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Abstracts

Abstracts of the 12th IIS (UK Group) Symposium*

"Synthesis & Applications of Labelled Compounds 2002"

Meeting Summary

The 12th annual symposium of the International Isotope Society's United Kingdom Group took place at GlaxoSmithKline Medicines Research Centre, Stevenage on Tuesday 15th October 2002. The meeting was attended by over 100 delegates from academia, life science and fine chemical companies. Delegates were welcomed by Dr John Mackinnon, Worldwide Head of Chemical Development Business Operations at GlaxoSmithKline.

The scientific programme consisted of presentations on isotopic chemistry and applications of labelled compounds, or of chemistry with potential implications for isotopic synthesis. Both short- and long-lived isotopes were represented, as were stable isotopes. The programme was divided into a morning and afternoon session chaired by Dr Malcolm Hill (GlaxoSmithKline, Stevenage, UK) and Dr John Harding (AstraZeneca, Alderley Park, UK) respectively. The meeting ended with concluding remarks from Dr Ken Lawrie (GlaxoSmithKline), chairman of the IIS UK Group. This year's symposium had a large attendance from students. Moreover, an excellent level of sponsorship was achieved, and the symposium proved self-financing.

The next IIS UK group symposium is planned for 16th October 2003.

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Meeting Programme

Prof J Staunton [University of Cambridge, UK]—*Isotopes and Mass Spectrometry*.

Dr JC Anderson [University of Nottingham, UK]—*Carbon-13 Labelling to Aid Development of the Catalytic Alkenation of Carbonyls*.

Dr M Glaser [IRSL, Hammersmith, London, UK]—*Production and Applications of ^{124}I for Positron Emission Tomography*.

Dr KI Booker-Milburn [University of Bristol, UK]—*Organic Photochemistry: Synthetic Approaches to Alkaloids in a Reagentless Environment*.

Dr DA Widdowson [Imperial College, London, UK]—*Fluorination for Positron Emission Tomography*.

Dr JM Herbert [Sanofi-Synthelabo, Alnwick, UK]—*Synthetic Consequences of Kinetic Isotope Effects: Synthesis of [$^{13}C_6$]J-SR31742A for Human Trial Purposes*.

Mr DJ Wilkinson [AstraZeneca, Charnwood, UK]—*Tritio-dehalogenation: New Variants on an Old Theme*.

Dr S Hollis [Biodynamics, Rushden, UK]—*The Synthesis of BOC-L-Proline-[$^{14}C_2$] Benzyl Ester*.

Dr AJ Bloom [Amersham, Cardiff, UK]—*The Preparation of 2-Methyl [ring-2-^{14}C]Benzyl chloride*.

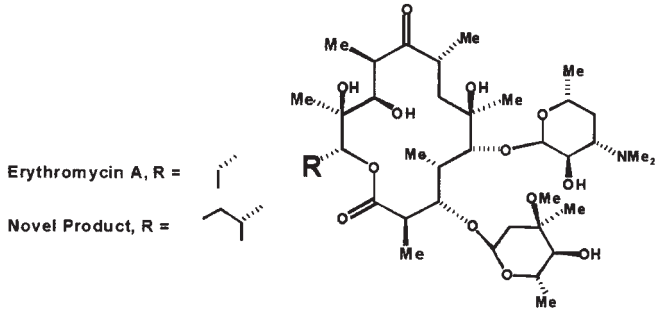
Dr P Johnström [University of Cambridge, UK]—*Peptide Labelling with Fluorine-18*.

ISOTOPES AND MASS SPECTROMETRY

J Staunton, Paul Gates, Gordon Kearney and Tatiana Fonseca

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 2ET, UK

The new science of 'combinatorial biosynthesis' has lead to the production of many novel natural products in recent years. It is now possible to create mixed biosynthetic pathways by which mixed natural product structures are generated. In this lecture the target molecules are molecular hybrids of the polyketide natural products erythromycin and avermectin in which the normal erythromycin 'head' (propyl) has been replaced by an avermectin 'head' (isobutyl).



These novel products are normally formed in minute quantities in exploratory experiments and so a rapid method for detection and identification is required. Mass spectrometry meets the need. However, classical technology has serious limitations.

We have overcome these by adopting new advances in mass spectrometry. First, we have shown that electrospray ionization is greatly superior to electron impact for these very polar molecules. Second, we have shown that ion trap analysis can be exploited to study detailed structure through analysis of fragment ions. Third, we have shown that the extraordinary precision of Fourier transform ion cyclotron mass spectrometry (FTICR) can be harnessed with enormous advantage to determine the accurate masses of fragment ions. The combination of these technologies allows us to detect alterations in structure and also to pin-point the sites of structural change with confidence.

To underpin this new analytical procedure we need to elucidate the fundamental mechanisms of the various gas-phase chemical reactions which determine fragmentation pathways. The ions produced by electrospray have no radical character, so the chemistry characteristic of radical cations does not apply. Instead, two-electron processes dominate. We have used isotopic labels to elucidate mechanisms and have found some surprising new chemistry. The new methods therefore present interesting new challenges to mechanistic chemists as well as natural product chemists. The power of this new technology will be illustrated by reference to erythromycin analogues.

CARBON-13 LABELLING TO AID THE DEVELOPMENT OF THE CATALYTIC ALKENATION OF CARBONYLS

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We are trying to develop a new catalytic methodology for the synthesis of alkenes. We have conceived a transition metal mediated catalytic cycle whereby a carbonyl compound and a ketene can be combined to give an alkene and carbon dioxide (Figure). There are examples of metal alkylidenes **1** that react with carbonyl compounds **2** to give alkenes and metal oxo species **3**. The metal oxo species **3** are presumed to be stable to further reaction. By judicious choice of metal and ligand tuning we are trying to perform new reactions between **3** and ketenes **4** to form metallo-β-lactones **5** which may decompose to give **1** and the stable gas molecule carbon dioxide.

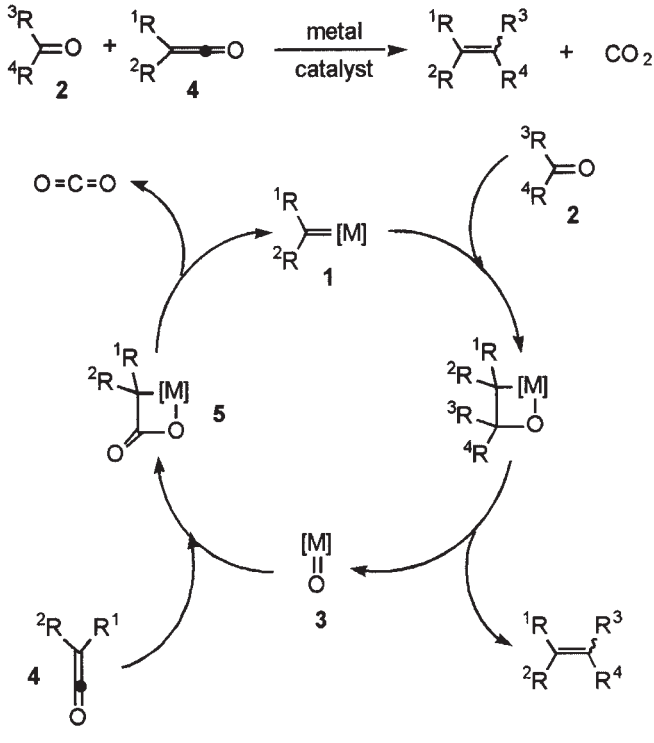
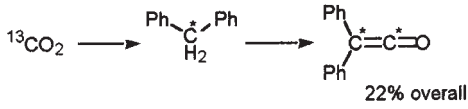


Figure. Hypothetical catalytic cycle for the transition metal catalysed olefmation of carbonyl compounds

To investigate the feasibility of this approach we have had to synthesise *bis-*^{13}C labelled diphenylketene. We developed an efficient synthesis from $^{13}CO_2$ (Scheme)[1]



Scheme.

This lecture will discuss the feasibility of our desired catalytic cycle with the use of ^{13}C NMR data from the reaction between complexes **3** and diphenyl [$^{13}C_2$]ketene.

Reference

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PRODUCTION AND APPLICATIONS OF ^{124}I FOR POSITRON EMISSION TOMOGRAPHY

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The positron-emitting radioisotope iodine-124 ($t_{1/2} = 4.2$ d) is a promising nuclide both for diagnostic and therapeutic applications. A reliable remotely operated system for the safe production of iodine-124 in high purity was required.

The ^{124}Te(p,n)^{124}I reaction was chosen using 12.5 MeV proton irradiation[1] of a solid target consisting of enriched [^{124}Te]tellirium dioxide in a platinum dish which was covered with an aluminium foil. An existing quartz glass furnace tube[2] was redesigned in order to provide a more robust system suitable for semi-automation of the dry distillation process. The distillation conditions have been optimized by using online detection of the collected iodine-124. All manipulations for target handling and distillation were carried out by remote operation. Sodium [^{124}I]iodide was obtained with a decay-corrected target yield of 257 $\pm$ 22 μCi/μAh ($n = 24$), a specific radioactivity of 746 mCi/μmol and a radiochemical purity of $>99\%$ (20 mM NaOH).

The presentation also features examples of the use of iodine-124 for labelling various proteins.

An improved apparatus for dry distillation of sodium [^{124}I]iodide was set up for routine supply. The product was obtained safely with satisfactory yield and purity to label biomolecules.

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ORGANIC PHOTOCHEMISTRY: SYNTHETIC APPROACHES TO ALKALOIDS IN A REAGENTLESS ENVIRONMENT

Kevin I. Booker-Milburn
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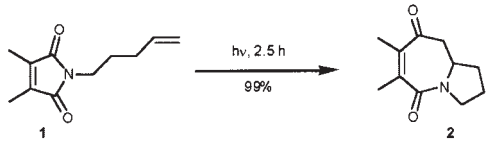
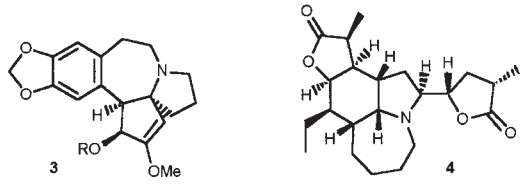
This lecture will highlight the use of organic photochemistry as a powerful tool in the construction of complex heterocyclic systems found in numerous alkaloids. For, example we have found[1] that *N*-pentenyl substituted maleimides **1** undergo efficient photocycloaddition to azepines **2** upon UV irradiation from a medium pressure Hg source.



1 2

This reaction can be considered as a formal [5 + 2] intramolecular cycloaddition, although is likely to proceed by a sequential [2 + 2] cycloaddition/fragmentation sequence. We have since found that this reaction is general for a wide variety of maleimide systems and allows rapid access to polycyclic ring systems. Currently we are investigating the use of this reaction as a key step in the synthesis of the naturally occurring alkaloids cephalotaxine[2] **3** and neotuberostemonine **4**.



3 4

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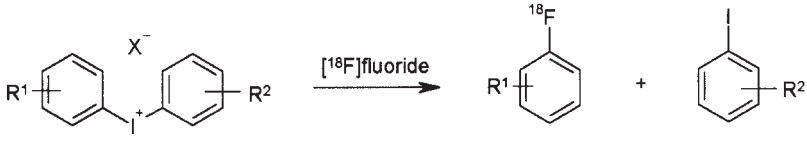
FLUORINATION FOR POSITRON EMISSION TOMOGRAPHY

M. A. Caroll, H. S. Rzepa, V. W. Pike and D. A. Widdowson
Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AZ, UK

Position emission tomography (PET) is an imaging technique for the absolute measurement, *in vivo*, of position emitters, enabling their pharmacokinetics and biodistribution to be elucidated by non-invasive means. In the case of fluorine-18 the desired label is typically introduced into aromatic systems using molecular fluorine [^{18}F] F_2 which is an 'electrophilic' reagent. Our goal was to utilize the [^{18}F] fluoride anion as the source of the label, this is because it can be produced in larger amounts and higher specific radioactivity.[1]



We have identified diaryliodonium salts as suitable substrates for this 'nucleophilic' approach and this has been demonstrated by the generation of a range of ^{18}F labelled aromatics.[2] The fluoridation process is both selective and results in products of high specific activity.

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SYNTHETIC CONSEQUENCES OF KINETIC ISOTOPE EFFECTS: SYNTHESIS OF [$^{13}C_6$]-SR31742A FOR HUMAN TRIAL PURPOSES

George J. Ellames, Jennifer S. Gibson, John M. Herbert and David I. Smith

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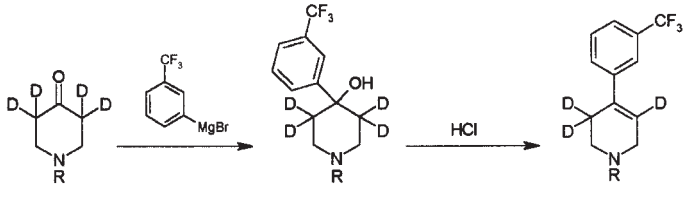
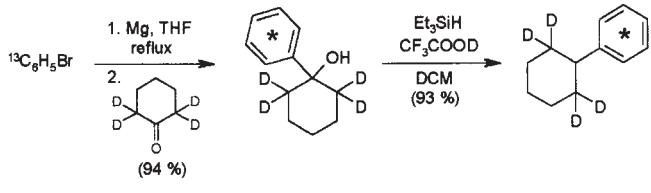
The efficiency of a labelled synthesis is assisted in some cases by the deuterium kinetic isotope effect in particular. For example, in the generic sequence shown in Scheme 1, the presence of deuterium suppresses the competing aldol condensation in the first step, while the isotopic purity is improved in the subsequent step, as a result of preferential loss of any hydrogen remaining from incomplete deuterium incorporation.



Scheme 1. General route to labelled 4-aryl-l,2,3,6-tetrahydropyridines

However, the kinetic isotope effect does not always work to our advantage. When the synthesis of [$^{13}C_6$,$^{2}H_4$]-SR31742A was used as a trial prior to the synthesis of [$^{13}C_6$]-SR31742A for use in a human trial, the product contained no significant novel impurities. However, when the same synthetic route (Scheme 2) was used to prepare the [$^{13}C_6$]-SR31742A, the product contained two impurities resulting from a trace of alkene impurity formed in the second step. Ultimately, a different labelled form of [$^{13}C_6$]-SR31742A was prepared *via* [$^{13}C_6$]-hexamethyleneimine.



Scheme 2. Early steps in the synthesis of [$^{13}C_6$,$^{2}H_4$]-SR31742A

Reference

Ellames GJ, Herbert JM. *J Label Compd Radiopharm* 2001; **44**:169.

TRITIO-DEHALOGENATION: NEW VARIANTS ON AN OLD THEME

D J Wilkinson[a], A N Mather[a], M J Hickey[a], L P Kingston[a] and W J S Lockley[b]

[a] *Department of Medicinal Chemistry, AstraZeneca R&D Chamwood, Bakewell Road, Loughborough, Leics, LEI 1 5RH, UK*

[b] *Department of Chemistry, School of Biological & Life Sciences, University of Surrey, Guildford, Surrey, GU2 5XH, UK*

The need to produce quality tritiated radiolabels rapidly to address the many varied problems encountered during the drug discovery process poses a significant challenge for radiochemistry groups. The use of homogeneous indium catalytic exchange provides the radiochemist with a powerful tool which allows the one step regioselective introduction of tritium into molecules containing an appropriate directing group. We have found that whilst this is a very useful approach and one which is made full use of in our own laboratories, there are limitations associated with it. The two main issues we frequently encounter are the low radiochemical purity of the isolated crude product from the exchange reaction and the limitation with respect to directing groups capable of promoting the exchange.

The reductive dehalogenation of chloro-, bromo- and iodo-compounds with tritium gas has long been a favoured approach for radiolabelling compounds. The introduction of the halogen can be accomplished either via a rational synthesis which often involves many steps or via an electrophilic substitution process directly into the substrate of interest using one of a number of reagents. Many of these halogenation reagents are focussed at the introduction of bromine into a molecule, however, from a radiochemist's viewpoint, iodine would be the preferred halogen for reasons of selectivity and higher isotopic incorporation of tritium.

This talk will review some of the work ongoing at AstraZeneca R&D Charnwood and the University of Surrey on the use of alternative electrophilic halogenation reagents and how they have been utilized in the synthesis of tritiated compounds.

THE SYNTHESIS OF BOC-L-PROLINE-[$^{14}C_2$] BENZYL ESTER

Stephen Hollis and Grant Johnston
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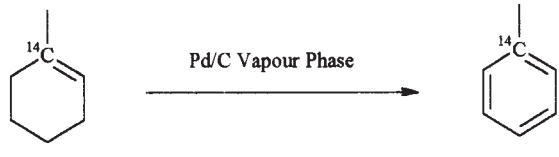
BOC-L-Proline-[$^{14}C_2$] benzyl ester, required as a synthesis precursor, was prepared using grycine-[$^{14}C_2$] prepared from barium carbonate-[^{14}C] and potassium cyanide-[^{H}C]. Enantiomeric excess was determined using HPLC after derivatization.

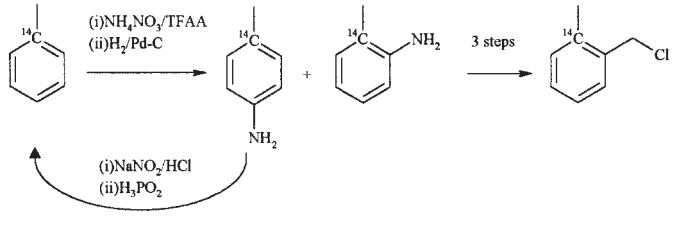
THE PREPARATION OF 2-METHYL[RING-2-^{14}C]BENZYL CHLORIDE

A. Jon Bloom
Amersham Biosciences, The Maynard Centre, Forest Farm, Whitchurch, Cardiff, CF14 7YT, UK

The title compound was prepared in 9 steps from [1-^{14}C]acetic acid, sodium salt. In the key reaction, 1-methyl[1-^{14}C]cyclohexene was converted into [1-^{14}C]toluene by vapour phase dehydrogenation over a palladium on charcoal catalyst at high temperature.



The [1-^{14}C]toluene was nitrated and reduced to yield a mixture of [^{14}C]toluidines. The o-[2-^{14}C]toluidine was separated and converted into the final product using standard chemistry. The p-[4-^{14}C] isomer was recycled by conversion back to [1-^{14}C]toluene using diazotization and reduction.



PEPTIDE LABELLING WITH FLUORINE-18

Peter Johnström and Anthony P. Davenport
BHF Human Cardiovascular Receptor Research Group, Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Centre for Clinical Investigation, Level 6, Box 110, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

In vivo imaging with positron emission tomography (PET) has proved to be a powerful technique to identify, study and diagnose the biological nature of disease as well as to provide biological information for development and assessment of therapies and drugs.[1,2] The technique is based on the administration of tracer levels of biochemicals and pharmaceuticals labelled with short-lived radionuclides such as ^{11}C and ^{18}F. The obtained data from a PET study will reflect the *in vivo* distribution of the radiolabelled compound with time and hence PET can provide pharmacokinetic and pharmacodynarnic information.

Recent years have seen a tremendous increase in applications of peptide radiopharmaceuticals in research and in clinical applications both in diagnosis and in therapy.[3] Peptides have the advantage that they are easily synthesised and there is considerable scope to modify the amino acid sequence to introduce the radiolabel or reduce metabolism (if needed), without effecting their biological properties. Radiolabelled peptides are generally cleared rapidly from the circulation with a subsequent high accumulation in the target tissue. Furthermore as it is now evident that most diseases are manifested at the protein level and with the mapping of the human genome and the subsequent messenger-RNA coding of novel protein receptors new potential targets for therapies will emerge.

Several methods have been developed for radiohalogenation of peptides.[4] In PET, the most widely used radiohalogen is ^{18}F. It can be readily produced in high yields and in high specific activity. It has high positron abundance (97%) and low positron emission energy (0.635 MeV). The label is usually introduced by conjugation of the peptide with a ^{18}F labelled prosthetic group.

In this presentation, we will review the variety of methods available for ^{18}F labelling of peptides as well as discussing our approach for the development of ^{I8}F labelled peptide ligands for the endothelin receptor system.[5,6]

References

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