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Abstracts

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Selected Abstracts

Edited by
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THE DIRECTED *ORTHO* METALATION – CROSS COUPLING SYMBIOSIS IN AROMATIC SYNTHESIS

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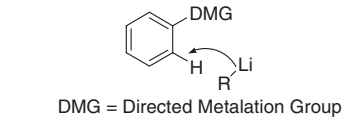
Beginning in the early 1970s, sp^2–sp^2 bond formation took on a new dimension with the discovery of a number of transition metal-catalyzed cross coupling reactions by chemists from many countries. The simple link between the directed *ortho* metalation reaction (**1**) and the rich cross coupling chemistry of B, Mg, Zn, and Sn (**2**) has become a useful strategy in aromatic and heteroaromatic synthesis and, especially in the case of B, has been adapted in industrial practice on large scale. The further connection of this sequence to directed remote metalation (DreM) (**3**) and directed remote alkenyl metalation (DreaM) (**4**) has allowed development of new regiospecific construction of condensed aromatics and heterocycles which equal and/or supercede classical protocols.

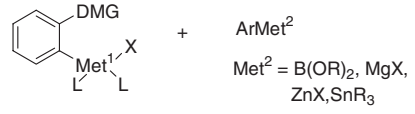
This lecture will present recent results from our laboratories following these themes, their application to bioactive and natural product construction, and with emphasis on the venerable Suzuki reaction.[1,2]



DMG = Directed Metalation Group

Directed *ortho* Metalation (DoM)

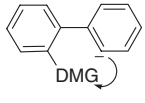
1



X = hal, $OCONEt_2$, $SCONEt_2$, OTf
Met^1 = Pd, Ni

Cross Coupling (XCOUPL)

2

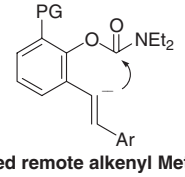


DMG = $CONEt_2$, $OCONEt_2$

X = O, NR, SO_2

Directed Remote Metalation (DreM)

3



Directed remote alkenyl Metalation (DreaM)

4

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ISOTOPICALLY LABELLED 4-FORMYLIMIDAZOLE

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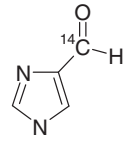
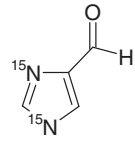
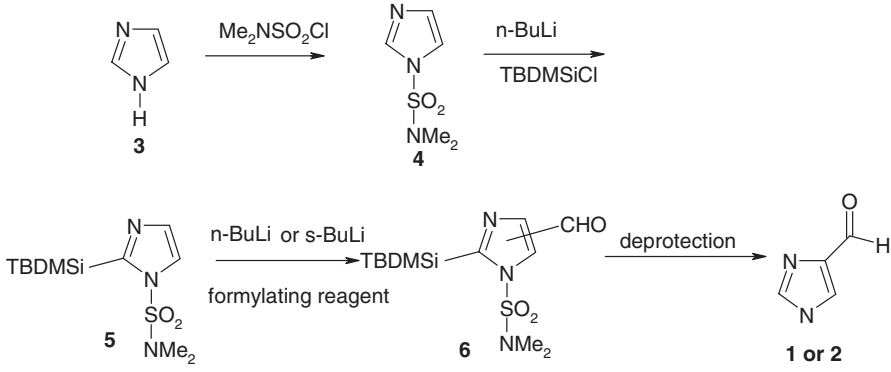


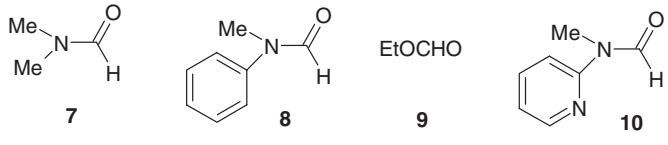
1



2

A contract synthesis required the preparation of isotopically labelled formylimidazoles as intermediates. A requirement was for the ^{14}C-label not to be in the imidazole ring. Therefore we focused our attention on the ^{14}C-labelling of the formyl carbon. Literature precedence suggested that the formyl group could be introduced by lithiating a protected imidazole and reacting with at least 7 equivalents of *N*,*N*-dimethylformamide **7**.[1] This presentation will describe the work involved in the preparation 4-[CO-^{14}C]formylimidazole **1** and how we overcame the need to use a large excess of radiolabelled formylating reagent. The method was then extended to using [$^{15}N_2$]imidazole **3** to prepare $^{15}N_2$-4-formylimidazole **2**.





7 **8** **9** **10**

We initially investigated the formylation of *N*-Dimethylsulfamoyl-2-(*tert*-butyldimethylsilyl)imidazole **5** by lithiation, followed by reaction with fewer equivalents of *N*,*N*-dimethylformamide **7**. We also investigated the use of *N*-methyl-*N*-phenylformamide **8** and ethylformate **9**. Following a paper which discusses the merits of various formylating reagents when reacted with

Grignard reagents, we also chose to try 2-(*N*-methyl-*N*-formylamino)pyridine **10** as the authors[2] reported that only 1 equivalent of **10** was necessary. The advantage of using **10** was that the ^{14}C-formyl labelled material could be prepared from commercially sodium [^{14}C]formate *via* the *in situ* formation of formylacetic anhydride and its reaction with 1 equivalent of *N*-methyl-*N*-(2-pyridyl)amine using modified literature procedures.[3]

Using this route we found that we could prepare 4-[CO-^{14}C]formylimidazole **1** in 50% yield over three steps from sodium[^{14}C]formate compared to the literature yield of 10% when using 7 equivalents of *N*,*N*-dimethylformamide **7**.[1]

The synthesis was repeated using [$^{15}N_2$]imidazole **3** and during this chemistry an improved method for the purification of the intermediate *N*-Dimethylsulfamoyl-[$^{15}N_2$]imidazole **4** was developed as the literature method [1] involved a low yielding distillation when carried out on a small scale.

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NEW CONCEPTS IN TIN-FREE RADICAL CHEMISTRY

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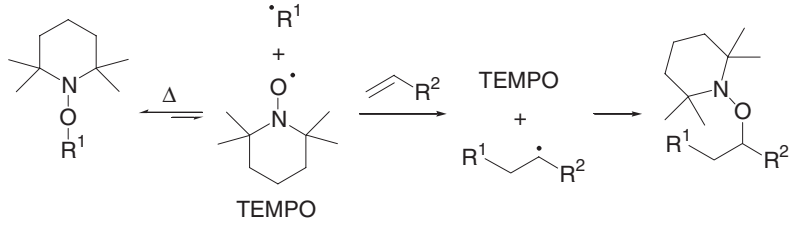
The persistent radical effect (PRE) is a general principle that explains the highly specific formation of the cross-reaction product (R^1–R^2) between two radicals R^1 and R^2 when one species is persistent (for example TEMPO, R^2) and the other transient (R^1), and the two radicals are formed at equal rates.[1] The initial buildup in concentration of the persistent species, caused by the self-termination of the transient radical ($^{\bullet}R^1$–R^1) steers the reaction to follow a single pathway (cross-reaction).

In the lecture, the concept of the persistent radical effect will be briefly discussed. Applications of the PRE for the conduction of tin-free radical cyclization and addition reactions will be presented.[2] The general scheme is depicted below. In our systems nitroxides are used as persistent species. Along with TEMPO other persistent nitroxides have been developed to conduct these thermal radical reactions. In addition, we will present first results on microwave-mediated PRE-controlled radical processes.[3] Moreover, we will present results on the use of our new nitroxides as regulators for the controlled polymerization of styrene and *n*-butyl acrylate.[4]



In the second part of the lecture we will present new applications of functionalised cyclohexadienes in tin-free radical chemistry.[5] In addition, we will also discuss some applications of metalated cyclohexadienes in natural product synthesis.[6]

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OPPORTUNITIES FOR ISOTOPE LABELLING *VIA SOLID* PHASE SYNTHESIS WITH ORGANOGERMANIUM LINKERS

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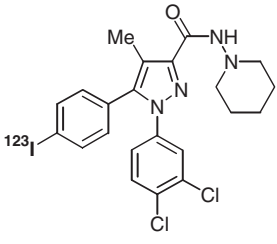
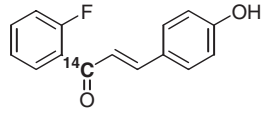
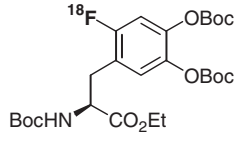
The development of germanium-based linkers for solid-phase synthesis will be outlined and their utility for the preparation of libraries of carbo- and heterocyclic compounds overviewed.[1–4] Specific applications of this type of linker relevant to isotopic labelling procedures will then be presented. Three areas of work will be discussed:



[^{123}I]-SR141716 analogue



[^{14}C]-SR47035



6-[^{18}F]-L-DOPA derivative

Electrophilic ipso-iodo-degermylative linker cleavage for the synthesis of SR141716 analogues

SR141716 (Rimonabant) is a cannabinoid antagonist under development within Sanofi-Synthelabo. Our work towards the development of a solid phase synthesis applicable to the preparation of radio-iodinated analogues of this compound suitable for SPECT imaging will be discussed.

The devolatilisation of intermediates en route to SR47035

SR47035 is an advanced intermediate *en-route* to the Sanofi-Synthelabo 5-HT_2 antagonist, SR46439B. During the development of ^{14}C-labelled SR47035 volatility of a key fluoroacetophenone intermediate was noted. Our work towards the development of a solid phase synthesis of SR47035, circumventing the containment issues associated with the solution phase route, will be discussed.

Electrophilic ipso-fluoro-degermylative linker cleavage for the synthesis of 6-fluoro-L-DOPA

6-[^{18}F]-L-DOPA is used clinically for the diagnosis of Parkinsons disease by positron emmission tomography (PET). The commercial synthesis of this compound employs electrophilic *ipso*-fluorodestannylation of a 6-trimethylstannyl-L-DOPA derivative in solution followed by rapid HPLC purification to remove toxic tin by-products. Our work towards the development of a method for the synthesis of 6-[^{18}F]-L-DOPA via electrophilic *ipso*-fluorodegermylation of an L-DOPA derivative bound to a solid support by a germanium linker will be discussed.

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OPTIMIZATION OF REACTION CONDITIONS ON MG-SCALE BY USE OF SCREENING DEVICES

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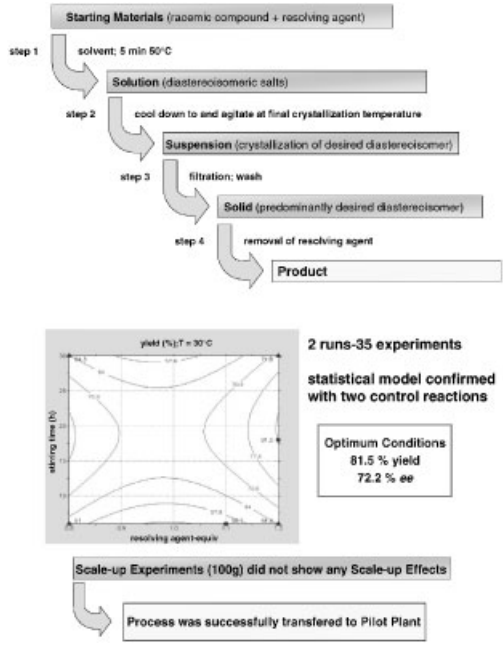
For a first screening of reaction conditions within Chemical Development (between 10 and about 100 reactions) by use of semi automatic procedures simple reaction blocks for parallel synthesis have been established. These systems with small reactor size (5–20 ml reaction volume per reactor) allow a straightforward block-by-block execution of the screening phase. This represents the substance efficiency, necessary for early synthesis development. Attempts to use such simple devices with magnetic stirring bars for optimization of reaction conditions produced consistent screening results. However a large scale-up effect was observed with heterogeneous reactions. These scale-up effects are related to reactor geometry, heating/cooling behavior and mostly to milling/activation effects due to the use of stirring bars grinding on the reactor bottom. A new screening device including adaptable heating/cooling and vortex mixing for the reaction vessels was chosen to minimize mechanical effects. Screening and reaction optimization of heterogeneous reactions will be reported. A classical resolution process, later scaled-up to pilot plant scale, will be presented.



REROUTING RADIOCHEMISTRY WITH MICROWAVES

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Microwave dielectric heating is being increasingly recognized as a valuable technique for reducing reaction times in synthetic transformations (e.g. see review in Reference[1]). With this type of heating, dipolar or ionic molecules attempt to, but are hindered from freely following the rapid oscillations of the electromagnetic fields. Therefore, temperatures increase very rapidly and immediately throughout the sample, instead of, as in conventional heating, slowly inward from the walls of the vessel that are in contact with the heating source. Analogously, the cooling profiles afterwards are also usually quite different for microwave- and conventionally heated samples.

Many types of reactions are driven to completion by performing them at elevated temperatures. In those instances, microwave heating may influence the transformations not only by the high temperatures which may be achieved, but also by the rapidity of the heating and cooling. Cleaner reaction mixtures due to decreased sample decomposition as well as altered product distributions have been reported. In some cases, an increase in the mobility of the reactants and/or local 'hot spots' in the sample may favorably affect the reaction progress, particularly in heterogeneous media. The ability to accelerate typically sluggish reactions of less activated substrates has widened our arsenal of feasible synthetic strategies.

Microwaving has offered very 'special' and/or unique advantages for our abilities to perform synthetic transformations with radionuclides (see reviews[2–4]). This presentation relates experiences from radiolabelling in microwave fields to illustrate the 'special' opportunities offered for the development and practice of radiochemistry.

Acknowledgements to my present and former collaborators in microwaving radiochemistry: Nils Elander, Jan-Olov Thorell, Peter Johnström, Anna Fredriksson, Ester Vázquez and Gareth Getvoldsen and for financial support from the Swedish National Board for Technical Research (210-1997-494) and Personal Chemistry AB (Labwell AB).

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CGMP AND [^{14}C]-LABELLED SYNTHESES OF CAPSAICIN

J. Goehl, B. Perry, J. Windels and M. H. Marx

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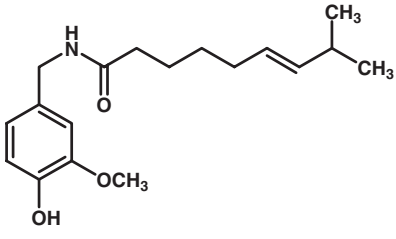
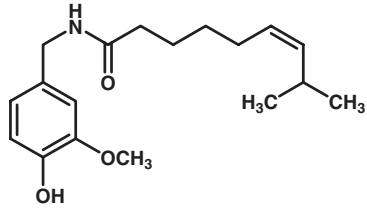
Capsaicinoids are a natural product group found in red chili peppers. The principal component is capsaicin, comprising approximately 85% of the extracted material. Medicinal Capsaicin is a mixture composed mostly of the E isomer[1] (**1**) and is widely used as a topical analgesic to relieve pain. This is apparently accomplished by interfering with Substance P. The remainder of medicinal Capsaicin is the Z isomer. Also known as Civamide (**2**), it is not a natural component but is a by-product of the synthesis route. Synthetic Civamide itself has also found use as an analgesic and exhibits anti-viral activity.



Capsaicin (*E*)

1



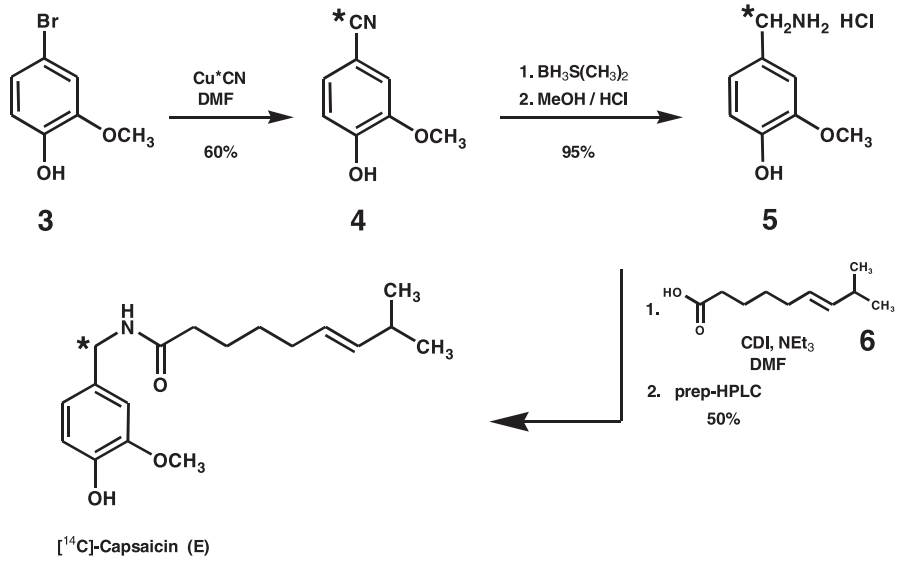
Civamide (*Z*)

2

As part of EPPS' ongoing program to provide a wide range of synthetic services, the opportunity presented itself to develop a synthesis of pure capsaicin for both a [14C]-labelled product and material prepared in large scale under cGMP protocols. The key component for large scale production is vanillamine. A major goal in the labelled synthesis was to prepare capsaicin utilizing as much of the same chemistry as for the large scale. A handful of syntheses have been reported in the literature, all employing an acyl chloride.[2–4] For large scale production the carboxylic acid is preferred. We thus modified a synthesis we first developed several years ago[5] and report now on its success and the symbiosis between production and the radiolabelled scale. The number of steps in the radiosynthesis was reduced, resulting in an increased yield and is shown below.

The new radiochemical synthesis embodied several improvements over the original[5] (see table below). The vanillamine intermediate (**5**) remained the same key intermediate although it was prepared in fewer steps. The label was introduced via Cu (I)[^{14}CN] displacement on aryl bromide **3** rather than [$^{14}CO_2$] incorporation on the benzyl-protected **3**. Reduction with borane methylsulfide proceeded cleanly to yield **5** in excellent yield. The amide linkage

of Capsaicin was formed using carbonyl diimidazole as activating reagent and an 8:1 E/Z mixture of 8-methyl-6-nonenoic acid (**6**). Preparative HPLC was used to separate the E and Z isomers to provide [benzyl-^{14}C]Capsaicin in an overall radiochemical yield of 27%.



	STEPS	YIELD ([^{14}C]) (%)	ISOMERIC PURITY(%)
1984 [^{14}C] Synthesis	**6**	**5.5**	**96.0**
New [^{14}C] Synthesis	**4**	**27**	**99.8**

Each synthesis employed a final chromatographic purification.

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H/D-EXCHANGE IN AROMATIC SYSTEMS USING TRANSITION METAL CATALYSIS

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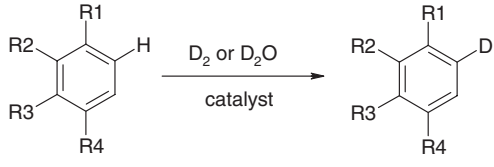
Starting from hydrogenation catalysts of the Crabtree-type, we have investigated parameters for the hydrogen/deuterium exchange in aromatic systems.[1] Our aim was the better understanding of this hard to predict reaction type, so that clear statements on expectable results can be given.



Therefore we have examined different modifications of ruthenium and iridium catalysts with respect to their catalytic properties, using deuterated water and deuterium gas as isotope source.[2,3] So far there had been mainly reports about successful exchange reactions, when the aromatic system was not highly substituated.[4,5] Multiple substrates were screened to examine the influence of different substituents on the reaction. We have tried to focus on substrates with a diverse substitution pattern, also employing potentially complex building groups such as allylic double bounds and methoxy groups.

Beside general parameters like reaction time and temperature, the substrate/catalyst ratio and the solvent influence were examined and optimized.

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SYNTHESIS OF A ^{11}C-LABELLED NONSTEROIDAL GLUCOCORTICOID RECEPTOR LIGAND AS POTENTIAL RADIOTRACER FOR IMAGING BRAIN GLUCOCORTICOID RECEPTORS WITH POSITRON EMISSION TOMOGRAPHY (PET)

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Glucocorticoids possess a variety of physiologic, biochemical and behavioral functions in the central nervous system, and they exert their biological effects through binding to the corresponding glucocorticoid receptor (GR). The interest in these steroids stems from their role which they play in psychiatric disorders such as depression and anxiety. The development of GR ligands which are appropriately labelled with short-lived positron-emitting radioisotopes would allow the non-invasive *in vivo* imaging and mapping of brain GRs by means of PET. For this purpose, various steroidal glucocorticoids have been labelled with the positron emitter ^{18}F. However, none of the investigated compounds were suitable for *in vivo* visualization of brain GRs with PET.[1–3]

An alternative approach is based on the discovery of structurally novel, nonsteroidal small molecules which show high binding to the GR in the nanomolar range.[4,5] The benzopyrano quinoline-based structure of these GR-binding compounds bears a methoxy group which is a potential site for radiolabelling with [^{11}C]methyl iodide starting from the corresponding demethoxy labelling precursor.

Therefore we set up the synthesis of precursor compound **2** capable of being labelled with [^{11}C]methyl iodide. The preparation of compound **2** commenced with commercially available 2,6-dimethoxyphenylboronic acid **1** and involves a multi-step synthesis sequence which was published recently.[5]

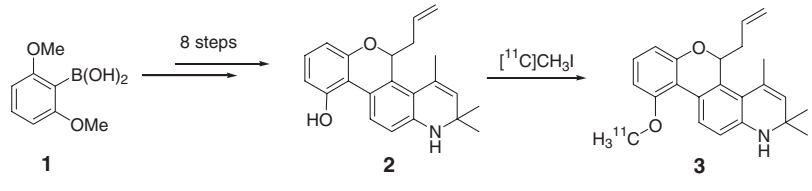

Figure 1. Synthesis of [^{11}C]NSGR ligand

The reaction of phenol precursor **2** with [^{11}C]methyl iodide was performed in an automated synthesis module (Nuclear Interface, Münster). [^{11}C]Methyl iodide was prepared via the 'wet' chemistry route, involving $LiAlH_4$ reduction of [^{11}C]CO_2 and subsequent treatment with HI (57%).

[^{11}C]Methyl iodide was trapped in a DMF solution containing labelling precursor **2** and NaOH as the base. The methylation reaction was accomplished within 5 min at 100°C, and the product was purified by semi-preparative HPLC. The total synthesis time including [^{11}C]methyl iodide preparation, synthesis of ^{11}C-labelled compound **3** and HPLC-purification was 40–45 min. Compound **3** was obtained in a radiochemical yield of 30–40% (decay-corrected, related to [^{11}C]CO_2). Starting from 20 GBq [^{11}C] CO_2, specific radioactivities ranging from 15 to 20 GBq/μmol were reached at the end of the synthesis. The radiochemical purity of **3** exceeded 98%.

Preliminary biodistribution studies in rats demonstrated a brain uptake of 1.5% ID/g after 5 min p.i., which decreased to 0.65% ID/g after 60 min.

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^{18}F-LABELLING OF A POTENT NONPEPTIDE CCR1 ANTAGONIST FOR THE DIAGNOSIS OF THE ALZHEIMER'S DISEASE

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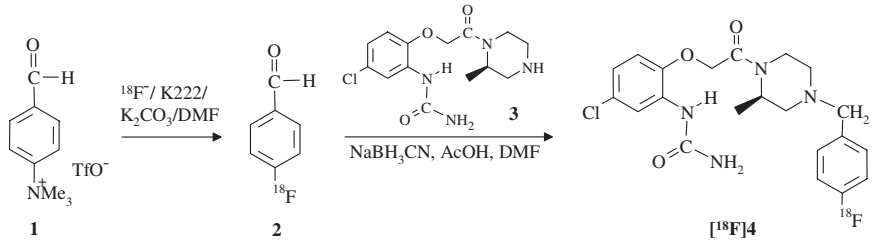
The hydrochloric acid salt of 1-(5-chloro-2-{2-[(2R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)urea (**4**) was described as a potent, selective and orally active nonpeptide antagonist of the CC chemokine receptor-1 (CCR1).[1] The CCR1 is a prime therapeutic target for treating autoimmune diseases, e.g. chronic inflammatory diseases. It was discovered that CCR1 is upregulated in dystrophic neurites found within and around the amyloid plaques of Alzheimer's disease.[2] These CCR1-positive plaques were visible in very early stages of dementia, and they were also found to increase as the degree of dementia increased. In healthy brain, expression of CCR1 is negligible.[2]

These data have encouraged us to develop a method for ^{18}F-labelling of the CCR1 antagonist **4**, mentioned above as promising radiotracer for the early diagnosis of the Alzheimer's disease by PET.[3] The labelled compound **[^{18}F]4** was synthesized in a two-steps one-pot procedure according to Scheme 1.

The first step consisted in the synthesis of 4–[^{18}F]fluorobenzaldehyde (**2**) by aromatic nucleophilic substitution of [^{18}F]fluoride on 4-trimethylammonium-benzaldehyde triflate (**1**) using Kryptofix222/K_2CO_3.



Scheme 1. Synthesis of [^{18}F]4 via 2

The reductive amination of **2** with piperazine derivative **3** and sodium cyanoborohydride gave the desired **[^{18}F]4**. Such a conversion was also described as possible one-pot process for ^{18}F-labelling of fluorodexetimides.[4]

Compound **2** was obtained in radiochemical percentages of 76–78% by heating dried [^{18}F]fluoride/K_2CO_3/K222 complex with **1** in DMF at 120°C for 10 min. Crude **2** was subsequently reductively aminated using piperazine **3**, sodium cyanoborohydride and acetic acid in the same vessel at 120°C for

10 min. The radiochemical percentage of the **[^{18}F]4** in the reaction mixture was up to 52–53%.

To produce this radiotracer suitable for human studies and on high radioactivity levels, the two-steps one-pot procedure had to be adapted to an automated, remotely controlled module, which is installed in a hot cell. It was used as commercially available module for nucleophilic fluorination (GE Medical Systems, former Nuclear Interface, Münster, Germany). The capability of the module includes the radiosynthesis of **2** and its reductive amination with the appropriate piperazine derivative **3** to give **[^{18}F]4**, HPLC purification of the final product, and its solid phase extraction and formulation.

The isolated (not decay-corrected) radiochemical yields of the purified and formulated **[^{18}F]4** ranged between 5 and 13% ($n = 28$). The time of the entire manufacturing process was 90–95 min (after EOB). The radiochemical purity of **[^{18}F]4** was greater than 95%, and the chemical purity $\geqslant$60%. The enantiomeric purity exceeded 99.5%. The specific radioactivity was in the range of 59–184 GBq/μmol starting from 24–77 GBq of [^{18}F]fluoride.

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USE OF [1,2-^{3}H] TESTOSTERONE IN 5A- REDUCTASE ENZYMATIC ACTIVITY DOSING IN DERMAL FIBROBLAST CULTURES FROM POLYCYSTIC OVARIAN PACIENTS

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Polycystic ovarian syndrome is an endocrine malady very frequent in women characterized by the presence of ovarian cysts, ultrasonograph visible or not, menstrual cycle deregulation and sometimes by high plasmatic concentrations of androgen hormones. Many cases of polycystic syndrome could not be easily diagnosed or had an eronate diagnostic. Therefore, it is useful knowing the plasmatic androgene hormones profile. This profile could indicate the cause for observed clinical manifestations; this cause was observed in ovarian, suprarenal glands or hypotalamo-hipofisar level. *In vitro* studies on dermal fibroblasts permit the detail determination of steroid hormones metabolism in target organs and offer important information regarding action mechanism. This study follows the identification of testosterone metabolites in fibroblasts and enzymatic activities of 5α-reductase using testosterone radioactive labeled with tritium.

Testosterone was labelled by selective hydrogenation of 1,2 dihydrotestosteron acetate. The forerunner was synthetized in two steps: esterification of testosteron using acetic anhydride, followed selective dehydrogenation with 2,6-dichloro-3,5-dicyan-1,4 quinone of the esther. The tritium labelled hormone was obtained in two steps: (1) selective hydrogenation of 1,2 dehydrotestosterone acetate in the presence of T_2 gas, at low pressure, and (2) hydrolysis of the esther at basic pH. The raw product obtained was purified by preparative thin layer cromatography. The physical and chemical characterization of labelled testosterone reveals a radiochemical purity higher than 98% and a specific activity of 1975.8 GBq/mmol.

Enzymatic activity was studied using human skin tissue homogenates incubated 1 h at 37°C with tritium labelled testosterone. As cofactor we used NADPH. After reaction stopped, testosterone metabolites were extracted with a mixture of cyclohexane/ethyl acetate. Product separation was realized using Celite chromatographic columns. As mobile phase we used a mixture of isooctane/toluene. Labelled testosterone used as substrate in enzymatic reaction was purified by column chromatography using previous system.

Collected fractions as result of chromatographic elution were determinate enzymatic activities using a Packard liquid scintillation counter.

For metabolites identification testosterone was used, and dihydrotestosterone, androstandione 3α and 3β androstandiols C-14 labelled as internal standards.

SYNTHESIS AND STABILITY STUDIES OF ACYCLOVIR LABELLED WITH TRITIUM

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The labelled Acyclovir was obtained by isotopic exchange reaction in heterogenous catalysis, using Acyclovir as substrate and T_2 as labelling agent. Pd/C and Pd/$BaSO_4$ were used as isotope exchange catalyst and the mixtures dioxane–water–acetic acid or dimethylformamide-phosphate buffer as solvents. Reaction time was 20–25 h. The raw labelled compound was purified by preparative thin layer chromatography using Silica Gel 60 GF_{254} activated at 110°C and butanol:acetic acid:water (4:1:1 v/v/v) as mobile phase. Distribution of the radioactivity on the plate was identifying using LB 2723 Berthold scanner with proportional counting detector.

The labelled compound was conditioned as aqueous solution. Characterization of labelled compound was done by determination of chemical concentration, radioactive concentrations and radiochemical purities. Chemical concentration was determined using PYE UNICAM UV spectrometer at 252 nm.Volumic activity of acyclovir-T-G aqueous solution was determined using LSC 1 Nucleare Enerprise using OptiPhase 'HiSafe' 3 as liquid scintillation cocktail. Radiochemical purity was determined using radio TLC system (see previous presentation).

The physical and chemical characterization of labelled aciclovir reveals a radiochemical purity higher than 95%, and a specific activity of 42 MBq/mmol. Radiolytical processes were evaluating by cuanto chemical methods. We analyzed the primary and secondary radiolytical effects.

The primary radiolytic effect was analyzed using a two-step radiolytic mechanism: (a) the ionization of molecule and spatial redistribution of atoms in order to reach a minimum value of energy, characteristic of the new quantum state; (b) the neutralization of molecule by capture of an electron and its rapid dissociation into free radicals. The period between the capture of electron and molecule dissociation in free radicals is shorter than the time required for geometric reoptimization. Chemical bonds suspected to break are located in the distribution region of LUMO orbital and have minimal bond energy.

The values of binding energies associated with LUMO orbital distribution indicate a radiolytical fragmentation especially for guanidic C–N bond.

Secondary effects study was developed by analysis of reactions between acyclovir (in fundamental, excitated, ionized states) water and active species from radiolytical act.

We analyzed the reaction enthalpies and activation energies.

The results also indicate the radio sensibility of guanidic C–N bond. The experimental results sustain the results obtained from radiolytical simulation.

STUDIES ON DIRECTED *ORTHO*-METALATION (D*O*M) AS CONVENIENT TOOL FOR THE SYNTHESIS OF LABELLED COMPOUNDS

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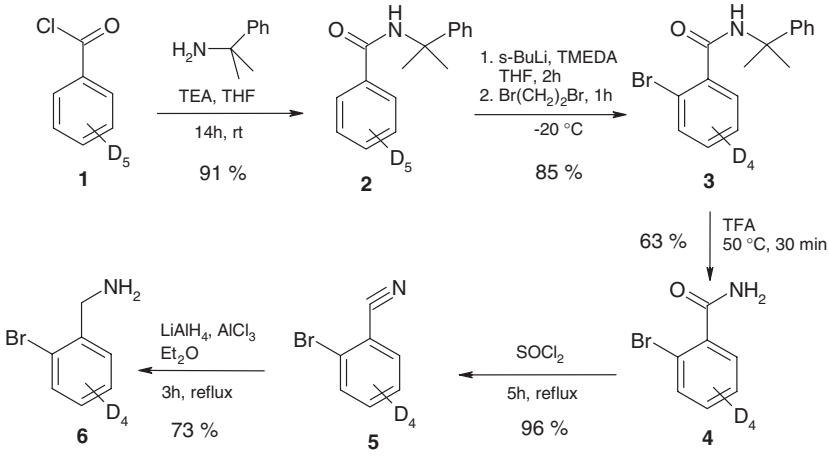
During development of new drug candidates isotopically labelled analogues are requested as internal standards in LC/MS assays. Stable isotope labelled aromatic and heteroaromatic precursors are widely used building blocks for the synthesis of these drug compounds. Problems of site specificity during electrophilic substitution reaction of benzene derivatives arise due to directing influence of the substituent already present in the aromatic substrate. As an alternative, the directed *ortho*-metalation (D*o*M) strategy has been proven as highly convenient for the regiospecific synthesis of polysubstituted aromatic and heteroaromatic compounds.

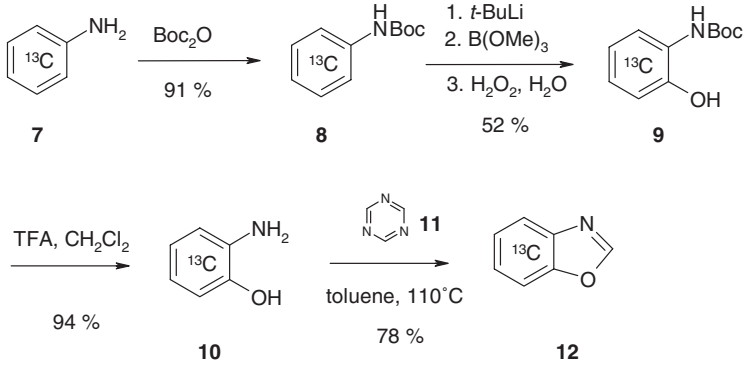
Based on Snieckus[1] protocols, we developed short and convenient lab procedures for the synthesis of 2-bromo benzylamine-[phenyl-d_4] **6** and benzoxazole-[phenyl-$^{13}C_6$] **12**.



2-Bromo benzylamine-[phenyl-d_4] **6** was synthesized starting from benzoyl chloride-[d_5] **1** which was treated with cumylamine to afford the deuterium labelled *N*-cumyl benzamide **2** in 91% yield. Surprisingly, direct application of the metalation procedure described by Snieckus[2] onto deuterium labelled benzamide **2** resulted in a low conversion, which could by improved by variation of temperature and equivalent of the metalation reagent.[3] Based on these optimised reaction conditions the desired 2-bromo *N*-cumyl benzamide **3** was isolated typically in 85% yield as a mixture with unreacted **2** (content of **3**: 86%). Decumylation of crude **3** was achieved with neat TFA at room temperature to give after chromatography the pure bromide **4** in 63% yield.

Treatment of **4** with thionyl chloride provided in nearly quantitative yield nitrile **5** which was reduced by $LiAlH_4/AlCl_3$ to afford the desired 2-bromo benzylamine **6** as the hydrochloride salt in 73% yield.

Aniline-[$^{13}C_6$] **7** was Boc-protected by reaction with Boc-anhydride to give *N*-Boc-aniline-[phenyl-$^{13}C_6$] **8** in 91% yield. *N*-Boc-aniline-[phenyl-$^{13}C_6$] **8** was *ortho*-metalated using *t*-BuLi and quenched with boronic ester to give, after aqueous workup, the boronic acid derivative as a crude product, which was directly converted into the phenol **9** by reaction with hydrogen peroxide in 52% yield, while 31% of *N*-Boc-aniline-[phenyl-$^{13}C_6$] **8** was also recovered. Best results for the deprotection of the amino function were achieved with TFA in dichloromethane (94% yield). Without further purification of aminophenol **10** the reaction with triazine **11** yielded benzoxazole-[phenyl-$^{13}C_6$] **12** as crude product which was purified by chromatography using pentane/diethylether as eluent to give **12** in 78% yield (purity > 98%).



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