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Short Research Article

The devolatilization of (^{14}C)-labelled aromatics towards the synthesis of (^{14}C)-labelled NK antagonists for PK studies†

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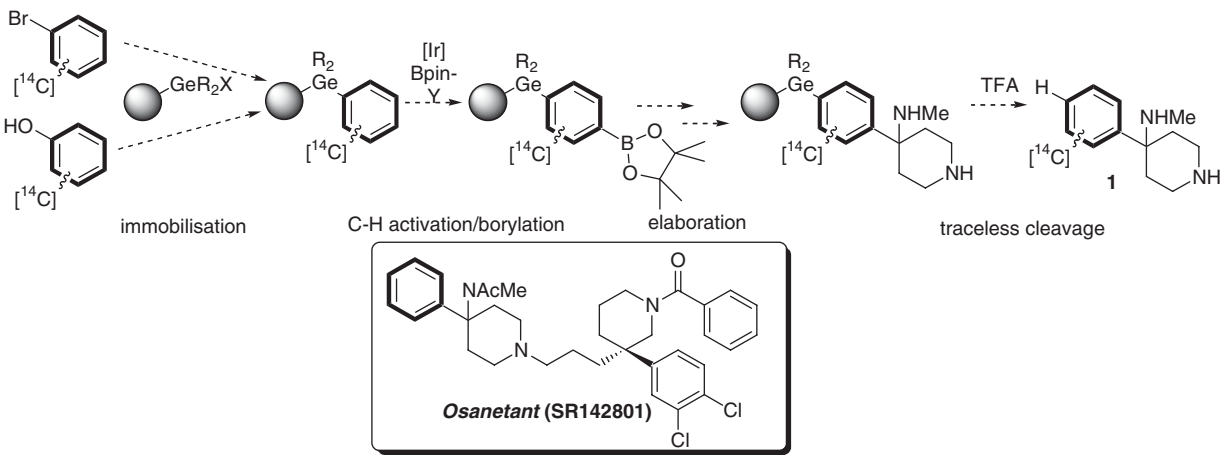
Introduction

Isotopically labelled compounds are widely used within the pharmaceutical industry as trace quantities can be detected[1] making them ideal for ADME studies on potential drug substances and their metabolites.[2] We wished to develop protocols for the phase-tagged synthesis of aryl-containing intermediates from [^{14}C]-bromobenzene (PhBr) and [^{14}C]-phenol (PhOH) so as to devolatilize these substances during the early stages of synthesis, thereby minimizing health, environmental, regulatory and cost issues associated with incomplete isotopic containment. In particular, we were interested in developing this chemistry in the context of the synthesis of 4-methylamino-4-phenylpiperidine **1** a key precursor to numerous neuroexcitatory pharmaceuticals including the sanofi-aventis neurokinin antagonist *Osanetant* (SR-142801).[3] The plan was to synthesize 4-methylamino-4-phenylpiperidine **1** employing isotopically labelled aromatic precursors PhBr and PhOH in conjunction with a Ge-based phase-tag and to cleave the final product from the tag in a traceless fashion (Scheme 1).



Scheme 1

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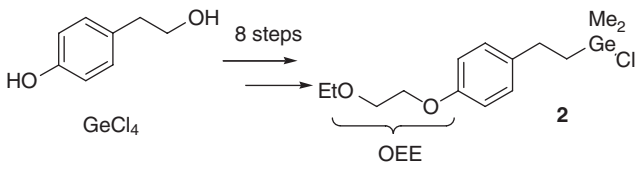
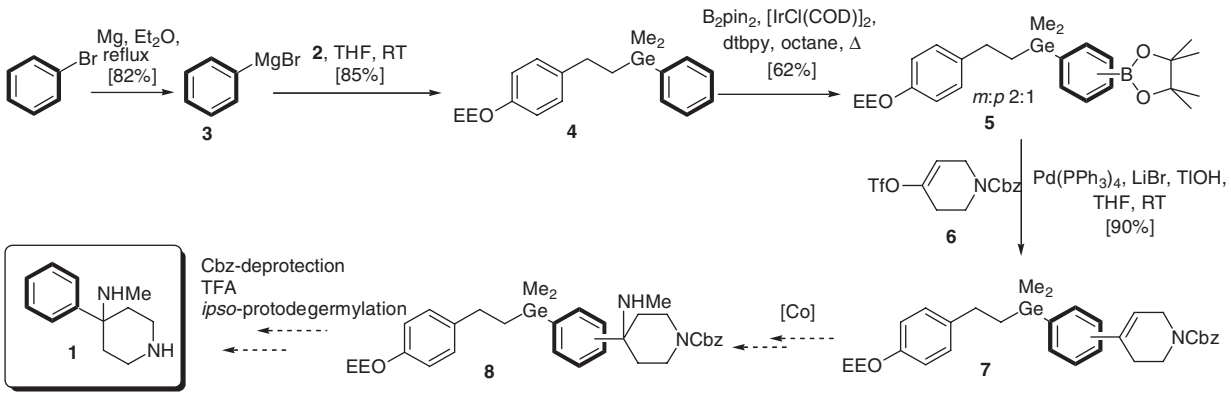


Scheme 2



Scheme 3

Results and discussion

Synthesis of a phase-tagged germanium linker **2** was achieved in eight steps from germanium(IV) chloride and 4-(2-hydroxyethyl)phenol (Scheme 2).[4] The ethoxyethylether unit in this phase tag was designed as a surrogate for a PEG-grafted polystyrene resin.

Unlabelled PhBr was conveniently attached to the germanium linker in good yield via reaction of its Grignard derivative **3** with germyl chloride **2** (Scheme 3). Extensive investigations were undertaken to obtain a regioselective and chemoselective borylation of the resulting phenylgermane **4**, and this was successfully carried out using an iridium-catalyzed C–H activation/borylation process.[5] Pd-catalyzed cross-coupling of boronic ester **5** with vinyl triflate **6** gave the expected aryl piperidine **7**. Our efforts are currently focused on developing a robust protocol for the functionalization of aryl piperidine **7** to give the desired 4-methylamino-4-phenylpiperidine **8** via cobalt-catalysis.

Future work will focus on the completion of the phase-tagged synthesis of 4-methylamino-4-phenylpiperidine **1** by Cbz-deprotection of 4-methylamino-4-arylpiperidine **8** followed by TFA-mediated *ipso*-protodegermylation to effect traceless cleavage of the target compound **1** from the phase-tag via *ipso*-protodegermylation.

Immobilization of PhOH is currently being investigated, in particular the immobilization of PhONf via Pd(0)-catalyzed cross-coupling with a phase-tagged germylhydride and various germylsilanes.

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