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Short Research Article

Tritium-labelling via an iridium-based solid-phase catalyst†

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Abstract: A solid-phase, iridium-based *ortho*-exchange catalyst has been developed, with the aim of producing cleaner, more efficient, systems for tritium and deuterium labelling. The catalyst, which is a solvated polystyrene-bound triphenylphosphine complex of cyclooctadienyliridium(I) hexafluorophosphate, was evaluated with respect to more conventional catalysts such as $CODIr(PPh_3)_2PF_6$ and the Crabtree catalyst using simple model compounds as substrates. Labelling of drug candidate molecules proceeds with high regioselectivity and, after a simple filtration step, affords products with high radiochemical purities directly from the exchange reaction. The solid-phase catalyst functioned well with a variety of traditional directing groups including nitro, amide, benzophenone and *N*-heterocycles. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: *ortho*-exchange; tritium; deuterium; iridium; solid-phase catalyst

Introduction

Homogeneous exchange using iridium (I) catalysts in the presence of tritium gas is a powerful and convenient one-step method for the preparation of drug-like compounds labelled with tritium. The reaction proceeds rapidly under mild conditions (room temperature and partial pressures of tritium gas) generally giving high isotopic incorporation, and is regioselective relative to a wide range of directing groups found in many drug molecules. Common catalysts such as Crabtree's catalyst and variants of the type $[(COD)Ir(L)_2]PF_6$ (COD = cis,cis-1,5 cyclooctadiene) have been used extensively for tritium exchange labelling for a variety of complex molecules.[1a–c] However, a major limitation to this approach can be the isolation of the labelled product from the catalyst and catalysed-derived products. Labelling of compounds containing additional functional groups requires the exchange reactions to be run with a super-stoichiometric excess of the catalyst as a result of competitive binding by these other functional groups to the iridium metal centre. Frequently this leads to complex reaction mixtures which make purification of the labelled compound problematic. A successful approach to this problem has utilized immobilized ligands such that the separation is reduced to a straightforward filtration.[2] The present paper will describe a heterogeneous iridium-based catalyst, based on easily separable polystyrene beads, which can be conveniently synthesized in a single step from commercially available starting materials. The preparation of a number of deuterium and tritium labelled drug candidate molecules will be presented.

Results and discussion

Synthesis and properties

The polymer-supported iridium exchange catalyst was prepared as follows[3]: a 1:1 molar ratio of commercial polystyrene-based triphenylphosphine and $[(COD)Ir(PCy_3)(Py)]PF_6$ (Crabtree's catalyst) in dichloromethane was stirred under nitrogen for 2 h at ambient temperature. The orange supernatant was decanted from the deep-red polymer and the polymer washed 5 times by re-suspension and stirring in dichloromethane. After drying, a dark red polymeric catalyst (**1**) was obtained

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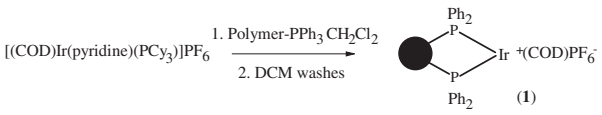
with high activity for *ortho*-directed isotopic exchange which was comparable to Crabtree's catalyst (Table 1).



- No loss of catalyst activity was observed when stored under nitrogen at −20°C over 10 weeks. Only 30% of the activity remained when stored at room temp in air over the same period.
- Routine small-scale preparation of the polymer catalyst can be undertaken prior to use. Activity is identical to the bulk preparation.
- There is ~0.6 μmol of iridium per mg of polymer as determined by cyclooctane release following exposure to hydrogen gas.
- Particle size and the commercial source of the polystyrene-based triphenylphosphine offered no differences in catalytic activity. However, a Fibre-Cat® polymeric support (based upon short fibres) is more easily handled than polystyrene beads.
- The same solvent limitations are observed with the polymer catalyst as with other homogeneous catalysts; dichloromethane being the solvent of choice.
- The catalytic activity resides in the solid phase and does not result from any species leaching into solution.

Labelling of complex molecules

As a further investigation, the catalytic potential of **1** was tested using a variety of different complex molecules (**2**–**6**). For comparison, the compounds were stirred for 2 h in dichloromethane with an excess of deuterium gas in the presence of Crabtree's catalyst or the polymer-supported complex **1** (2 mol equiv). All the compounds were labelled efficiently with high isotope incorporation in the presence of Crabtree's catalyst. However, using the polymer catalyst, compounds **2** and **3** labelled poorly (<5 and 0% incorporation, respectively), possibly due to increasing steric demand at the amide function or constraints at th coordinating centres. In the case of **4**, **5** and **6** (indomethacin), labelling was successful with similar isotope incorporation to that observed for the homogeneous catalyst. Importantly, after filtration of the polymer-supported reagent analysis of the reaction mixtures by analytical HPLC/MS and ^{1}H NMR revealed pure compounds with no trace of catalyst-derived products.

Tritium labelling examples

Using the quinoline nitrogen as a directing group, compound **7** was labelled efficiently and exclusively at the indicated positions (33 Ci/mmol) using **1** (1 equiv, 1.6 Ci of tritium gas) to provide material of radiochemical purity 84% directly after filtration (Figure 1).

Initial attempts to label compound **8** mediated by the aryl nitro function using Crabtree's catalyst gave disappointly low incorporation of tritium in the molecule. By using an alternative catalyst, $CODIr(EtPPh_2)_2BF_4$

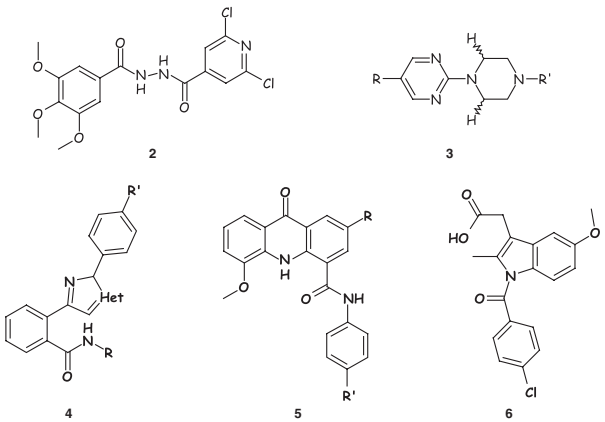


Table 1 Deuteration of various substances with polymer 1 and Crabtree's catalyst

Substrate	Labelling with Polymer (**1**)	Labelling with Crabtree's
N,*N*-Dimethylbenzamide	27%D	56%D
7,8-Benzoquinoline	14%D	7%D
Benzophenone	69%D	49%D
4-Nitroacetophenone	45%D	32%D
3-Methylacetophenone	79%D	81%D
2-Phenylpyridine	17%D	21%D
Benzanilide	73%D ortho to amide 36%D ortho to anilide	68%D ortho to amide 18%D ortho to anilide

Conditions: the substrate (0.05 mmol), catalyst (0.001 mmol Crabtree's or 1.6 mg of **1**), were stirred in dichloromethane (1 ml) at room temperature for 1 h under D_2 gas (9 ml, 0.4 mmol).

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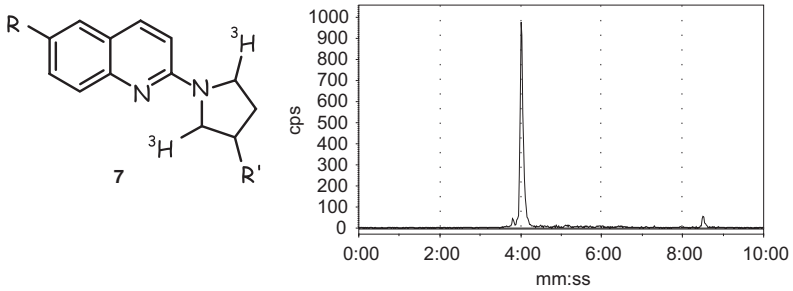

Figure 1 Radiochromatogram of the crude reaction mixture from titration of 7 with polymer 1.

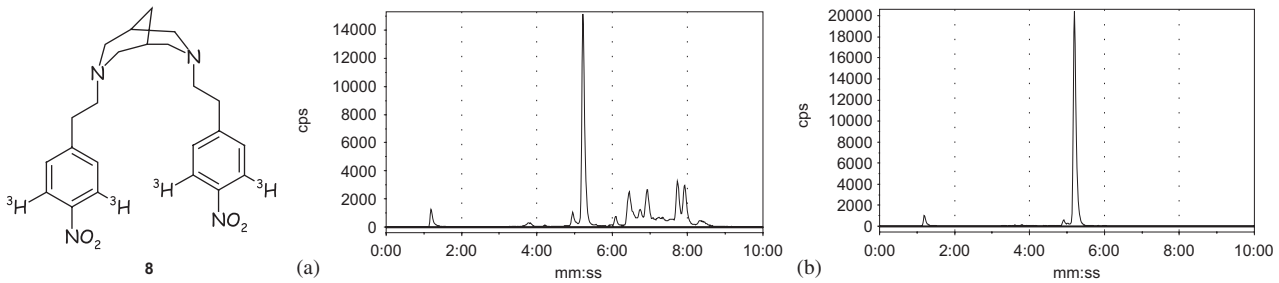

Figure 2 Comparison of labelling 8 with tritium gas in the presence of (a) CODIr $(EtPPH_2)_2BF_4$ and (b) polymer 1.

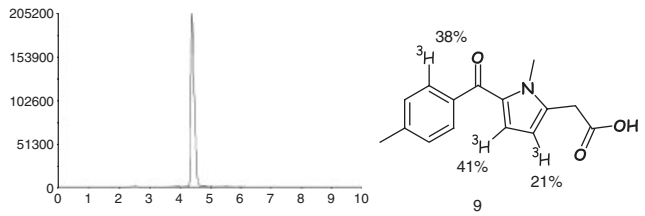

Figure 3 Radiochromatogram of the crude reaction mixture from titration of Tolmetin 9 with polymer 1.

(1.5 equiv, 2.6 Ci of tritium gas), the compound was labelled to a high degree at all four positions with a radiochemical purity of 35% (Figure 2(a)). When the reaction was repeated with 2 equivalents of polymer catalyst, **8** was labelled to a specific activity of 33 Ci/mmol. However, all the labelled catalyst-derived material has been removed to give a radiochemical purity of 92% (Figure 2(b)).

Tolmetin (**9**), a non-steroidal anti-inflammatory drug is metabolized to chemically reactive acyl glucuronides which have been shown to form covalent adducts with protein, possibly contributing to drug toxicity. The radiolabel was employed as a control to determine the reactivity of the acyl glucuronide metabolites from carboxylic drugs. Tolmetin (1 mg) was labelled in dichloromethane with polymer **1** (1.1 equiv) and 1.8 Ci of tritium gas for 3 h. Filtration and removal of labile tritium directly provided [^{3}H]tolmetin (130 mCi, 41 Ci/mmol, 98.5% radiochemical purity). Tritium NMR analysis showed distribution of the label at the indicated positions (Figure 3).

Conclusion

A new catalytic method for *ortho*-labelling substrates has been developed. The catalyst is simple to prepare from commercially available materials and labelling occurs efficiently and regioselectively with simple and complex molecules. The polymer-supported catalyst can be readily screened alongside conventional homogeneous complexes before committing to a reaction with tritium gas. The catalyst is now routinely used within our laboratories to radiolabel drug candidates, which after a simple filtration step, affords products of good radiochemical purities thereby simplifying the purification effort.

REFERENCES

1. (a) Chen W, Garnes KT, Levinson SH, Saunders D, Senderoff SG, Shu AYL, Villani AJ, Heys JR. *J Label Compd Radiopharm* 1997; **39**: 291–298; (b) Hesk D, Das PR, Evans B. *J Label Compd Radiopharm* 1995;

36: 497–502; (c) Cross PWC, Ellames GJ, Gibson JS, Herbert JM, Kerr WJ, McNeil AH, Mathers TW. *Tetrahedron* 2003; **59**: 3349–3358.

2. Salter R, Chappelle MR, Morgan A, Moenius T, Ackerman P, Studer M, Spindler F. *Synthesis and Applications of Isotopically Labelled Compounds Proceedings of 7th International Symposium, Dresden, Germany, June 2000*, vol. 7, Pleiss U, Voges R (eds). Wiley: New York, 2001; 63–67.
3. Hickey MJ, Kingston LP, Jones JR, Lockley WJS, Mather AN, Wilkinson DJ. *Tetrahedron Lett* 2004; **45**: 8621–8623.

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