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Research Article

Iridium-mediated β-deuteration of enones

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Summary

Exposure of captodative enone systems to deuterium in the presence of Crabtree's catalyst (**1**) results in deuteration at the vinylic site β- to the ketone carbonyl, as well as at any accessible *ortho*-position. β-exchange is also observed during the reduction of ethyl cinnamate (**3**) catalyzed by **1**. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: iridium complexes; isotope exchange; vinylic deuteration; ortho-deuteration; [^{2}H]-SR46349

Introduction

The initial development of iridium complexes as catalysts for isotopic exchange by Heys[1] was inspired by observations of aryl C–H activation during studies on the iridium-mediated hydrogenation of double bonds.[2] In the course of studies in this area, we found that $Ir(cod)(PCy_3)(Py)^+ \cdot PF_6^-$ (**1**) and other iridium catalysts also promote exchange at sites adjacent to nitrogen in *N*,*N*-dialkylamides and 2-dialkylaminopyridines.[3] We proposed that exchange in these instances was occurring *via* a five-membered metallacycle in the same manner as for isotope exchange in arenes. Indeed, a metallacyclic intermediate derived from 2-dimethylaminopyridine has since been isolated.[4] On this

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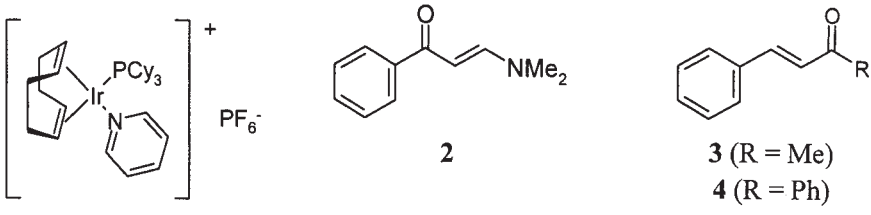
basis, it seemed likely that deuteration of vinylogous amide **2** in the presence of **1** would not result in incorporation into the *N*-methyl groups. This proves to be the case in practice, but we were a little surprised to find that **2** was deuterated at the vinylic centre β- to the carbonyl, and that the double bond remained unreduced (Scheme 1). Following this observation, we have investigated exchange in a number of other enone systems, the results of which are described in this paper.

Results and Discussion

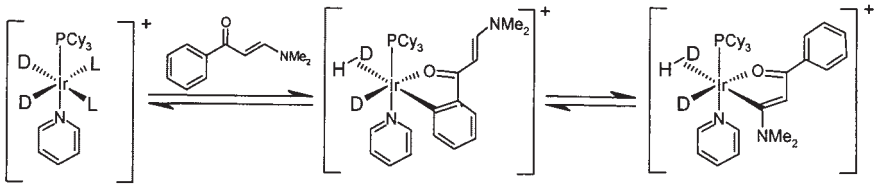
Deuteration of the vinylogous amide **2** was carried out in order to provide evidence that the observed incorporation of deuterium into *N*-alkyl groups of dialkylamides occurred by a similar cyclometalation process to that implicated in *ortho*-exchange, rather than resulting from a more general labilization of C–H bonds α- to nitrogen. Indeed, when **2** was exposed to deuterium in the presence of catalyst **1**, 1.8 atoms of deuterium per molecule were incorporated at the *ortho* sites, but no deuterium was incorporated into the *N*-methyl groups. However, what was more surprising was that the substrate was recovered without reduction of the double bond, and that 0.7 atoms of deuterium per molecule were incorporated at the vinylic site adjacent to nitrogen. This can again be explained by a mechanism involving a five-membered metallacycle (Scheme 2).

In view of this result, we examined the deuterium exchange of several related substrates mediated by **1**. Conjugated systems **3 – 5** all undergo double-bond reduction with deuterium in the presence of **1** at atmospheric pressure, in line with expectations (Table 1)[5] (Hydrogenation of cinnamic acids catalysed by iridium-phosphine complexes has been reported). In the case of **4** and **5**, NMR spectra of the reduction



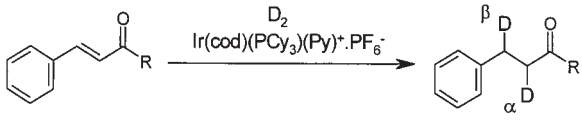
1 **2** **3** (R = Me) **4** (R = Ph) **5** (R = OEt)

Scheme 1. Partial Mechanism for Deuterium Exchange in 2.



Scheme 2.

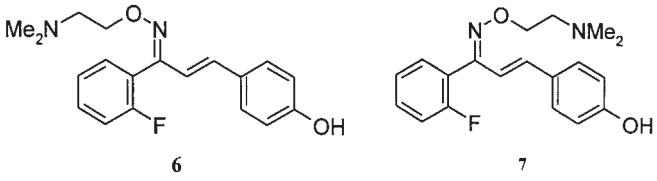
Table 1 Reduction of substrates 3 – 5 with deuterium mediated by 1



Substrate	Dα	Dβ
3	0.5	1.5
4	0.3	1.0
5	0.5	1.0

products show the expected incorporation of a single atom of deuterium β- to the carbonyl group, the deuterium incorporation at the α- position being significantly less, reflecting quenching of an intermediate by adventitious water, or another source of labile hydrogen. However, reduction of **3** with deuterium under the same conditions results in a product containing 1.4 atoms of deuterium β- to the carbonyl group. This can only be a consequence of exchange occurring prior to conjugate reduction, since benzylacetone does not undergo any form of isotopic exchange mediated by **1**. The exchange process appears to be less favoured with **3** than with **2**, but occurs nonetheless: the absence of exchange upon reduction of **4** and **5** may be no more than a consequence of reduction itself being faster than with **3**.

It is interesting that exchange is observed at the β-position of enone systems, which may be regarded as analogous to the *ortho*-sites at which the corresponding process occurs in aromatic systems, but not at the corresponding sites in saturated ketones. This may be a geometric effect, the proton attached to an sp^2 centre being suitably positioned for an agostic interaction with the metal centre to occur, whereas those attached to an sp^3 centre are not, and therefore, are less susceptible to



6 7

Scheme 3.

exchange. It is therefore of considerable interest that protons attached to *N*-methyl groups appear to exchange by a similar mechanism.

The oxime-derived drug development candidate, SR46349 (**6**)[6] and its isomer SR46615 (**7**) represent a more interesting case (Scheme 3). Judging by the model substrate, acetophenone *O*-methyl oxime, *O*-alkyl oximes in general are expected to be excellent substrates for the iridium-mediated exchange reaction using a number of iridium complexes, including **1**.[3,7] Interestingly, when deuterium exchange of **6** is carried out in the presence of **1**, incorporation is not observed in the fluorophenyl ring, but quantitative incorporation occurs at the vinylic centre β- to the carbonyl group: this is reflected in the complete absence of the expected resonance around δ 6.2–6.3, which corresponds to this proton, and the collapse of the signal at δ 6.84, which is normally a doublet (*J* 16.9 Hz), to a singlet (correlation experiments have shown that, unlike enones, the proton β- to the oxime in these substrates gives rise to the further upfield of the two vinylic signals). In contrast, 7 incorporates 0.4 atoms of deuterium per molecule in the fluorophenyl ring (reflected in a diminution of the intensity of the highest-field resonance) but does not incorporate deuterium into the enone unit. The regioselectivity of deuteration of these two substrates is clearly a consequence of iridium-substrate binding involving the nitrogen lone pair of each isomer. Since the isomers are not interconverted appreciably under the reaction conditions, incorporation occurs at the only centre able to become involved in cyclometalation in each case.

Conclusion

The factors governing the course of the reaction of enones with deuterium in the presence of **1** are not entirely clear. Captodative systems such as **2**, **6** and **7** do not appear to be particularly susceptible to reduction under these conditions and undergo isotopic exchange at

accessible sp^2 centres, including vinylic centres, instead. However, the incorporation of significantly more than the theoretical quantity of deuterium at the β-position during reduction of **3** attests to the fact that captodative enones are not the only ones susceptible to exchange.

Experimental

Mass spectra were recorded using a Hewlett-Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5972MSD). ^{1}H NMR spectra were recorded using Jeol GSX-270 and Bruker 500 instruments. Catalyst **1** was obtained from Fluka and Strem.

[*Benzene*-2, 6-$^2H_2$, *acryloyl*-3-^2H]-*3-dimethylamino-1-phenylpropanone,* ([^2H]-*2*)

A solution of **1** (20 mg, 25 μmol)[8] and **2** (4 mg, 25 μmol) in DCM (2 ml) was stirred under a deuterium atmosphere for 70 h. The mixture was subjected to preparative t.l.c. on silica in ethyl acetate – triethylamine (96:4) to afford [*benzene*-2,6-$^2H_2$,*acryloyl*-3-^{2}H]-**2** (2 mg). $\delta_H(CDCl_3)$ 2.90, 3.10 (6 H, 2 br s), 5.69 (1.0 H, s, *J* 12.0 Hz), 7.40 (3 H, m), 7.77 (0.3 H, s overlapping with d, *J* 12.0 Hz), 7.87 (0.2 H, br d, *J* 7.0 Hz); *m*/*z* 176, 175, 159, 158, 99, 98 (100%).

[2-*Butanone*-3, 4, 4-$^2H_3$]-*4-phenyl-2-butanone,* ([^{2}H]-*3*)

Treatment of **3** (43 mg, 0.29 mmol) as above gave [2-butanone-3,4, 4-$^2H_3$]-4-phenyl-2-butanone (26 mg, 60%). $\delta_H(CDCl_3)$ 2.11 (3 H, s), 2.72 (1.5 H, m), 2.88 (0.5 H, m), 7.17 (3 H, m), 7.26 (2 H, m); *m*/*z* 152, 151, 150, 149, 107, 106 (1 0 0), 105, 93, 92.

[*Chalcone-β*, 2'-$^2H_2$]-*E-Chalcone,* ([^2H]-*4*)

Treatment of *E*-chalcone (**4**; 12 mg, 58 μmol) as above gave [*chalcone*-β,2'-$^2H_2$]-*E*-chalcone (10 mg). $\delta_H(CDCl_3)$ 3.06 (1.0 H, m), 3.27 (1.7 H, m), 7.18 (1 H, br t, *J* 7.1 Hz), 7.22-7.30 (4 H, m), 7.43 (2 H, m), 7.53 (1 H, br t, *J* 7.5 Hz), 7.94 (1.1 H, d, *J* 7.5 Hz); *m*/*z* 215, 214, 213, 212, 211, 210, 109, 108 (100%), 107.

Ethyl [*propionic acid*-2,3-$^2H_2$]-*3-phenylpropionate*

Treatment of ethyl cinnamate (**5;** 10 mg, 56 μmol) as above gave ethyl [*propionic acid*-2,3-$^2H_2$]-3-phenylpropionate (9 mg). $\delta_H(CDCl_3)$ 1.22 (3 H, t, J 7.3 Hz), 2.59 (1.5 H, m), 2.93 (1.0 H, m), 4.11 (2 H, q, *J* 7.3 Hz), 7.19 (2 H, br d, *J* 6.9 Hz), 7.26 (3 H, m); *m*/*z* 181, 180, 179, 107, 106, 105, 104 (100%), 103.

[*Chalcone-β-*^2H] *-SR46349,* ([^2H]*-6*)

Treatment of SR46349 (**6**; 24 mg, 77 μmol) as above gave [*chalcone*-β-^{2}H]-**6** (18 mg, 75%). $\delta_H(CD_3OD$, 270 MHz) 2.20 (6 H, s), 2.67 (2 H, t, *J* 5.6 Hz), 4.15 (2 H, t, *J* 5.6 Hz), 6.65 (2 H, d, *J* 9.0 Hz), 6.84 (1 H, s), 7.2 (5 H, m), 7.4 (1 H, m).

[*Fluorobenzene*-6-^2H]-*SR46615,* ([^2H]-*7*)

Treatment of SR46615 (**7**; 16 mg, 50 μmol) as above gave [*fluorobenzene*-6-^{2}H]-**7** (3 mg, 15%). $\delta_H(CD_3SOCD_3)$ 2.40 (6 H, s), 2.80 (2 H, t, *J* 5.2 Hz), 4.35 (2 H, t, *J* 5.2 Hz), 6.12 (1.0 H, d, *J* 16.1 Hz), 6.65 (2 H, d, *J* 8.9 Hz), 7.60 (2 H, d, *J* 8.9 Hz), 7.08 (1 H, d, *J* 16.1 Hz), 7.18 (2 H, m), 7.37 (1.6H, m).

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