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Research Article

Labelling of anilines, benzylamines and some *N*-heterocyclics using cycloocta-1,5-dienyliridium(I) -1,1,1,5,5,5-hexafluoro-pentan-2,4-dionate and isotopic hydrogen gas in DMF or DMA

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Summary

A wide range of anilines, benzylamines and some *N*-heterocyclics can be *ortho*-deuterated at room temperature using deuterium gas and cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate in DMF or DMA. The method is applicable to labelling with tritium. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: anilines; benzylamines; *ortho*-labelling; cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate; deuteration; CH-activation; isotope-exchange; COD.Ir.F_6Acac

Introduction

The preparation of compounds labelled with isotopes of hydrogen is of great importance in the biological and life sciences. Amongst the most powerful of the methods used is *ortho*-directed exchange between an aromatic substrate and isotopic hydrogen gas (Figure 1). The most commonly employed catalysts for this process are Crabtree's catalyst or variants thereof.[1]

Such catalysts are essentially limited to compounds soluble in non-polar solvents, or which are easily recovered from ionic liquid matrices[2] and a consequence of this is that it excludes many polar and ionic compounds of interest.

If the compound to be labelled is not amenable to the above techniques, recourse can still be made to *ortho*-exchange using isotopic water as the

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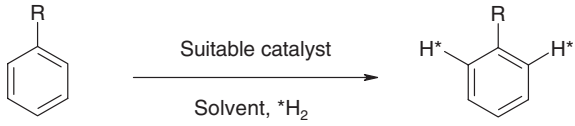


Figure 1. *Ortho*-exchange with isotopic hydrogen gas

isotope donor. This method is compatible with several dipolar aprotic solvents and, since deuterium oxide may easily be employed in high molar concentrations, it is the preferred option for labelling with deuterium at high isotopic abundance. The approach is also applicable to the preparation of tritium-labelled compounds at low[3] and high[4] specific activities, though tritium gas is usually preferred in the latter case, since it is easier to handle and generally produces less radiolysis than high specific activity tritium oxide.

Recently we developed several new and efficient catalysts for this isotopic water exchange[5] and in the current paper we report the application of the most effective of these catalysts, (cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate, **1**), to the labelling of several classes of aromatic substrates using isotopic hydrogen gas. A preliminary account of some of these studies has been published.[6]

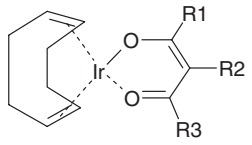
Results and discussion

In a previous paper in this journal,[7] we identified a wide selection of cycloocta-1,5-dienyliridium(I)-2,4-pentandionates as catalysts for the *ortho*-labelling of a range of aromatic substrates using isotopic water as the isotope donor. Several of these catalysts also proved capable of promoting isotopic exchange between deuterium gas and suitable substrates in dichloromethane.

When the solvent was changed to DMF or DMA, only three of the catalysts showed good activity. Of these three compounds, catalyst **2** could not be prepared routinely in high purity and was unstable upon storage. Furthermore, when compared directly across a range of substrates, **2** proved less active than **1**. Although easily prepared, catalyst **3** was less active and yielded lower regiospecificity for the *ortho*-exchange process than **1**. Consequently, all further studies concentrated upon **1** alone (Figure 2).

When screened in DMA against a range of substrate classes, **1** proved most active with anilines, benzylamines and with those *N*-heterocyclics which could promote *ortho*-exchange into an adjacent ring (Table 1). The activity of the catalyst with the two classes of amines, is particularly useful since these functions are not efficient directing groups for catalysts of the Crabtree type.

It should be noted that a sub-optimal catalyst loading (25%) was used throughout these studies to enable a good differentiation between the extent of labelling obtained for the various substrates. Labelling at higher abundance is



1, R1=CF_3, R2=H, R3=CF_3
2, R1=CF_3, R2=F, R3=CF_3
3, R1=CH_3, R2=H,R3=CO_2Et

Figure 2. Cycloocta-1,5-dienyliridium(I) dionate catalysts active with deuterium gas in DMF or DMA

easily achieved by the use of either higher catalyst loading or longer reaction times, or both.

No significant labelling was seen with acids, amides or esters when the solvent was DMA or DMF, however, the catalyst was active with a wider range of directing groups in both acetone and acetonitrile. Interestingly, the latter is a solvent in which the Crabtree catalyst shows little activity with any substrate.

Table 1. Deuteration of various substrates by 1 and D_2 gas in DMA

Substrate	Atom%D (No. of atoms)	Labelling assigned by
4-Aminoacetophenone	72% (2)	^{1}H-NMR/MS
4-Aminobenzoic acid	80% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Aminotoluene	77% (2)	^{1}H-NMR/MS
3-Aminoquinoline	30% (2)a	^{1}H-NMR/MS
7,8-Benzoquinoline	36% (1)	^{1}H-NMR/^{2}H-NMR/MS
Benzylamine	70% (2)	MS only
Biphenyl-2-ylmethylamine	38% (1)	MS only
Biphenyl-3-ylmethylamine	49% (2)	MS only
4-Dimethylaminobenzoic acid	11% (2)	MS only
N,*N*-Dimethylbenzylamine	35% (2)	^{1}H-NMR/MS
1,2-Diphenylethylamine	57% (4)	MS only
1,1-Diphenylmethylamine	50% (4)	^{1}H-NMR/^{2}H-NMR/MS
1-(4-Fluorophenyl)ethylamine	66% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Amino-2-hydroxybenzoic acid	55% (2)b	^{1}H-NMR/MS
4-Iodobenzylamine	42% (2)	MS only
3-Methoxybenzylamine	48% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Methoxybenzylamine	55% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Methylaminobenzoic acid	53% (2)	^{1}H-NMR/MS
4-Methylbenzylamine	69% (2)	^{1}H-NMR/^{2}H-NMR/MS
N-Methylbenzylamine	94% (2)	^{1}H-NMR/MS
1-Methyl-1-phenylethylamine	60% (2)	^{1}H-NMR/^{2}H-NMR/MS
Naphthalen-2-ylmethylamine	45% (2)	MS only
2-Phenyl-1*H*-imidazole	34% (2)	^{1}H-NMR/^{2}H-NMR/MS
2-Phenylpyridine	51% (2)	^{1}H-NMR/^{2}H-NMR/MS
4-Trifluoromethylbenzylamine	69% (2)	^{1}H-NMR/^{2}H-NMR/MS

Reaction conditions: the substrate (0.04 mmol) and catalyst (0.01 mmol) in DMA (250 µl) stirred under D_2 gas for 4 h at room temperature.
[a] ca. 30% at each of positions 2 & 4.
[b] 65% at position 5, 45% at position 3.

The labelling reaction shows little sensitivity to the electronic activation or deactivation state of the substrate, a behaviour previously noted for other metal-catalysed isotope exchanges of this type.[1(a),8,10] Interestingly, mono-substitution on nitrogen is well tolerated whilst di-substitution results in some inhibition of labelling. Such inhibition has been observed in a number of analogous homogeneous systems,[1g,3a,9] though the Crabtree catalyst seems not to display this behaviour, at least for *N*-substituted benzamides.[1(e),10] Some evidence of steric inhibition of labelling was observed in the case of 4-amino-2-hydroxybenzoic acid, whilst additional examples are also included in Table 3.

Unlike the Crabtree catalyst, **1** did not catalyse the exchange between deuterium gas and the aldehyde proton of DMF and hence could be used effectively in this solvent. However, in common with the Crabtree catalyst, it did yield reduction of double bonds. Nitro groups were also reduced and in this case, the corresponding *ortho*-deuterated anilines were recovered. Aromatic bromides and iodides proved stable to the exchange conditions.

The nature of the effective catalytic species is uncertain. The reaction often shows an induction period (Figure 3), which varies with the substrate, presumably whilst the active catalytic species is formed.

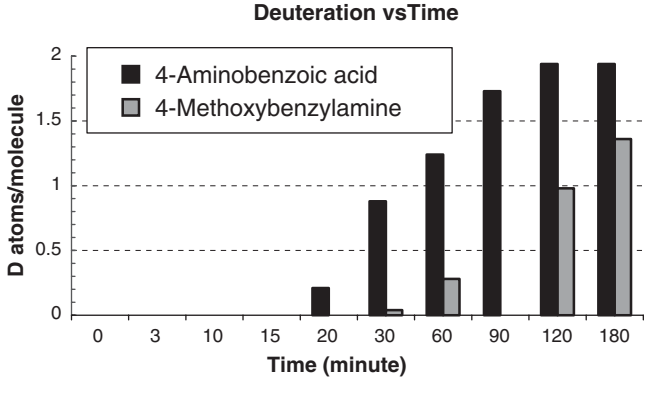


Figure 3. Catalyst induction demonstrated with two substrates

The delay could represent the removal of the COD ligand by hydrogenation or by substrate substitution. Figure 4 shows that the catalyst can be activated by treatment with hydrogen gas, a useful property for the efficient use of the tritium isotope. An additional example is provided by the deuteration/tritiation of 4-aminoacetophenone described later.

Since iridium metal is precipitated during the reaction with some substrates, the possibility exists that the reaction is catalysed by a heterogeneous process. However, when the effect of added liquid mercury[11] on the labelling of four substrates (7,8-benzoquinoline, 2-phenylpyridine, 1-methyl-1-phenylethylamine and 4-trifluoromethylbenzylamine) was examined, no definitive

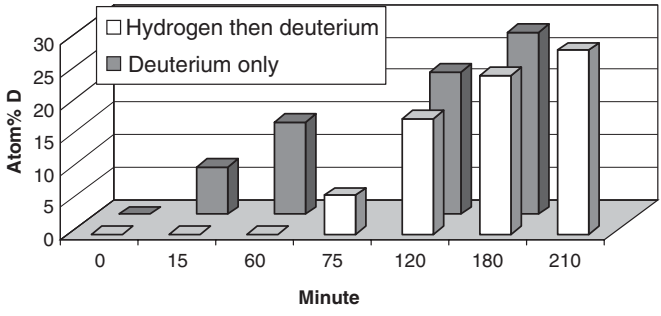


Figure 4. Comparison of 7,8-benzoquinoline deuteration with and without 1 h pre-incubation with hydrogen gas

conclusions could be drawn. The first two substrates showed no significant effect of mercury whilst the third showed a 40% increase and the last, a 58% decrease in the extent of labelling under the non-equilibrium conditions used.

Further studies to investigate the catalytic process are shown in Table 2.

Here the catalytic activity of various iridium metal preparations was examined using three representative substrates. None of the metal preparations yielded significant labelling in comparison with **1**, though this does not eliminate the possibility of catalysis via a species on the reductive pathway to iridium metal, such as an iridium cluster or colloid. The differentiation between homogeneous and heterogeneous catalysis has always proved problematic as excellent recent reviews make clear.[12]

Several other Group VIII metal blacks also proved inactive. Although the analogous cycloocta-1,5-dienylrhodium(I)-1,1,1,5,5,5-hexafluoropentanedionate did show some activity with the 1-methyl-1-phenylethylamine substrate (67% *ortho*-D), it showed no activity with several other anilines and benzylamines.

Table 2. Labelling vs catalyst employed for three substrates (as % D_2)

Catalyst	4-Aminobenzoic acid	4-Amino-acetophenone	1-Methyl-1-phenylethylamine
$CODIrF_6Acac$, 1	91	92	68
Iridium from $CODIrF_6Acac/D_2$	<3	<3	<4
Ir black (Commercial)	<2	<2	<2
Iridium from $IrO_2/NaBH_4$)	—	<3	<2
Palladium from $PdO/NaBH_4$)	—	Decomposed	—
Platinum from $PtO_2/NaBH_4$)	—	<2	—
Rhodium from $RhCl_3/NaBH_4$)	—	<2	—
Ruthenium from $RuCl_3/NaBH_4$)	—	<2	—
Crabtree's catalyst	<2	—	—

—Indicates that the experiment was not carried out.

All the above studies were carried out with deuterium gas, however the most frequent use of the method is likely to be with tritium. Hence a tracer study, employing 4-aminoacetophenone as substrate, was carried out to investigate the use of this isotope. In this study, the reaction was initiated with deuterium gas, to demonstrate the isotope-sparing option shown in Figure 4, and then a tracer amount of tritium gas added and the reaction continued. The product of the reaction was then studied by ^{1}H and ^{3}H-NMR. The results are shown in Figure 5.

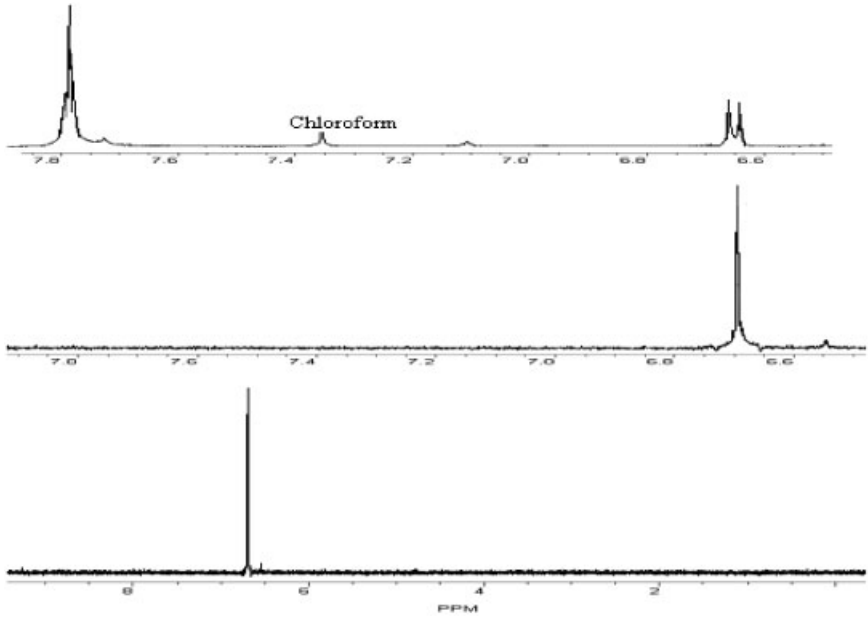


Figure 5. NMR spectra of the product from deuteration/tritiation of 4-aminoacetophenone catalysed by 1 Top spectrum: ^{1}H-NMR of the product in $CDCl_3$ showing reduction in the proton intensity at δ 6.65 ppm and partial collapse of the 2 and 6 doublet resonance at δ 7.78 ppm to a singlet, confirming deuteration at the 3 and 5 positions. Middle spectrum: ^{3}H-NMR spectrum of the same sample showing ^{3}H-labelling at the 3 and 5 positions. Bottom spectrum: as above but showing full range and absence of labelling at the methyl group.

The results presented in this paper show a quite different selectivity for directing groups when the same catalyst is employed with a D_2O or D_2 isotope donor. This raises the possibility of controlling the regiochemistry of labelling for some substrates by selection of the donor. Table 3 shows the control which can be exercised with various aminobenzoic acids. Moreover, given that the acetophenone grouping is an excellent director for catalysts of the Crabtree type, the results with the aminoacetophenones bodes well for the control of labelling regioselectivity for these substrates also.

Table 3. Regiochemistry achieved with 1 and D_2 or D_2O donors

Substrate	Deuterium oxide donor		Deuterium gas donor	
	Atom % D (No. of sites)	Regiochemistry	Atom % D (No. of sites)	Regiochemistry
4-Aminobenzoic acid	60% (2)	2,6 (*ortho* to CO_2H)	94%(2)	3,5 (*ortho* to NH_2)
3-Aminobenzoic acid	53% (2)	Mainly 6 (*ortho* to CO_2H)	93%(1)	4 (*ortho* to NH_2)
2-Aminobenzoic acid	53% (1)	6 (*ortho* to CO_2H)	79%(1)	3 (*ortho* to NH_2)
4-Aminoacetophenone	<1.5% (2)	nd	83%(2)	3,5 (*ortho* to NH_2)
3-Aminoacetophenone	<2.5% (2)	nd	49%(2)	Mainly 4 (*ortho* to NH_2)
2-Aminoacetophenone	<5.0% (2)	nd	40%(1)	3 (*ortho* to NH_2)

Experimental

Di-μ-chlorobis(1,2,5,6-η)-1,5-cyclooctadiene]diiridium (Fluka item 14691), deuterium oxide (99.8%D), DMF and DMA (water content <0.03 and 0.05%, respectively) were obtained from Sigma-Aldrich (Poole, Dorset, UK). Deuterium gas (99 atom%) was purchased from CK Gas Products Ltd (Hook, Hampshire, UK) and tritium gas from RC Tritec (Teufen, Switzerland). All other solvents and reagents were obtained from recognised chemical suppliers, including the above, and were used as received.

Cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate (1)

Commercial [di-μ-chlorobis(1,2,5,6-η)-1,5-cyclooctadiene]diiridium (300 mg) is stirred under nitrogen in degassed ether (6 ml) at which point it is only partly dissolved. Commercial 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (0.3 ml) in ether (0.6 ml) is then added via a syringe and the reaction stirred for 10 min. Sodium hydroxide solution (1 M, 1.25 ml) is added, dropwise via a syringe. During this phase the remaining crystals of precursor dissolve and the mixture becomes a deep claret colour. Water (3 ml) is added, again via a syringe, and the biphasic mixture stirred under nitrogen for a further 20 min. The ether layer is evaporated under a slow stream of nitrogen leaving suspended clumps of fine claret-coloured crystals. The aqueous supernatant is decanted and the crystals washed twice more by decantation with portions of water (2 ml). Finally, the crystals are filtered and dried over silicagel overnight to leave cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate (412.5 mg, 91%) as a fine free-flowing stable[15] red-purple solid. ^{1}H-NMR: δ ($CDCl_3$) 1.75 (4 H, *q*, $J=7.5$ Hz), 2.30 (4 H, m), 4.31 (4 H, s), 6.32 (1 H, s) p.p.m. ^{13}C-NMR: δ ($CDCl_3$) 31.1, 62.6, 93.1, 118.5 (quartet), 174.3 (quartet) p.p.m. MS (EI mode): *m*/*z* 508/506 (mol. ion), 301-292 (cluster) a.m.u. Found C 30.55%, H 2.91%, required C 30.67%, H 2.91%.

Typical deuteration protocol for anilines and benzylamines

The substrate amine (0.04 mmol) and catalyst (0.01 mmol) were dissolved in DMF or DMA (250 μl) and stirred under deuterium gas for 3–4 h at room temperature. The labelled substrate was isolated by a diethyl ether/hydrochloric acid (2 M) partition, followed by basification of the aqueous extract with NaOH solution (1 M), extraction with diethyl ether, drying with anhydrous magnesium sulphate and removal of the solvent under a stream of dry carbon dioxide free nitrogen. At this point the labelled substrates were usually sufficiently pure for reliable analysis by ^{1}H- and ^{2}H-NMR and LC-MS.

[3,5-^{2}H, 3,5-^{3}H]-4-Aminoacetophenone

Cycloocta-1,5-dienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate (**1**, 5 mg) and 4-aminoacetophenone (5.4 mg) were dissolved in *N,N*-dimethylacetamide (0.3 ml) and stirred under an atmosphere of deuterium gas for 1 h. A tracer quantity of tritium gas was then admitted and the reaction allowed to

proceed for a further 3 h. The reaction was partitioned between aqueous sodium hydrogen carbonate solution (5% v/v, 3 ml) and chloroform (6 ml) and the chloroform layer separated and evaporated under a stream of dry nitrogen to yield [3,5-^{2}H,3,5-^{3}H]-4-aminoacetophenone. ^{1}H-NMR of the product showed it to be $>90\%$ pure with an abundance of $>60\%$ ^{2}H at the 3 and 5 positions. The ^{3}H-NMR of the product showed the expected resonance at δ 6.7 ppm for the 3- and 5-positions. Moreover, no labelling was detectable at the positions of the acetyl methyl group or the 2- and 6-positions. An unidentified impurity was observable at the $<10\%$ level in both the triton and proton NMR spectra (see text).

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