Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 558–560.
DOI: 10.1002/jlcr.1273

JLCR

Short Research Article

Selective tritio-dehalogenations†

PAUL H. ALLEN*, MICHAEL J. HICKEY, LEE P. KINGSTON and DAVID J. WILKINSON
AstraZeneca R&D Charnwood, Bakewell Rd, Loughborough, Leics, LE11 5RH, UK

Received 14 August 2006; Revised 2 January 2007; Accepted 20 January 2007

Keywords: tritium; isotope-exchange

Introduction

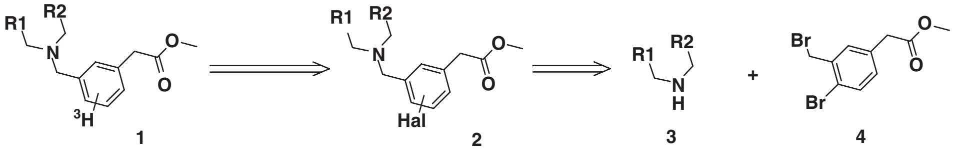
Obtaining early information on the metabolism of compounds representative of a lead series can provide invaluable information to a project. For one particular series, we were interested in synthesizing a number of tritiated compounds and, based upon the structural type and the specific activity required, decided that the best approach would be to use a tritio-dehalogenation procedure with the label being incorporated at the last step. Initially four compounds were identified, each of which possessed the common fragment **1** depicted in Scheme 1. A suitable halogenated meta-substituted aromatic derivative **2** was sought which we were able to access from the secondary amine **3** and aryl bromide **4**, both of which were available in house.

Results and discussion

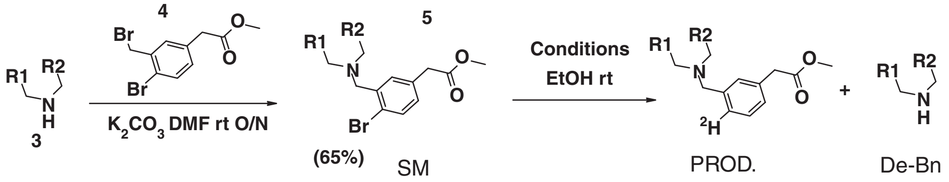
The aryl bromide **5** was readily synthesized from secondary amine **3** and aryl bromide **4** under standard alkylation conditions shown in Scheme 2.

Optimizing the conditions for the reductive dehalogenation of the aryl bromide **5** using deuterium instead of tritium and a range of catalysts generated the results summarized in Table 1.

Although some selectivity for the product could be achieved using $Pd(OH)_2$ as catalyst and 1 atmosphere



Scheme 1



Scheme 2

---

*Correspondence to: Paul H. Allen, AstraZeneca R&D Charnwood, Bakewell Rd, Loughborough, Leics, LE11 5RH, UK.
E-mail: paul.allen@astrazeneca.com

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

Table 1 Deuteration of aryl bromide **5** under a range of conditions

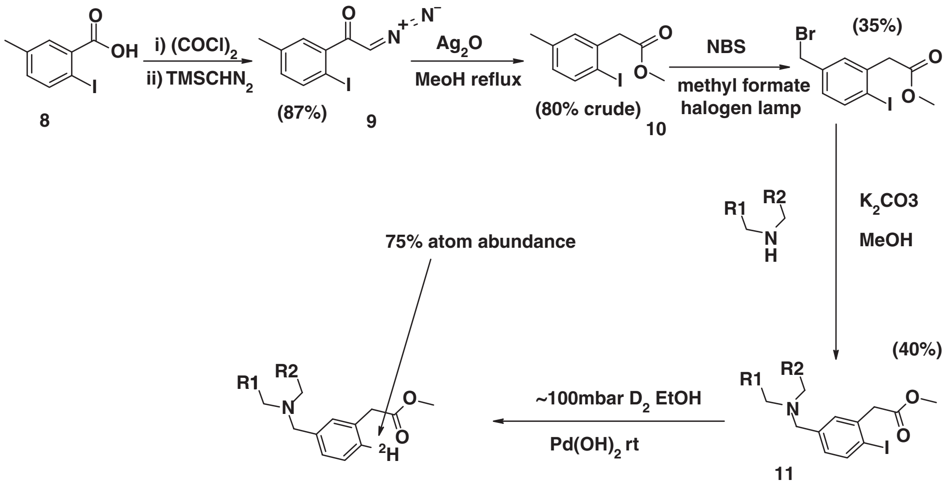
Entry	D_2 pressure	Catalyst	Base	Ratio SM	Product	De–Bn
1	1 atm	PtO_2	Et_3N	15	30	55
2	1 atm	PtO_2	X	20	30	50
3	1 atm	$Pd(OH)_2$	X	5	55	40
4	200 mbar	PtO_2 5 min	X	70	5	25
		30 min	X	0	0	100
5	200 mbar	$Pd(OH)_2$ 5 min	X	70	5	25
		20 min	X	50	10	40
6	200 mbar	5% Pd/C20 min	X	99	1	0
		type35 60 min	X	99	1	0

of deuterium (entry 3), significant amounts of debenzylation were still observed. On switching to a partial pressure of deuterium gas (entries 4 and 5), to reflect the conditions under which the tritiation would be performed, sufficient selectivity for the desired product could not be achieved, even when using Type 35 5% Pd/C (entry 6), which is recommended for such reactions.[1]

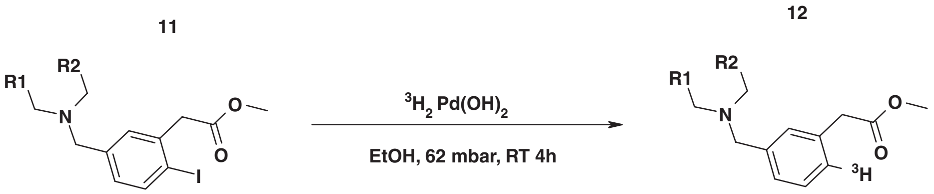
Whilst the debenzylation of amines is a well-known reaction under reductive conditions in the presence of palladium we hoped that by switching to the aryl iodide[2] we might be able to achieve better selectivity than was observed with the aryl bromide. Initial attempts to synthesize the iodo compound using firstly Buchwald exchange chemistry to convert the bromo derivative **5** to the iodo derivative and secondly using electrophilic iodination conditions (e.g. TFA and *N*-iodosuccinimide) on the parent compound were unsuccessful. Consequently, the synthesis of the iodo-derivative was undertaken from a commercially available iodo-precursor.

One such precursor was the iodobenzoic acid **8**, however, since we required a phenylacetic acid moiety, this precursor had to be first homologated as shown in Scheme 3. This was achieved using a two step Arndt–Eistert rearrangement of the diazoketone **9** using silver oxide. Following standard bromination of the toluene compound **10** and reaction of the resulting benzyl bromide with the secondary amine afforded the desired aryl iodide **11**. The optimized deuterium exchange conditions of $Pd(OH)_2$ in ethanol, initially identified for the bromo derivative, were used and found to selectively incorporate deuterium without any debenzylation after 2 h reaction time (100% product); after 20 h reaction time, there was around 50% debenzylation.

Having now identified conditions which gave rise to good deuterium incorporation and selectivity, the reaction could be carried out with tritium in an analogous manner. Therefore, the aryl iodide **11** was reduced under a partial pressure of tritium gas



Scheme 3



6mg, 2 Ci used

110 mCi crude yield (91% RCY)

5 mCi isolated @ 98.08% pure

42% atom abundance

Spec. Act. 12.3 Ci/mmol

Scheme 4

(62 mbar, 2 Ci) for a total of 4 h using the optimized conditions identified previously and shown in Scheme 4. This gave the desired tritiated product **12** in good radiochemical yield (91%) and with adequate specific activity and crucially, with no sign of starting material or de-benzylation.

REFERENCES

1. From discussions with Johnson Matthey Catalysis group.
2. Rousseau B, Faucher N, Ambroise Y, Cintrat JC, Doris E, Pillon F. *J Org Chem* 2002; **67**: 932.

DOI: 10.1002.jlcr