DEUTERATION OF ACETANILIDES AND OTHER SUBSTITUTED AROMATICS USING $[Ir(COD)(Cy_3P)(Py)]PF_6$ AS CATALYST

D. Hesk, P.R. Das, B. Evans

Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth NJ 07033. USA.

SUMMARY

Deuterium exchange labelling using $[Ir(COD)(Cy_3P)(Py)]PF_6$ as catalyst and deuterium gas was studied on a number of substituted acetanilides. In most cases products containing deuterium *ortho* to the anilide group were obtained with a high degree of enrichment. With one exception no evidence for *meta, para* or anilide methyl labelling was seen. The catalyst was also effective in the *ortho* deuteration of acetophenone, benzophenone and the β-lactam containing compound Sch 48461.

Key Words: Acetanilides, deuteration, regioselective.

INTRODUCTION

Homogeneous metal catalysed hydrogen isotope exchange, first developed by Garnett and Hodges in 1967, using tetrachloroplatinate, was originally used for the labelling of alkyl and halobenzenes and polycyclic aromatics.[1,2] It had several advantages over heterogeneous platinum, namely, the lack of poisoning by nitro groups and could also be used to carry out extensive kinetic and mechanistic studies.[3] It did however produce generally labelled products, a feature in common with heterogeneous platinum. Subsequently a number of homogeneous metal complexes have been found to catalyse the regioselective deuterium and tritium exchange in a wide range of organic compounds. Homogenous rhodium trichloride has been found to promote *ortho* deuteration and tritiation in a wide variety of aromatic carboxylic acids, amides, aralkylamines, anilides and certain heterocycles.[4-9] Tristriphenylphosphine ruthenium (II) chloride is known to catalyse regiospecific α–exchange in alcohols and amines as long as reaction times are kept short.[10-12]

Most recently Heys has used $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ with deuterium gas to regioselectively label benzoate esters, N,N-dimethylbenzamides and benzophenones.[13,14] The use of deuterium gas and therefore by analogy tritium gas, is desirable over isotopic water because of the much higher achievable specific activities. We have recently discovered in our laboratory that the commercially available complex $[Ir(COD)(Cy_3P)(Py)]PF_6$ (Crabtree's Catalyst)[15-17] will regioselectively catalyse the *ortho* deuteration of acetanilides, acetophenones and benzophenones. Such a method would

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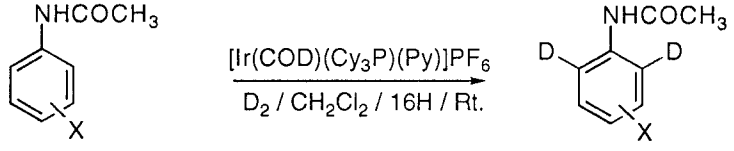
be extremely useful, given that the anilide group is extensively found in pharmaceutical products. In addition, labelled benzophenones are widely used to prepare photo affinity ligands for mechanism of action studies.[18] The paper reports the results of our initial investigations.

RESULTS AND DISCUSSION

i) Substituted acetanilides

A number of substituted acetanilides were reacted in duplicate as shown in Scheme 1.

Scheme 1: Deuteration of acetanilides



In initial experiments, complete deuteration was obtained after 4 hours when employing about 25mM acetanilide and 1.25mM catalyst. However many of the substituted acetanilides were not sufficiently soluble at this concentration, hence the reactions were run for 16 hours using about 8.3mM acetanilide and 0.42mM catalyst. Isolation of the products was carried out by evaporation of the solvent, redissolving in ethanol and re-evaporation. The catalyst was removed by passing the sample through a silica 'Sepak' column and the products were analysed by ^{1}H-NMR and Mass Spectrometry. No cases of decomposition were seen. The results are summarized in Table 1. The percentage incorporations are estimated to be within ±5%.

Table 1: Deuteration of Acetanilides.

Name	Labelling Site	d0	d1	d2	d3	d4
Acetanilide	2,6	0	7	93		
p-CH_3-	2,6	4	8	88		
p-OCH_3-	2,6	0	13	87		
p-OEt-	2,6	1	6	93		
p-NO_2-	2,6,3,5	3	22	62	11	2
p-CN-	-	100				
p-Cl-	2,6	2	20	78		
p-F-	2,6	0	12	88		
p-Br-	2,6	0	3	97		
p-CF_3-	2,6	3	22	76		
p-NH_2-	2,6	31	44	25		
p-OH-	2,6	76	3	21		
p-COOH-	-	96	4	0		
o-F-	6	4	96			
o-Cl-	6	13	87			
o-CF_3-	6	41	59			
o-CH_3-	6	21	79			
o-OH-	6	38	62			
o-COOH	6	83	17			
m-F-	2,6	1	25	74		
m-CH_3-	6	2	94	4		
m-CF_3-	6	19	80	1		
m-OH	2,6	46	15	39		
m-COOH	-	97	3	0		

As can be seen the reaction is very general and largely insensitive to substituent effects. Low incorporations were found with the carboxyl and hydroxyl substituted acetanilides due to observed poor solubility in methylene chloride. No deuteration was seen with p-cyano acetanilide which was probably due to complexation of the catalyst by the cyano group.

In the remaining substrates good incorporation was seen exclusively *ortho* to the anilide group. No evidence of *meta* labelling or deuteration of the anilide methyl groups was seen. The lone exception to this was p-nitroacetanilde with small amounts of d3 and d4 species found, which suggests that the nitro group may be a weak director.

In the *meta* substituted acetanilides, the *meta* group effectively blocked deuteration in the 2-position with the result that mainly monodeuterated species were present. The exception to this was m-fluoroacetanilide which produced mainly a di-deuterated species which presumably is due to the relatively small van der waals radius of the fluorine substituent.

Finally no evidence of reductive debromination or dechlorination was seen in any of the halo-substituted acetanilides which adds to the versatility of the method.

ii) Investigation of other Directing Groups

A number of other potential directing groups were studied with [Ir(COD)(Cy_3P)(Py)] PF_6 as catalyst with the results shown in Table 2. Each of the substrates studied was soluble in methylene chloride.

Table 2: Investigation of other Functional Groups

Name	Labelling Site	d0	d1	d2	d3	d4
Ph-$COCH_3$	2,6		5	95		
Ph-CO-Ph	2,6				5	95
Ph-COOH	-	100				
Ph-SO_2NH_2	-	100				

As can be seen that acetophenone and benzophenone are active substrates, the latter being particularly important because of its use in photo affinity ligands. Indeed this reaction has successfully been used to prepare a tritiated photo affinity ligand at >100 Ci/mmole, which will be the subject of a future publication. Investigation into other directing groups continues.

iii) Investigation of Alternative Solvents/Solvent Mixtures

A few experiments using other solvents such as acetone, DMF, dioxane and methylene chloride solvent mixtures have been run using acetanilide as the reference. The results are shown in Table 3:-

Table 3: Investigation of other Solvents with Acetanilide

Solvent	d0	d1	d2
CH_2Cl_2		7	93
Acetone	100		
DMF	100		
Dioxane	100		
5% Acetone in CH_2Cl_2	4	19	77
10% Acetone in CH_2Cl_2	6	31	63
5% MeOH in CH_2Cl_2	14	46	40
5% DMF in CH_2Cl_2	100		

As can be seen methylene chloride is critical to the success of the reaction, which is in agreement with Crabtree[15], but it will tolerate small amounts of acetone as co-solvent which could be useful in improving the solubility, and thus the reactivity, of poorly soluble substrates such as the Hydroxyl and Carboxyl acetanilides. Further work in this area continues.

iv) β-Lactam Labelling Application

Sch 48461, Figure 1, is under development as a Cholesterol Absorption Inhibitor.

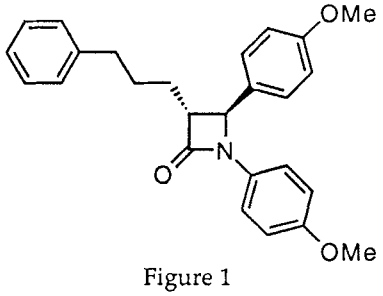
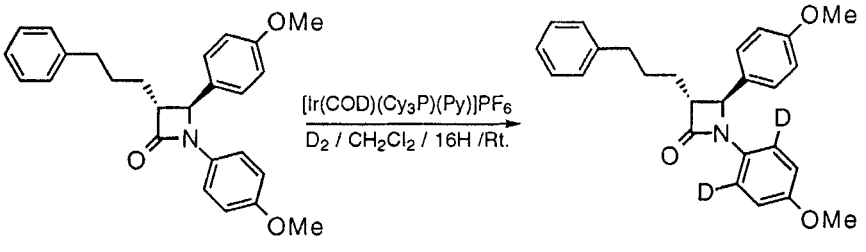


Figure 1

It was believed that the β-lactam ring ought to behave as an anilide group and direct deuterium into the ring attached to the β-lactam nitrogen. To test this hypothesis Sch 48461 was run under the standard conditions as used for the acetanilides (Scheme 2) and analysed by Mass Spectrometry and ^{1}H-NMR.

Scheme 2: Deuteration of Sch 48461



Results showed that indeed, deuterium was incorporated into the ring attached to the nitrogen and in addition all the label was located in the *ortho* position. Subsequently a number of other β-lactams have been successfully labelled with deuterium and also with tritium at high specific activity. These findings will be the subject of a future publication.

Conclusions

In the absence of any detailed kinetic studies, it is only possible to speculate on the mechanism of labelling. However from Crabtree's work[15-17] and by analogy from the work of Heys[14] with $[IrH_2(Me_2CO)_2(PPh_3)_2]BF_4$ and Lockley[4-9] with Rhodium trichloride, it is likely that the 6-membered cyclometallation species shown in Figure 2 is a key intermediate.

Such an intermediate would readily account for the high regioselectivity in the *ortho* positions.

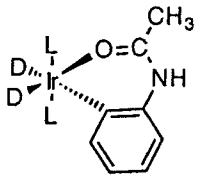


Figure 2

In summary the use of $[Ir(COD)(Cy_3P)(Py)]PF_6$ offers a simple, rapid, one step method to *ortho* deuterate a wide range of substituted acetanilides with high regioselectively. Additionally, $[Ir(COD)(Cy_3P)(Py)]PF_6$ is commercially available, thus eliminating the need for costly and time consuming catalyst preparations. The method can also be extended to prepare *ortho* deuterated acetophenone, benzophenones and β-lactams. Further work in these latter areas continues.

EXPERIMENTAL

$[Ir(COD)(Cy_3P)(Py)]PF_6$ was obtained from Aldrich and used without further purification. The acetanilides, acetophenone and benzophenone were obtained from a number of commercial suppliers and also used without further purification. Sch 48461 was obtained from Schering Plough Research Institute, Chemical Development Department. ^{1}H-NMR spectra were run in d6 DMSO or $CDCl_3$ on a Varian 200 MHz instrument, with TMS as reference.

Chemical Ionization (CI) and Electron Ionization (EI) mass spectra of acetanilide and substituted acetanilides were obtained on a HP 5989A MS Engine. Methane was used as the reagent gas for CI and typical mass spectrometer source temperatures were 260°C and 300°C for CI and EI respectively.

In a typical run, in a flame dried flask, the acetanilide (about 0.025 mmoles) and $[Ir(COD)(Cy_3P)(Py)]PF_6$ (about 0.00125 mmoles) were dissolved in methylene chloride (3 mL) and stirred under deuterium gas (supplied by a balloon) for 16 hours at room temperature. At the completion of the reaction, the deuterium gas was removed and the solvent removed by evaporation. The residue was re dissolved in ethanol and then re-evaporated to leave the crude acetanilide. The catalyst was then removed by passing the sample through a silica gel 'Sepak' column using methylene chloride: MTBE or methylene chloride: acetone solvent systems depending on the polarity of the acetanilide. The sample was analysed by ^{1}H-NMR and Mass Spectrometry and compared to an unlabelled standard.

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