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COMMUNICATION

Selective deuteration of (hetero)aromatic compounds *via* deutero-decarboxylation of carboxylic acids†

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A practical, mild and highly selective protocol for the mono-deuteration of a variety of arenes and heteroarenes is presented. Catalytic amounts of Ag(I) salts in DMSO/D_2O are shown to facilitate the deutero-decarboxylation of *ortho*-substituted benzoic and heteroaromatic α-carboxylic acids in high yields with excellent levels of deuterium incorporation.

Synthetic procedures able to incorporate deuterium (D) and tritium (T) into organic molecules are highly sought after for a plethora of applications:[1] deuterium-labelled compounds are commonly used for mechanistic investigations of catalytic cycles and reaction pathways,[2] in stable-isotope tracer studies, as analytical standards,[3] in neutron scattering,[4] and for the synthesis of drug compounds with enhanced metabolic stability.[5] On the other hand, tritium is arguably the most versatile radionuclide available, with tritiated compounds regularly exploited as radiotracers in the pharmaceutical industry from drug discovery level to clinical studies.[1,6] Synthetic methods for the preparation of deuterated compounds are regularly applied towards the synthesis of their tritium-labelled isotopologues, and deuteration methodologies are commonly used as synthesis optimisation tools for subsequent tritium labelling.[1] Despite the high demand, methods for the selective incorporation of a single deuterium into an aromatic ring are scarce.[1,7,8] The most common protocol involves halogen/D exchange; this is usually mediated by strong bases, with the consequent limitation in functional group scope. H/D exchange reactions can also be employed with the use of strong acids,[9] bases,[10] or transition metal catalysts.[11] However,

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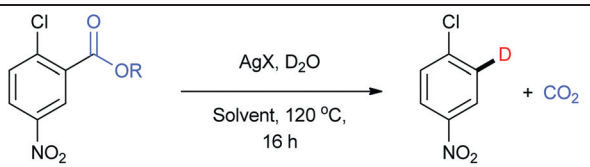
Table 1 Optimisation of the Ag(I)-catalysed deutero-decarboxylation[a]

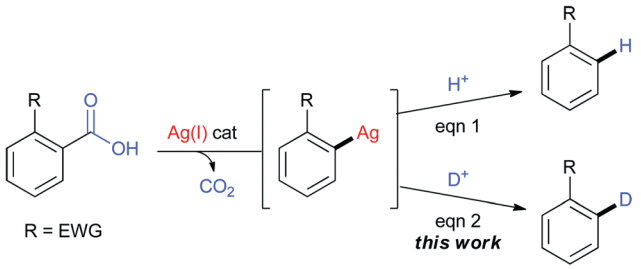


R = H, **1a**
R = Na, **Na-1a**
R = K, **K-1a**

2a

Entry	Substrate	AgX	(Mol %)	D_2O (equiv.)	Solvent	Yield[b] (%)	D (%)[c]
1	**Na-1a**	$AgNO_3$	(20)	10	DMSO	35	87
2	**Na-1a**	AgOTFA	(20)	10	DMSO	20	92
3	**Na-1a**	AgOAc	(20)	10	DMF	61	85
4	**K-1a**	$AgNO_3$	(20)	10	DMF	39	77
5	**K-1a**	AgOTFA	(20)	10	DMF	30	70
6	**K-1a**	AgOAc	(20)	10	DMF	20	77
7	**1a**	Ag_2CO_3	(10)	0	DMSO	100	0
8	**1a**	Ag_2CO_3	(10)	10	DMSO	100	82
9	**1a**	**Ag_2CO_3**	**(10)**	**50**	**DMSO**	**92**	**92**
10	**1a**	Ag_2CO_3	(10)	100	DMSO	48	91

[a] Reaction conditions: the reactions were carried out using 1.0 equiv. of the substrate and the indicated amounts of Ag(I) catalyst and D_2O in a 0.2 M solution of the stated solvent. [b] The yield of **2a** was determined by ^1H NMR analysis using mesitylene as an internal standard. [c] The extent of deuteration of **2a** was determined by ^1H NMR analysis using mesitylene as an internal standard.



Scheme 1 Ag(I)-catalysed proto- and deutero-decarboxylations of benzoic acids (eqn (1) and (2), respectively).

these processes are generally non-selective, and only several examples are known where good selectivity is achieved.[12] Accordingly, there is a great need for the development of mild and selective methodologies for the incorporation of deuterium into aromatic rings.

Recently, we developed an operationally simple, high yielding proto-decarboxylation of *ortho*-substituted benzoic and hetero-aromatic α-carboxylic acids catalysed by Ag_2CO_3.[13,14] This process is believed to proceed *via* an aryl–Ag(I) intermediate that is subsequently protonated (Scheme 1, eqn (1)). We hypothesised that if this reaction was carried out in the presence of a D^+ source, it could lead to selective incorporation of deuterium (Scheme 1, eqn (2)).[15]

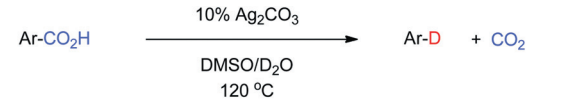
Initially, in order to completely avoid the presence of H^+ in the reaction, we tested the decarboxylation of K and Na salts of benzoic acid **1a** (Table 1, entries 1–6) with a variety of Ag(I) catalysts, in combination with 10 equiv. of D_2O.[16] Gratifyingly, good levels of deuterium incorporation were observed in the resulting arene **2a**, albeit in moderate to good yields. Pleasingly, direct decarboxylation of the carboxylic acid **1a** with Ag_2CO_3 afforded higher yields and a similarly good level of deuteration when carried out in the presence of 50 equiv. of D_2O (entries 7–10).

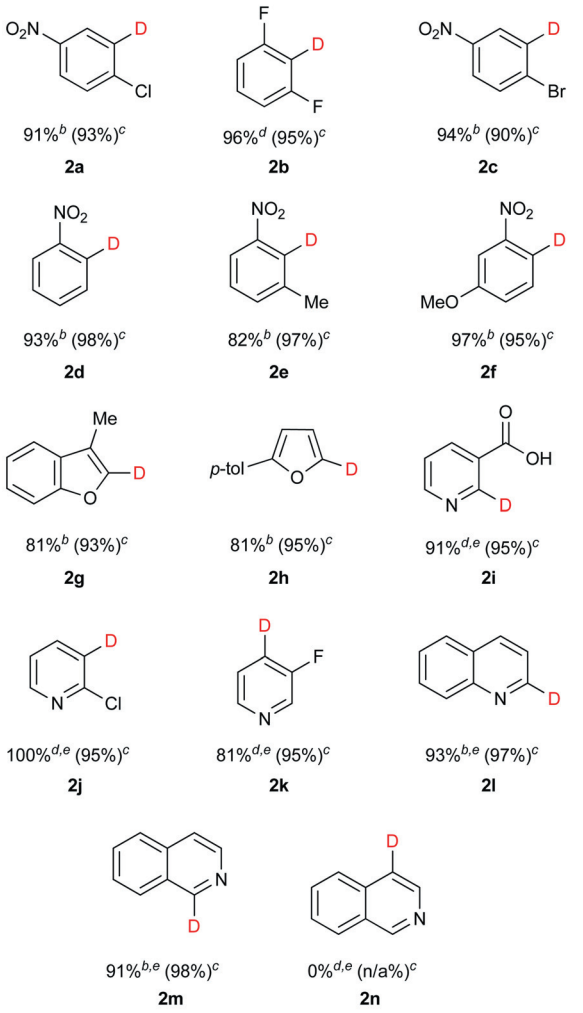
With this optimised protocol in hand, we examined the scope of the reaction (Table 2). The standard reaction conditions consistently afforded high yields (82–100%) and deuteration selectivities (91–99%) with a variety of substituted benzoic acids.

This methodology allows the synthesis of arenes deuterated *ortho* to a variety of electron-withdrawing substituents such as Cl (**2a**), F (**2b**), Br (**2c**) and NO_2 (**2d–f**) under very mild and practical conditions: the benzoic acid is simply mixed with the catalyst and 50 equiv. of D_2O, and heated up in DMSO. After the reaction, the residual amounts of starting material are easily removed during aqueous workup, affording high purity product after solvent evaporation, thus removing the need for column chromatography or distillation. Alternative routes to these substrates generally involve treatment of the corresponding *ortho*-halo arene with a strong alkyl-lithium base, followed by quench with D^+, and sometimes challenging purifications.[17]

This protocol can also be successfully applied to heteroaromatic carboxylic acids (Table 2, **2g–m**). Thus, furans and benzofurans, selectively deuterated at position 2, can be easily prepared. Similarly, it is possible to selectively deuterate pyridine at positions 2, 3 or 4 by judicious choice of the carboxylic acid starting material (**2i–k**). Finally, quinolines are also amenable for selective deuteration at the position α to the heteroatom (**2l–m**).

Table 2 Substrate scope for the deutero-decarboxylation of homo- and hetero-aromatic carboxylic acids[a]





[a] Reaction conditions: all the reactions were carried out with 10 mol% Ag_2CO_3, 1.0 equiv. of aromatic carboxylic acid (**1**) and 50 equiv. of D_2O in a 0.2 M DMSO solution at 120 °C for 16 h. [b] Yields of isolated analytically pure material. [c] Percentage of deuteration was determined by ^1H NMR analysis using mesitylene as an internal standard. [d] The yield was determined by ^1H NMR analysis using mesitylene as an internal standard. [e] The reaction was carried out at 140 °C.

Remarkably, this method is completely selective for the C bearing the carboxylic acid and no deuteration is observed at any other position, as determined by ^2H NMR, even for arenes bearing electron-donating MeO substituents (**2f**) and for the nucleophilic furan **2h**.

In conclusion, we have developed a mild and practical methodology for the Ag(I)-catalysed deutero-decarboxylation of a variety of aromatic acids, bearing the carboxyl motif *ortho* to a functional group or α to a heteroatom. The protocol is

chemoselective and compatible with a wide range of synthetically useful functionalities such as halogens and nitro groups. Moreover, it is high yielding and affords excellent levels of selective deuterium incorporation. It is envisaged that this methodology should be easily adapted towards the tritium-labelling of pharmaceutically interesting molecules to aid drug development and clinical studies.

During the preparation of this manuscript, a methodology describing silver and copper mediated decarboxylative deuterations was reported by Goossen.[18]

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