Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 519–520.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1236

JLCR

Short Research Article

Hydrogen isotope exchange at alkyl positions using Crabtree's catalyst and its application to the tritiation of methapyrilene†

NICK BUSHBY* and DAVID A. KILLICK

Isotope Chemistry, AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Received 2 August 2006; Revised 18 December 2006; Accepted 20 December 2006

Keywords: methapyrilene; isotope-exchange; *ortho*-labelling; iridium; Crabtree's catalyst

Introduction

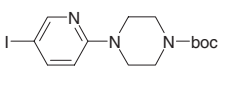
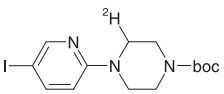
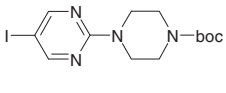
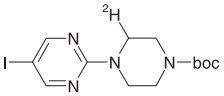
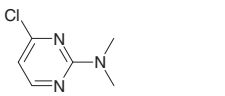
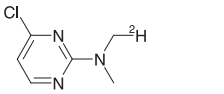
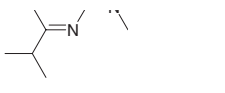
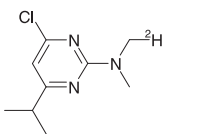
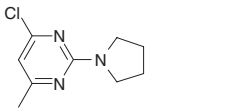
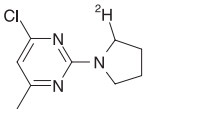
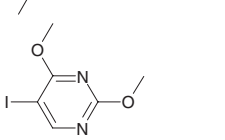
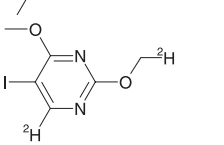
Crabtree's catalyst is known to promote hydrogen–deuterium (or hydrogen–tritium) exchange on aromatic systems where there is a directing group on the aromatic ring, the exchange being directed *ortho* to the directing group.[1] Although there have been reports in the literature of iridium(I) based catalysts facilitating hydrogen isotope exchange at alkyl positions,[2] there are many fewer examples of this exchange process than for exchange at aromatic positions.

Results and discussion

A set of model compounds were reacted with Crabtree's catalyst in the presence of deuterium gas under standard conditions: Substrate (0.1 mmol) and Crabtree's catalyst (0.05 mmol) stirred in DCM (4 ml) under deuterium gas (1 to 0.46 atm) for 16 h (Table 1). After the reaction, the products were isolated by flash chromatography, the site of labelling was identified by ^{1}H NMR and the extent of deuterium incorporation determined by mass spectrometry. In all cases a high degree of deuterium incorporation was achieved, often close to the theoretical maximum. Only in one case was exchange into an aromatic position observed.

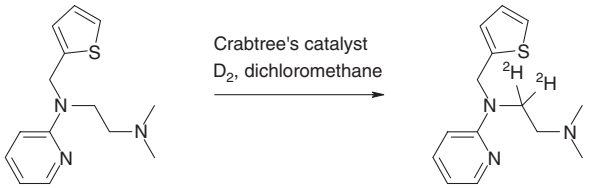
Tritium labelled methapyrilene had previously been prepared by the bromination of methapyrilene, which gave material exclusively brominated in the pyridine ring, followed by tritio-debromination.[3] Tritium labelled methapyrilene was required for metabolism studies and material labelled in the pyridine ring would not have been suitable for the work planned. However, it was found that Crabtree's catalyst would direct

Table 1 Extent of hydrogen–deuterium exchange on model compounds

Substrate	Product	Yield (%)	Deuterium incorporation (*d*/molecule)
		90	4.0
		74	3.9
		52	5.8
		47	3.5
		56	1.9
		66	2.9

*Correspondence to: Nick Bushby, Isotope Chemistry AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK.
E-mail: nick.bushby@astrazeneca.com

†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compound, Edinburgh, 16–20 July 2006.



Scheme 1

hydrogen–deuterium exchange exclusively into one of the alkyl positions of methaprilene (Scheme 1).

Material with high deuterium incorporation (1.9 d/molecule) was obtained and when similar conditions were applied to the tritium labelling, [^{3}H]-methapyrilene was obtained with high specific activity (25.8 Ci/mmol) and acceptable purity (RCP>95%) after purification by prep-HPLC.

Conclusions

Directing hydrogen–tritium exchange into alkyl positions with Crabtree's catalyst can provide a rapid method for labelling certain drug-like molecules in metabolically stable positions with high specific activity. The reaction appears to be quite general for compounds with the structures exemplified in Table 1.

REFERENCES

1. Ellames GJ, Gibson JS, Herbert JM, McNeill AH. *Tetrahedron* 2001; **57**: 9487–9497.
2. Shu AYL, Saunders D, Levinson SH, Landvatter SW, Mahoney A, Senderoff SG, Mack JF, Heys JR. *J Label Compd Radiopharm* 1999; **42**: 797–807; Chen W, Garenes KT, Levinson SH, Saunders D, Senderoff SG, Shu AYL, Villani AJ, Heys JR. *J Label Compd Radiopharm* 1996; **39**: 291–298.
3. Marrian DH, Hill SJ, Sanders JKM, Young JM. *J Pharm Pharmacol* 1978; **30**: 660.

DOI: 10.1002.jlcr