Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **44**, 209-214 (2001)

Organoiridium catalysed hydrogen isotope exchange of benzamide derivatives

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SUMMARY

Hydrogen-tritium exchange in a series of benzamide derivatives and acetanilide has been investigated using $[Ir(cod)(Cy_3P)(Py)]PF_6$ as catalyst. Specific activities of 6-43 Ci/mmol were obtained. Tritium NMR spectroscopy showed that exchange occurred *ortho* to the amide group.

Key words: Tritium exchange, benzamide, acetanilide, iridium catalysis, Crabtree's catalyst.

INTRODUCTION

In the development of new drugs there is an increased focus on speed and quality. Studies on the pharmacokinetics and metabolism are important in the selection of new drug candidates. To support these studies radiolabelled tracers have to be synthesised. Since ^{14}C-labelling is often time consuming, tritium labelling is an attractive alternative.

Direct exchange of hydrogen by tritium is attractive as it avoids the need for synthesis of a precursor. Homogeneous iridium can catalyse such exchange reactions on compounds of several structural types. The incorporation of the isotope is in most cases highly regioselective, and can be determined by ^3H-NMR spectroscopy.

The extensive work of Heys and colleagues at SmithKline Beecham has inspired us to use this approach as a " fast track" tool for preparing several tritium ligands within each project [1,2]. We now report our initial results on some benzamide derivatives using $[Ir(cod)(Cy_3P)(Py)]PF_6$ (Crabtree's catalyst) as catalyst.

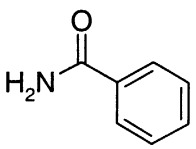
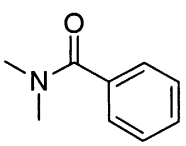
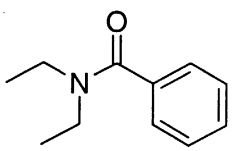
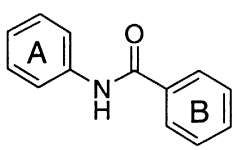
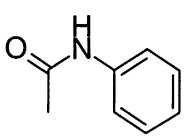
Received 11 October 2000
Revised 23 October 2000
Accepted 7 November 2000

RESULTS AND DISCUSSION

Regioselective ortho isotope exchange of acetanilides can be achieved by use of Crabtree's catalyst [3]. For our investigation we chose this catalyst since it is commercially available and therefore readily accessible.

Normally we use 10-20 mol% of catalyst, but it has been reported that often larger amounts of iridium catalyst are needed to achieve a high degree of labelling due to the competitive coordination of the metal center to other functional groups [1]. For this reason we performed nearly all of the experiments using an approximately ratio of 1:1 (substrate : catalyst).

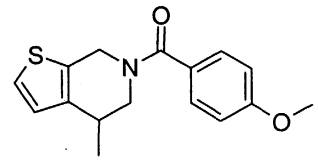
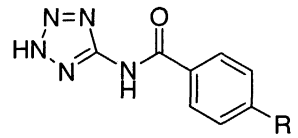
Table 1

No.	Substrate	Catalyst loading (molar equiv.)	Specific Activity	Location (NMR)
1		0.94	15 Ci/mmol	ortho only
2		0.94	17 Ci/mmol	ortho (>95%)
3		1.00	43 Ci/mmol	ortho (>95%)
4		0.94	28 Ci/mmol	A-ring: ortho B-ring: ortho
5		1.10	6 Ci/mmol	ortho only

In some cases two or more compounds were labelled simultaneously as a "one-pot" mixture. Purification by HPLC then yielded the desired products in radiochemical purities >95%. This approach has been used successfully in several cases.

Table 1 shows the results from experiments on a series of related benzamides and acetanilide. The benzamides are substrates requiring five-membered metallocyclic intermediates for hydrogen exchange. As it can be seen from Table 1 satisfactory incorporation is achieved with good regioselectivity resulting in labelling in the *ortho* positions. Acetanilide is a substrate requiring a six-membered metallocyclic intermediate for hydrogen exchange. Again, incorporation was observed in the *ortho* positions to the anilide group.

Table 2

No.	Substrate	Catalyst loading (molar equiv.)	Specific Activity	Location (NMR)
6		6.7	26 Ci/mmol	ortho only
7	 R = CHO or H	1.3	No reaction	

To extend the investigations we labelled some more complex benzamides containing "drug-like" substituents. The data are shown in Table 2. It is interesting to observe that when the substituent is tetrazole no reaction occurs. This is probably due to the presence of the coordinative nitrogen function at the tetrazole, which reduces the ability of the iridium complex to participate in the reversible interactions with the amide group. A similar case has previously been reported [4].

The mechanism for the hydrogen-tritium exchange reactions has been described in a previous publication [5]. The Crabtree catalyst has been reported to catalyse exchange of hydrogens exactly four bonds away from the coordinative heteroatom in the substrate [3]. The key intermediate is the formation of a five- or a six-membered cyclometallic compound depending on the substrate (Figure 1).

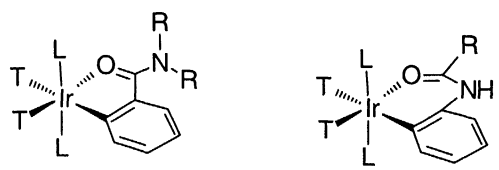


Figure 1 Hydrogen-tritium exchange involving a five- or six-membered metallocyclic intermediate.

CONCLUSIONS

By using $[Ir(cod)(Cy_3P)(Py)]PF_6$ as catalyst we have successfully labelled different benzamide derivatives and acetanilide in the *ortho* positions in the ring. The procedure is simple and the catalyst is commercially available. There is no need for specially designed precursors. The "one-pot" technique can be applied as a resource saving alternative where labelling of a series of compounds is needed.

EXPERIMENTAL

$[Ir(cod)(Cy_3P)(Py)]PF_6$ was obtained from Aldrich. The benzamides were obtained from a number of commercial suppliers and from Novo Nordisk A/S, Medicinal Chemistry. Dichloromethane was from Merck, and used without prior purification. Tritium gas was stored in the form of solid UT_3 and prepared "in situ" by heating the uranium bed. Tritium gas was purchased from RC Tritec, Teufen, Switzerland. All tritium NMR spectra were obtained on a Bruker DRX-400 instrument. Mass spectra were run on a Sciex API 300 mass spectrometer equipped with an Ionspray® interface (Thornhill, Canada).

Typical reaction procedure: To the flask containing the substrate (generally 1-3 mg) and $[Ir(cod)(Cy_3P)(Py)]PF_6$ was added solvent (400 μl) and the mixture was attached to a stainless steel manifold system where the appropriate amount of tritium was introduced. The mixture was stirred overnight (generally 15-72 hours) at room temperature. Excess tritium gas was then reabsorbed on a uranium bed and labile tritium was further removed by lyophilisation with ethanol (3 x 1ml). The catalyst was removed by HPLC purification or by precipitation of the Ir complex residues in ether and filtration. All products were compared to an unlabelled standard by HPLC, MS and NMR.

Compound 1:
HPLC purification (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 100% A to 50% B in 30 minutes; then 50% B in 20 minutes. 1 ml/min, UV at 254 nm, R_t=11.5 min. Radiochemical purity >95%.
^{3}H-NMR (proton-decoupled mode, $CDCl_3$): 7.86 (100% T, s).
MS: t_0 (55%), t_1 (38%), t_2 (7%); specific activity: 15 Ci/mmol (with 0.94 molar equiv. cat.)

Compound 2:
HPLC purification (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 100% A to 50% B

in 30 minutes; then 50% B in 20 minutes. 1 ml/min, UV at 254 nm, R_t=20.5 min. Radiochemical purity >95%.
^{3}H-NMR (proton decoupled mode, $CDCl_3$): 7.43 (100% T, s).
MS: t_0 (52%), t_1 (39%), t_2 (10%); specific activity: 17 Ci/mmol.

Compound 3:
HPLC analysis (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 100% A to 50% B in 50 minutes; then 100% B in 10 minutes. 1 ml/min, UV at 254 nm, R_t=30.7 min.
MS: t_0 (8%), t_1 (37%), t_2 (55%); specific activity: 43 Ci/mmol.

Compound 4:
HPLC purification (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 90% A to 30% B in 30 minutes; then 100% B in 10 minutes. 1 ml/min, UV at 254 nm, R_t=22.2 min. Radiochemical purity >92%.
Specific activity: 28 Ci/mmol determined by HPLC.

Compound 5:
HPLC analysis (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 95% A in 20 minutes; then 100% B in 10 minutes. 1 ml/min, UV at 254 nm, R_t=14.5 min.
^{3}H-NMR (proton decoupled mode, $CDCl_3$): 7.53 (100% T, s).
Specific activity: 6 Ci/mmol determined by HPLC.

Compound 6:
HPLC purification (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 50% A to 100% B in 25 minutes. 1 ml/min, UV at 254 nm, R_t=11.6 min. Radiochemical purity >95%.
^{3}H-NMR (proton decoupled mode, $CDCl_3$): 7.38 (100% T, s).
Specific activity: 26 Ci/mmol determined by HPLC.

Compound 7:
HPLC analysis (Novo Nordisk A/S RP C-18, 250 x 4.6 mm, 5 μm). Solvent A: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 10/90. Solvent B: acetonitrile (0.1% TFA)/aqueous 0.1% TFA; 90/10. Linear gradient from 90% A to 100% B in 30 minutes; then 100% B in 10 minutes. 1 ml/min, UV at 254 nm, R_t=5.2 min.

ACKNOWLEDGEMENT

We are grateful to Mrs. Liselotte Hansen for ^{3}H-NMR measurements and Mr. Ole Wassmann for mass spectra analyses.

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