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One-step exchange-labelling of pyridines and other *N*-heteroaromatics using deuterium gas: catalysis by heterogeneous rhodium and ruthenium catalysts

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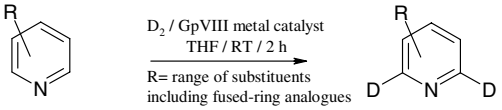
Abstract—A wide range of pyridines and other nitrogen heteroaromatics can be labelled with deuterium at room temperature and pressure by isotopic exchange with deuterium gas in THF in the presence of rhodium black, ruthenium black or 5% rhodium on alumina. The labelling is rapid, isotope efficient and applicable to both electron-rich and electron-poor substrates. In a few cases, a degree of reduction accompanies the exchange.

Pyridine and other *N*-heteroaromatic sub-units occur in many industrially important chemicals including a range of agrochemical and pharmaceutical agents. Methods for labelling these units with isotopes of hydrogen are therefore of interest since they provide routes to the tritium-labelled compounds for use in environmental, absorbtion, distribution, metabolism or toxicokinetic radiotracer studies. They also provide access to the deuterium-labelled compounds for use in stable-isotope tracer studies or for GC–MS or LC–MS internal standardisation.

Unfortunately, efficient methods for direct labelling of such *N*-heterocyclics via isotopic exchange are quite limited. Most involve a requirement for a directing group within the substrate to facilitate *ortho*-labelling[1] or for some other such activating substituent.[2] Others necessitate the use of isotopic water in conjunction with a Group VIII metal[3] with the consequent problems of potential radiotoxicity, or of product radiolysis, should high specific activity tritium-labelling be required. Sometimes, reaction conditions involve acid-catalysis or very high temperatures.[4] In many cases, labelling of the pyridine moiety has only been observed as an artefact[5] alongside the labelling of other targeted molecular sites.

Only a few methods describe the direct exchange-labelling of unactivated *N*-heteroaromatics using an isotopic hydrogen gas donor with commonly available catalysts.[6] One such report, describes the use of 5% ruthenium on carbon catalyst for the labelling of pyridines using deuterium gas and deuterated methanol.[6b] Unfortunately, we have shown that the isotopic labelling achieved with this method results to a significant degree from the deuterated solvent as well as from the D_2 gas, rendering the method unsuitable for tritium labelling applications. An additional drawback of the method is that the activity of the catalyst is very low, necessitating the use of pressurised D_2, again an undesirable operation with the tritium isotope.

Recognising all the above limitations, we have screened other potential Group VIII metal catalysts for this type of deuterium gas exchange process (Scheme 1) so as to identify systems with greater potential for use with both the deuterium and tritium isotopes.



Scheme 1.

Keywords: Pyridine; *N*-Heteroaromatic; α-Exchange; Deuteration; Tritiation; Ruthenium black; Rhodium black; Rhodium on alumina; Isotope-exchange; Deuterium gas.
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A wide range of supported and unsupported noble metal catalysts were screened and three catalysts were identified, which transferred the isotope efficiently from deuterium gas to the substrate. Moreover, these catalysts were far more active than the literature catalyst, allowing their use at ambient temperature and pressure in non-hydroxylic solvents. The active catalysts were rhodium black, ruthenium black and 5% rhodium on alumina. Next, these new catalysts were evaluated against a panel of pyridines and other *N*-heteroaromatics specifically selected to investigate various stereoelectronic and regiochemical aspects of the labelling processes.

The results of this study are summarised in Table 1.

Overall, the data shows that many *N*-heteroaromatics can be efficiently labelled using this simple procedure. Moreover, combined ^{1}H and ^{2}H NMR studies demonstrated clearly that the procedure leads to highly regioselective (and in many cases regiospecific) labelling in positions α to nitrogen.

Six of the substrates (3- and 4-acetylpyridine, 7,8-benzoquinoline, 2-phenylpyridine, 4-dimethylaminopyridine and 2-methoxypyridine) were selected to check for concomitant labelling at other favourable sites via base-catalysed, *ortho*-directed[1] or heteroatom-directed methyl/methylene labelling processes.[1c,d,5d] However, only one example of such behaviour was observed: both α- and *ortho*-labelling[1] was observed with 2-phenylpyridine.

Previous work has shown that tight binding of the substrate to the catalyst surface can inhibit labelling in metal catalysed exchange[3b,i,6b] and indeed 2,2′-bipyridyl does show a reduced extent of labelling in comparison with the 4,4′-linked analogue, consistent with the expected bidentate complexation with the surface. However phthalazine, another bidentate substrate, and 2-bromopyridine, both of which are able to bind strongly, and which were indeed recovered unlabelled from a previous study,[6b] were nevertheless labelled by the new catalysts.

In common with many other metal-catalysed isotopic exchange methods[7] the procedure appears to be applicable to both electron-rich and electron-deficient substrates. Moreover, various fused-ring pyridine analogues are labelled. Both these behaviours bode well for the general applicability of the method.

In a few cases, a degree of reduction or other decomposition accompanied the isotope exchange, though for most substrates examined this behaviour was absent or of marginal significance. Moreover, selection of a different catalyst can avoid such behaviour in some cases (see Table 1).

An important parameter for any labelling reaction is the isotopic incorporation and this was satisfactorily high under the simple protocol utilised.[8] Indeed in separate experiments with no changes of deuterium gas it was close to the equilibrium value calculated for the exchangeable hydrogen isotope pool in the reactions.

The method has also proved amenable to use with the tritium isotope, at least at low specific activity. Thus exchange of 4,4′-bipyridyl with deuterium tritide over rhodium black yielded [2,6,2′,6′-^{2}H, 2,6,2′,6′-^{3}H]4,4′-bipyridyl in a single high-yielding exchange step. ^{3}H NMR analysis of this product showed a single triton resonance corresponding to tritium-labelling exclusively at the α-positions. There were no other resonances,

Table 1. Labelling of pyridines and other nitrogen heteroaromatics using heterogeneous Ru and Rh catalysts and deuterium gas in tetrahydrofuran at ambient temperature and pressure

Substrate	Deuterium labelling α to nitrogen		
	Rh black	Ru black	5% Rh/alumina
3-Acetylpyridine	—[a]	99%	99%
4-Acetylpyridine	99%	0%	83%
3-Aminoquinoline	83%	99%	43%
7,8-Benzoquinoline	90%[a]	0%	0%
2-Benzylpyridine	99%	8%	22%
4-Benzylpyridine	99%	0%[a]	76%
2,2′-Bipyridyl	35%	0%	19%
4,4′-Bipyridyl	75%	47%	75%
2-Bromopyridine	28%	0%[a]	0%
4-Dimethylaminopyridine	100%	47%	50%
Isoquinoline	90%(C-1)	62%(C-1)	11%(C-1)
	86%(C-3)	87%(C-3)	11%[c](C-3)
2-Methoxypyridine	16%	9%	4%
4-Methylpyridine	98%[a]	85%	83%
2-Phenylpyridine	20%[b]	11%	0%
Phthalazine	61%	23%	27%
Quinoline	99%[a]	27%	53%[c]

Conditions: The substrate (ca. 0.13 mmol) and catalyst (10 mg) in THF (1 ml) were stirred under D_2 gas for 2 h at ambient pressure and temperature, replacing the D_2 gas twice during the course of the exchange.

[a] Indicates concomitant decomposition or significant reduction under the reaction conditions.

[b] In addition there was ca. 35 atom % D at each of the *ortho*-positions of the phenyl ring.

[c] Indicates a small amount of concomitant reduction.

confirming the absence of any concomitant reduction or other decomposition.

In summary, the labelling procedure is highly regioselective with all three catalysts. Moreover, it is simple to carry out, yields are high and isolation of the product is generally straightforward, often a simple filtration and evaporation of the solvent.[8] The scale of the sample preparation was chosen to model the preparation of tritiated compounds or of MS internal standards (where a small scale is often required for the efficient utilisation of the tritium isotope or by the limited availability of the substrate or analyte), however, it has been successfully scaled-up by two orders of magnitude.

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8. 4,4′-Bipyridyl (22 mg) and rhodium black (10 mg) were dissolved in dry THF (1.0 ml) and stirred under deuterium gas at room temperature and pressure for 5 h. During this period, the deuterium gas (99 atom % D) was replaced five times. The catalyst was filtered off and washed with THF and the combined filtrates evaporated under a stream of nitrogen to yield essentially pure labelled bipyridyl (22 mg,

98%), which was crystallised by dissolution in a minimum of dichloromethane and treatment with hexane to yield [2,6,2′,6′-$^{2}H_4$]4,4′-bipyridyl (first crop, 15 mg, 67%, mp 112–113 °C) (authentic unlabelled standard, 112–113 °C), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (4H, s, β-protons), 8.76 (0.1H, d, $J = 6.0$ Hz, residual α-protons) ppm. ^{2}H NMR ($CHCl_3$, 77 MHz) δ 8.76 (s, α-deuterons) ppm, EI-MS ($M+4\times{}^{2}H$) gives 160.093 amu, $C_{10}H_4{}^{2}H_4$ requires 160.093 amu. The overall α-deuteration achieved by this procedure was 97.5 atom %.