source under mild reaction conditions.



Scheme 1.

2. Results and discussion

We first investigated as a model the transfer deuteration reaction of 4-carboxyl-pyridine N-oxide **4a** with different deuterated (D_{3-5}) ammonium formate salts in methanol (CH_3OH, CH_3OD and CD_3OD) and Pd/C (10%) as catalyst to study the influence of the deuterium source and the solvent on the yield and deuteration level (Scheme 2, Table 1). Independent of the deuterium source all reactions carried out in methanol (CH_3OH) yielded a low deuterium level (entries 3 and 7). However, in reactions in methanol (CH_3OD) with undeuterated ammonium formate a moderate deuterium transfer was observed (entry 1). Also, we observed no difference

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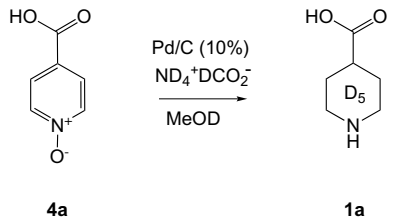


Scheme 2.

in reactions using methanol-D_1 (CH_3OD) or methanol-D_4 concerning deuteration level or yield (entries 5 and 6). Next we investigated the influence of differently deuterated ammonium formate (D_0–D_5) salts on the deuterium level of the product. Transfer deuteration reactions in methanol-D_1 with ammonium formate (ND_3HCO_2H, entry 2) and (ND_3HCO_2D, entry 4) yielded only moderate deuterium levels in the product. The deuterium content in the product could be increased when fully deuterated ammonium formate (ND_3DCO_2D) in deuterated methanol (CH_3OD, CD_3OD) (entries 5 and 6) was utilised. Remarkably, we detected in the products of these reactions a higher level of deuterium ($D_{6,7}$) than expected (D_5).

Further we applied the transfer deuteration reaction to different types of pyridines. In all reactions wherein halogenated pyridines were used under the described reaction conditions all halogen atoms were substituted by deuterium (Fig. 1). However, we found again that reactions with partly halogen-substituted pyridines yielded a broader mass distribution in the products. We suggest that under our reaction conditions next to the reduction of the aromatic ring a hydrogen/deuterium exchange takes place.

For the transfer hydrogenation there are two possible mechanistic pathways discussed in the literature (Scheme 3). While the homogeneous hydrogenation predominantly follows pathway (a)[6a] wherein the active species is formed by an intermediate with only one formate molecule substituted to palladium, it is suggested by Yu and Spencer that palladium diformate plays a major role in heterogeneous hydrogen transfer reaction. The deuterium is transferred in pairs from either the

Table 1. Reaction of 4-carboxyl-pyridine N-oxide **4a** with Pd/C (10%) and 10 equiv ammonium formate at room temperature

Entry[e]	H/D-source	Solvent	Yield **1a**[d] (%)	$M_{D_0}{}^{+H}$	$M_{D_1}{}^{+H}$	$M_{D_2}{}^{+H}$	$M_{D_3}{}^{+H}$	$M_{D_4}{}^{+H}$	$M_{D_5}{}^{+H}$	$M_{D_6}{}^{+H}$	$M_{D_7}{}^{+H}$
1	NH_3HCO_2H	CH_3OD	85	2.3	11.8	28.0	31.8	19.5	5.7	0.8	—
2	ND_3HCO_2H[a]	CH_3OD	83	0.4	2.4	12.0	27.3	33.1	19.7	4.8	0.2
3	ND_3HCO_2H[a]	CH_3OH	92	87.4	11.6	1.0	0.1	—	—	—	—
4	ND_3HCO_2D[b]	CH_3OD	86	0.3	2.1	10.5	26.9	33.6	21.4	5.4	0.6
5	ND_3DCO_2D[c]	CH_3OD	83	—	—	—	0.3	5.4	37.5	36.5	16.3
6	ND_3DCO_2D[c]	CD_3OD	85	—	—	—	0.5	5.7	38.5	35.2	15.9
7	ND_3DCO_2D[c]	CH_3OH	76	44.1	37.6	14.7	3.1	0.5	0.1	—	—
8	DCO_2Na	CH_3OD	35	—	0.7	1.9	2.5	11.7	48.0	25.1	10.1

[a] Prepared by titration of ammonia (25% ND_3 in D_2O) with formic acid (D_0).
[b] Prepared by three times hydrogen/deuterium exchange from ND_3HCO_2H[a] in D_2O (99% deuterium).
[c] By titration of ammonia (25% ND_3 in D_2O) with formic acid (D_2).
[d] Isolated yield of the hydrochloride.
[e] M^{+H} determined by MS,[9] sum of values not always reach 100%.

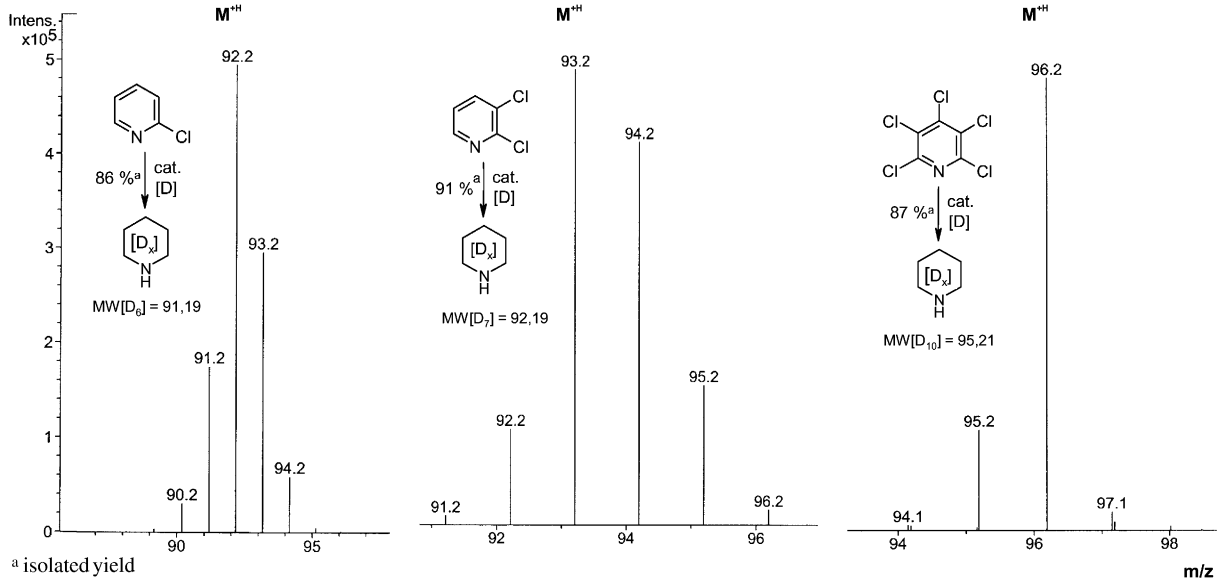
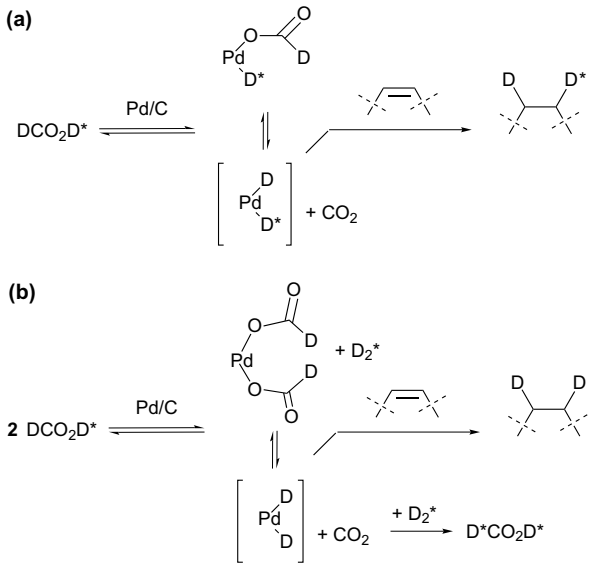


Figure 1. Mass distribution of deuterated piperidine from the transfer deuteration reactions of 2-, 2,3- and pentachloro pyridine.[9,10]



Scheme 3.

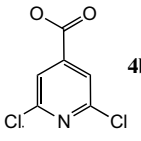
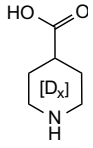
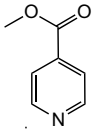
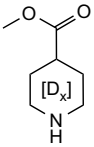
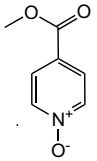
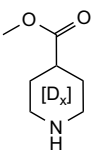
formyl or carboxy position of two molecules of formic acid.[6b] The dramatic influence of the solvent in the model reactions (Table 1) can be explained by the reduction of carbon dioxide with in situ generated hydrogen/deuterium, which is formed from the labile carboxy position.

The reaction of 4-carboxy-2,6-dichloropyridine yielded the deuterated 4-carboxy piperidine in 86% yield (Table 2, entry 1). Even 2-fluoropyridine **4c** was completely reduced to deuterated piperidine (D_6) **1b** (entry 2) after prolonged reaction time. In the reactions of isonicotinic acid methylester **4d** and the corresponding N-oxide **4e** we found similar isotope ratios in the two products **1d** (entries 5 and 6). As reported by *Balicki* in 1989 pyridine N-oxides can easily be deoxygenated to pyridines by 2 equiv of ammonium formate and Pd/C at room temperature within a few minutes.[7] Furthermore Zacharie et al. reported that pyridine N-oxides can be reduced to piperidines by a transfer hydrogenation reaction under similar reaction conditions.[8] This suggests that for the reduction to piperidines there is no need to start from the N-oxides as was shown in our example reaction with isonicotinic acid methylester and the corresponding N-oxide (Table 2, entries 5 and 6).

The scope of this method was broadened by reduction of pyrazines **5a–c** and quinolines **6a,b** (Table 3). In the transfer deuteration reactions of pyrazines **5a–c** the deuterated piperazines **2a–c** were obtained in 84–92% yield (entries 1–3) with high deuterium content. However, we observed a broad mass distribution in the isotopic products. In the reductions of the quinolines **6a,b** only moderate yields from 57% to 67% were observed (entries 4 and 5)—the mass distribution was analysed to be much narrower. We suggest that depending on the higher flexibility in the ring system of piperazines **2** compared to isoquinolines **3** hydrogen/deuterium exchange should be increased.

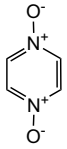
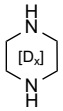
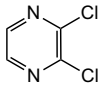
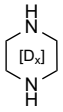
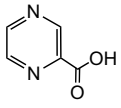
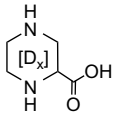
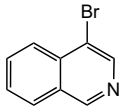
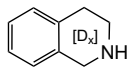
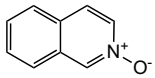
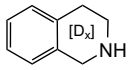
In general, depending on the substituent pattern of the aromatic compound the reactions reached complete conversion after 12–18 h. However, we proved in a single

Table 2. Transfer deuteration reactions of pyridines **4b–e** with Pd/C (10%) as catalyst and $ND_4^+DCO_2^-$ as deuterium source

Entry	Starting material	Product	Yield[a] (%)	[%D_x][b]
1	 **4b**	 **1a**	86	D_5 D_6 D_7 D_8 D_9 4 19 43 31 3
2[c]	 **4c**	 **1c**	83	D_5 D_6 D_7 D_8 D_9 5 31 48 14 2
3	 **4d**	 **1d**	87	D_3 D_4 D_5 D_6 D_7 1 8 34 32 17
4	 **4e**	 **1d**	85	D_3 D_4 D_5 D_6 D_7 3 12 48 25 10

[a] Isolated overall yield of deuterated products [D_x], chemical purity >95% (determined by NMR, HPLC or LC–MS).
[b] Determined by MS analysis[10] of a single experiment after filtration of the reaction mixture; replications of the experiments yielded slightly different mass distributions; [%D] value shows the relative distribution of mass units in the product.
[c] Doubled reaction time.

Table 3. Transfer deuteration reactions of pyrazines **5** and isoquinolines **6** with Pd/C (10%) as catalyst and $ND_4^+DCO_2^-$ as deuterium source

Entry	Starting material		Product		Yield[a] (%)	$[\%D_x]$[b]
1		**5a**		**2a**	88	D_2 D_3 D_4 D_5 D_6 2 7 15 24 27
2		**5b**		**2a**	92	D_4 D_5 D_6 D_7 D_8 3 12 27 32 23
3		**5c**		**2b**	84	D_2 D_3 D_4 D_5 D_6 2 9 35 34 16
4		**6a**		**3a**	57	D_3 D_4 D_5 D_6 D_7 1 4 62 27 6
5		**6b**		**3a**	67	D_3 D_4 D_5 D_6 D_7 1 7 65 22 4

[a,b]See Table 2.

experiment that it is possible to accelerate the reaction by microwave-assisted conditions. In this reaction of 4-carboxyl-pyridine N-oxide **4a** with deuterated ammonium formate in methanol (CH_3OD) and Pd/C (10%) we yielded the desired product **1a** after 20 min (80 °C) in 86% yield and a comparable deuteration level.

3. Conclusion

We have developed a simple procedure for the preparation of deuterated piperidines **1**, piperazines **2** and tetrahydroquinolines **3** by transfer deuteration reaction. All products were obtained in moderate to good yields with a high deuterium content. We are confident that this method tolerates a high variety of functional groups like amines, amides, esters, carboxylic acids, alcohols, etc., and therefore can be widely used. Furthermore we found that for the preparation of deuterated standards for LC/MS assays fully halogen-substituted precursors are particularly suitable.

Acknowledgements

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References and notes

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9. *Typical reactions conditions*: Into a round bottom flask was given 1 mmol pyridine and 20 mg dry Pd/C (10% Pd) and the flask was filled with argon during 10 min. The pyridine was dissolved in 5 mL methanol (CH_3OD)

followed by addition of 10 equiv solid ammonium formate (ND_3DCO_2D). The reaction mixture was warmed to 50 °C over 12–18 h in a sealed flask, filtered and 1 mL HCl in methanol (1.25 M) was added. The solvent was removed in vacuo and the residue was purified by HPLC reversed phase chromatography (>95% purity by HPLC or LC/MS).

10. The MS spectra were recorded on a Bruker esquire 3000 mass spectrometer or a Agilent 1100 series LC–MS system.