

## New approach to the nucleophilic synthesis of $^{18}\text{F}$ -labelled aromatic amino acids

Franziska M. Wagner, Johannes Ermert, Heinz H. Coenen

Institut für Neurowissenschaften und Biophysik: Nuklearchemie (INB-4), Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

**Abstract** – A novel possibility of preparation of  $^{18}\text{F}$ -labelled aromatic amino acids, capable of being easily automated, was developed and evaluated, using a direct nucleophilic  $^{18}\text{F}$ -fluorination of a protected amino acid derivative. This strategy is exemplified by the synthesis of 6- $^{18}\text{F}$ fluoro-L-DOPA and yields products with a high enantiomeric purity.

**Keywords** –  $^{18}\text{F}$ -labelled aromatic amino acid, 6- $^{18}\text{F}$ fluoro-L-DOPA,  $^{18}\text{F}$ -fluorination

### I. INTRODUCTION

In nuclear medical diagnosis,  $^{18}\text{F}$ -labelled aromatic amino acids are widely used as radiopharmaceuticals with positron emission tomography (PET) for the *in vivo* imaging of tumours and, using 6- $^{18}\text{F}$ fluoro-L-3,4-dihydroxyphenylalanine (6- $^{18}\text{F}$ fluoro-L-DOPA **4b**), of the presynaptic dopaminergic metabolism. The currently used method of its routine preparation by electrophilic labelling is limited to low amounts of activity at high costs. The alternatively developed nucleophilic syntheses using the advantage of large scale production of  $^{18}\text{F}$ fluoride, however, result either in insufficient enantiomeric purity [1] or the used multi-step-syntheses are difficult to automate, due to their complexity [2]. In this study a novel nucleophilic approach to the preparation of  $^{18}\text{F}$ -labelled aromatic amino acids, here exemplified by the synthesis of 6- $^{18}\text{F}$ fluoro-L-DOPA, was developed and evaluated, using a direct nucleophilic  $^{18}\text{F}$ -fluorination of protected amino acid derivatives.

### II. RESULTS AND DISCUSSION

Nucleophilic aromatic substitution reactions using no-carrier-added  $^{18}\text{F}$ fluoride generally require an arene ring activated by substituents with  $-M$  effect in combination with a leaving group. In this study a formyl group serves as activating group of an  $^{18}\text{F}$ -for- $^{19}\text{F}$  exchange reaction which can be converted to a hydroxy group by a Baeyer-Villiger oxidation or removed by a decarbonylation reaction using the Wilkinson's catalyst as depicted in Figure 1. Both methods were earlier introduced in  $^{18}\text{F}$ -chemistry using model toluene derivatives [3,4]. In this study the side chain of the arene ring contained the chiral amino acid building block (S)-BOC-BMI [5]. The general suitability of these (S)-BOC-BMI-derivatives (cf. Figure 1) for the synthesis of  $^{18}\text{F}$ -labelled aromatic amino acids was examined at first using (2S,5S)-2-tert.-butyl-5-(2-fluoro-5-formylbenzyl)-tert.-butyl-3-methyl-4-oxo-imidazolidine-1-carboxylate **1a** (X=H) as precursor. Radiochemical yields of about 30 % were obtained using a

tetrabutylammonium hydrogencarbonate activated exchange reaction in DMF.

In the next step, this concept was modified to synthesize a precursor for the preparation of 6- $^{18}\text{F}$ fluoro-L-DOPA. Thus, (2S,5S)-tert.-butyl-5-(4-benzyloxy-2-fluorobenzyl)-2-tert.-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate **1b** (X=OBn) was synthesized via an eleven step organic synthesis. By optimization of the  $^{18}\text{F}$ -isotopic exchange on this precursor a radiochemical yield of about 50 % was obtained under the above described conditions.

After a three step synthesis, including the labelling, a Baeyer-Villiger oxidation using mCPBA and a subsequent hydrolysis by HBr, c.a. 6- $^{18}\text{F}$ fluoro-L-DOPA **4b** was isolated by HPLC containing more than 99 % of the desired L-isomer. The complete preparation and isolation of c.a. 6- $^{18}\text{F}$ fluoro-L-DOPA, using optimised conditions, resulted in a decay corrected yield of about 22 % within a synthesis time of 105 minutes. Preliminary experiments demonstrated also the formation of the amino acids **4a** and **6a,b** according to this method.

### III. CONCLUSION

The presented synthetic pathway of  $^{18}\text{F}$ -labelled aromatic amino acids (e.g. 6- $^{18}\text{F}$ fluoro-L-DOPA) is not only more efficient than known methods of preparation, but furthermore, is capable of being easily automated.

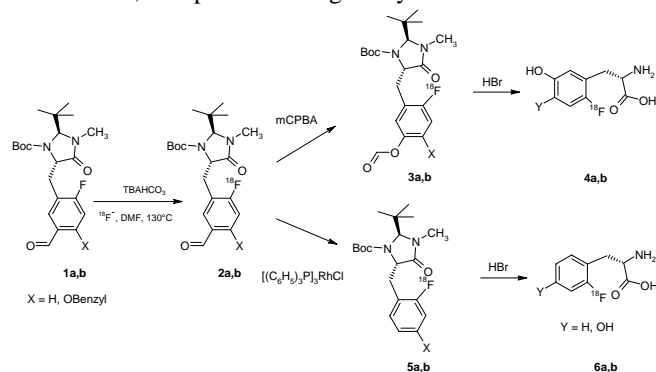


Figure 1

- [1] Tierling T., Berichte des Forschungszentrum Jülich, 2001; Jül-3952 1-121.
- [2] Lemaire, C., Gillet, S., Guillouet, S.P., Plenevaux, A., Aerts, J., Luxen, A. Eur J Org Chem 2899 (2004).
- [3] Chakraborty, P.K., Kilbourn, M.R. Appl. Radiat. Isot. **42**: 673 (1991).
- [4] Chakraborty, P.K., Kilbourn, M.R. Appl. Radiat. Isot. **42**: 1209(1991).
- [5] Seebach, D., Dziadulewicz, E., Behrendt, L., Cantoreggi, S., Fitz, R. Liebigs Ann. Chem. 1215 (1998).