

Short Research Article

Opportunities for isotopic labelling via phase-tagged synthesis with organogermanium linkers[†]

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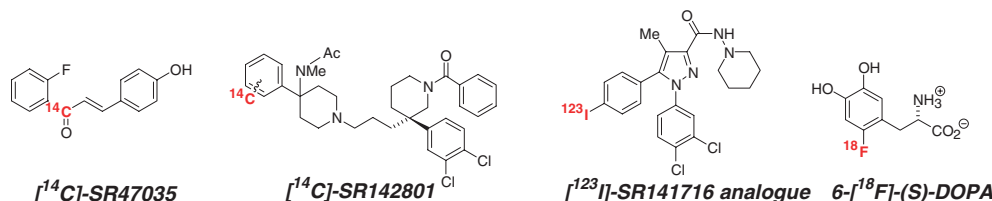
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Abstract: Strategies for the use of germanium-based linkers for the phase-tagged synthesis of isotopically labelled intermediates are described. Protocols of potential use in the devolatilization of volatile intermediates prepared from [¹⁴C]-CO₂ and [¹⁴C]-PhBr to aid ADME studies on drug substances and their metabolites are discussed in relation to SR47035 (an advanced intermediate *en-route* to the 5-HT₂ receptor antagonist SR46349B) and 4-amino-4-phenylpiperidine (a key intermediate in the synthesis of NK₃ receptor antagonist SR142801, osanetant). Additionally, protocols with potential for the preparation of [¹²³I] and [¹⁸F]-labelled SPECT/PET imaging/diagnostic agents are discussed in relation to an [¹²³I]-labelled analogue of SR141716 (rimonabant, a CB₁ receptor antagonist) and 6-[¹⁸F]-(S)-DOPA (for diagnosis of Parkinson's disease). Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: phase-tagged synthesis; solid-phase synthesis (SPS); isotope labelling; organogermanium; devolatilization; SPECT; PET



Introduction

Phase-tagged synthesis encompasses methods of synthesis in which either the reagents/catalysts or substrates used in a synthetic sequence are covalently

attached to a 'phase-tag' which allows the molecule to be readily separated from compounds that are not tagged.^{1,2} The best known example is solid-phase synthesis (SPS) wherein an insoluble polymer support is used as the phase-tag and separation is by simple filtration; which can be automated. In an isotopic labelling context, SPS offers two additional benefits: firstly, the process of phase-tagging renders the substrate involatile and secondly, if an appropriately low loading of the substrate onto the tag is achieved, then conveniently handled quantities of, e.g. derivatized polymer can be used for the preparation of the extremely small quantities of labelled product required for many applications. Herein, we describe the development of potentially generic strategies for the preparation of isotopically labelled compounds of

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pharmaceutical/pharmacological interest exploiting the above features of phase-tagged synthesis. Additionally, we exploit the unique properties of an arylgermanium bond between the substrate and the phase tag.^{3–6} The precise properties of the aryl germanium linkage can be tuned by varying the two 'spectator groups' on the germanium atom,⁶ but in general this linkage is extremely resistant to cleavage by basic and nucleophilic conditions but is readily cleaved in a 'traceless' fashion by, e.g. TFA or with concomitant introduction of functionality at the position of previous attachment by, e.g. I^+ , Br^+ , Cl^+ and F^+ . This allows 'traceless' devolatilization on the one hand and late-stage introduction of potentially isotopically labelled I and F atoms for SPECT/PET imaging on the other. All the work described has been performed using non-isotopically enriched materials as proof-of-concept for the approaches – clearly, optimization will be required prior to 'hot' application.

Results and discussion

Preparation of the germanium-based linkers

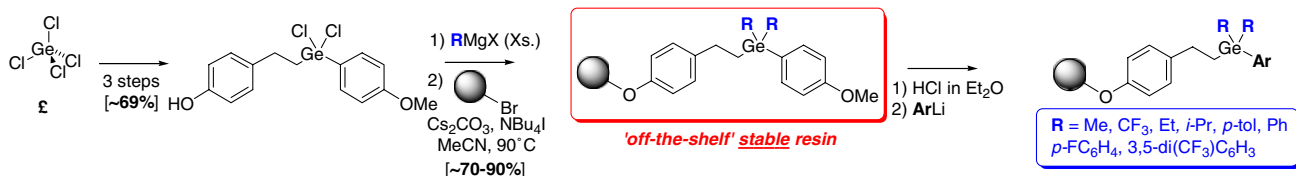
The efficient synthesis of germanium-based linkers for SPS from commercial $GeCl_4$ has been described previously (Scheme 1).^{3,4,6}

Immobilization of an aromatic substrate to a polymer support in this fashion provides a robust platform for further chemical manipulation while benefiting from the above-mentioned synthetically appealing attributes of the germanium-aryl bond.

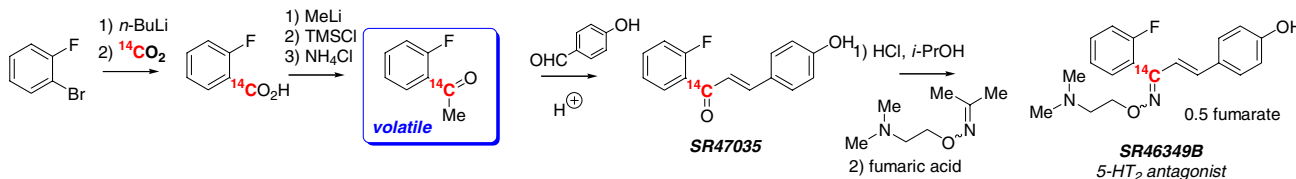
Devolatilization of potentially ^{14}C -labelled pharmaceutical intermediates for ADME studies

Radioisotopically labelled intermediates are generally toxic at high concentrations and require rigorous containment. Issues of containment are invariably most acute during the first steps in a synthesis starting from a volatile-labelled starting material and proceeding via low-molecular weight volatile synthetic intermediates. Devolatilization by direct immobilization of the labelled precursor onto a polymeric support would clearly solve these problems by rendering the labelled material completely involatile during subsequent transformations. That only a limited set of isotopically labelled 'building blocks' are employed routinely by radiochemists is advantageous for developing generic devolatilization protocols – only a limited number of key immobilization techniques and subsequent functionalization protocols need to be developed in order for these techniques to be widely applicable. It was therefore our objective to develop modes of attachment that would prove as robust and flexible as possible.

Our initial objective was to provide proof-of-concept for the devolatilization of $[^{14}C]$ -labelled intermediates formed following carboxylation of an aryl lithium species with CO_2 generated from $[^{14}C]$ - $BaCO_3$. Specifically, we decided to develop a SPS approach to SR47035, which is an advanced intermediate *en-route* to the sanofi-aventis 5-hydroxytryptamine (5-HT₂) receptor antagonist, SR46349B. During preliminary studies within sanofi-aventis towards the synthesis of a $[^{14}C]$ -labelled analogue it had been noted that the 2-fluoroacetophenone intermediate was appreciably volatile (Scheme 2).



Scheme 1 Scheme available in colour online at www.interscience.wiley.com



Scheme 2 Scheme available in colour online at www.interscience.wiley.com

We developed a solution-phase surrogate for SPS using an ethoxyethanol functionalized derivative of a dimethylgermyl linker as a mimetic for the same linker attached to a commercial polyethyleneglycol (PEG)-grafted polystyrene (PS) resin (Scheme 3).

For this solution phase model, the key carboxylation step proceeded smoothly using an excess of solid CO₂ (78% yield) and traceless cleavage from the linker was accomplished using 50% trifluoromethansulphonic acid in dichloromethane. As yet, however, yields for the carboxylation step when using strictly one equivalent of gaseous CO₂ in conjunction with a hypogel[®] immobilized precursor have been poor. Further optimization of this process is ongoing.

We also wanted to address some of the challenges presented by the handling and use of [¹⁴C]-bromobenzene. This compound is among the most commonly employed labelled starting materials in radiosynthesis after [¹⁴C]-CO₂ and can be difficult to contain. If immobilization is to be the very first step, and the bromine 'handle' of bromobenzene is used to attach the molecule to the resin then the immobilized labelled benzene needs to be activated to allow further functionalization. We considered that iridium catalyzed C–H activation/borylation might provide a powerful method by which to achieve this as the resulting aryl boronic ester would constitute a versatile precursor to a wide number of synthetically diverse functional groups. Specifically, we decided to explore this concept by developing a SPS approach to SR142801 (osanetant), which is a sanofi-aventis neurokinin (NK₃) receptor antagonist. This molecule contains the 4-amino-4-phenylpiperidine pharmacophore that is common to several neuroactive pharmaceuticals. Our initial work,

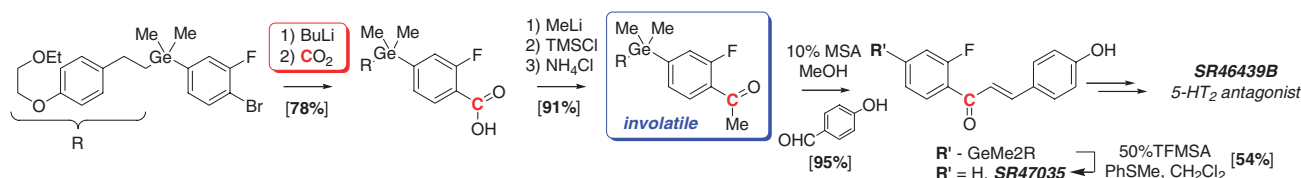
using a solution-phase surrogate for SPS, has established an efficient protocol for immobilization of the Grignard reagent derived from bromobenzene and for its conversion to a mixture of *meta*- and *para*-substituted pinacolboronic esters (Scheme 4).

Suzuki coupling then allows access to a functionalized styrene derivative that we hope to convert via e.g. hydroamination and then *ipso*-protodegermylative traceless cleavage into the requisite 4-amino-4-phenylpiperidine *en route* to the target structure.

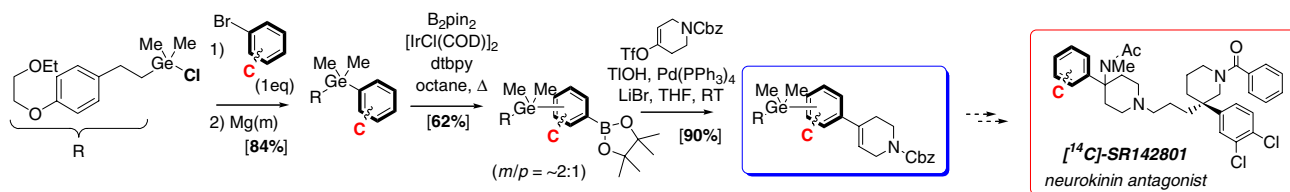
Isotopically labelled halo-degermylation → SPECT/PET imaging agents

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are emerging medical imaging methods which allow the concentration and movement of short-lived emitters in living tissues to be imaged in real time. Consequently, there is a growing demand for efficient methods for the preparation of molecules containing appropriate nuclei [e.g. [¹²³I] (*t*_{1/2} 13.2 h) for SPECT and [¹⁸F] (*t*_{1/2} 110 min) and [¹¹C] (*t*_{1/2} 20 min) for PET]. The preparation of molecules labelled in this manner presents some unique synthetic challenges, primarily due to their short half-lives. As a consequence, a synthesis must be completed from the appropriate precursor and the product purified to a high level very rapidly (within 2–3 half-lives).

Our objective to develop methods for the introduction of isotopically labelled halogens into aromatic precursors concomitant with cleavage from a phase tag via electrophilic *ipso*-halodegermylation. The analogous process of electrophilic *ipso*-halodestannylation of



Scheme 3 Scheme available in colour online at www.interscience.wiley.com



Scheme 4 Scheme available in colour online at www.interscience.wiley.com

aryltrialkylstannane precursors is used widely for this purpose.⁷ However, the tin-containing precursors and the tin halide by-products are extremely toxic making precursor synthesis and product purification hazardous. We considered that it would be highly advantageous if the labelling precursor contained non-toxic germanium (cf. tin) and was bound to the solid phase – allowing release of pure labelled product into solution. This would obviate the need for purification thereby saving valuable time and improving activity (and hence imaging resolution).

Our initial objective was to provide proof-of-concept for *ipso*-halodegermylative cleavage of an aryl group from a solid-supported arylgermane precursor under conditions appropriate for introduction of isotopically labelled iodide {e.g. [¹²³I]-NaI}. Thus, treatment of 4'-methoxybiphenyl immobilized on argogel[®] resin³ with dichloramine-T (DCT) as the oxidant in conjunction with unlabelled NaI afforded the analytically pure biaryliodide in 45% yield (unoptimized). This concept was adopted for the preparation of an iodine analogue of CB₁ receptor antagonist SR141716 (rimonabant) (Scheme 5).

Iodo-rimonabant was prepared by a route adapted from those of Seltzman⁸ and Lan⁹ and immobilized onto hypogel[®] resin following conversion to the corresponding Grignard reagent. Oxidative iodination using DCT when applied to this substrate resulted in some oxidative degradation of the hydrazide moiety of rimonabant and so alternative, milder oxidants are

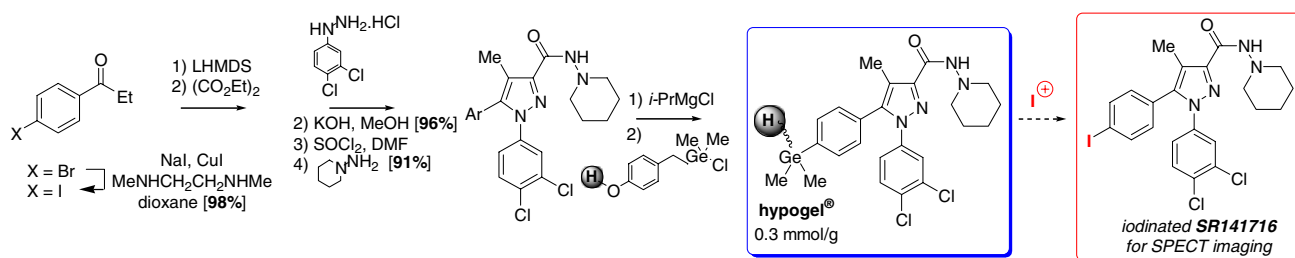
currently being screened to optimize the key cleavage step.

We were also interested in introducing fluorine into aromatic compounds in this fashion. 6-[¹⁸F]-Fluoro-(S)-DOPA is a clinically important tracer molecule which is routinely employed for the diagnosis of Parkinson's disease by PET. Using the electrophilic fluorinating agent Selectfluor[®], we found that a suitably protected (S)-DOPA derivative, immobilized via germanium at the 6-position onto a solution phase surrogate for SPS, could be cleaved to give a clean mixture of *ipso*-fluorodegermylated and *ipso*-protodegermylated products (Scheme 6).

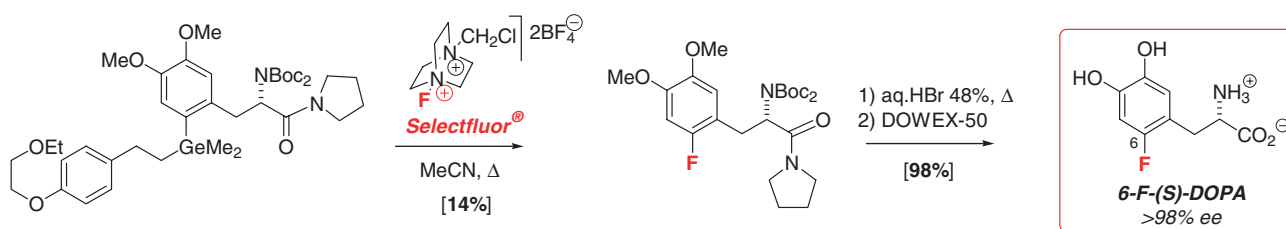
It is expected that optimization of the cleavage conditions, using [¹⁸F]-F₂ or [¹⁸F]-AcOF should allow for an improved ratio of fluorinated to protonated products and that the application of microfluidic and microwave technology in combination with a flow-through cell containing the immobilized precursor will enable much shorter reaction and deprotection times.

Conclusion

We have provided proof-of-concept for phase-tagged synthesis of isotopically labelled compounds exploiting the unique reactivity profile of an aryl germanium bond between the phase tag and the substrate. The methods hold promise for the devolatilization of early synthetic intermediates derived from [¹⁴C]-CO₂ and [¹⁴C]-bromobenzene for ADME studies and for the preparation of



Scheme 5 Scheme available in colour online at www.interscience.wiley.com



Scheme 6 Scheme available in colour online at www.interscience.wiley.com

SPECT/PET tracers containing [^{123}I]-aryliodide and [^{18}F]-arylfluoride moieties.

Acknowledgements

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