3-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy)prop-1-yne as a prosthetic group for "^{18}F-Click-labeling" reactions

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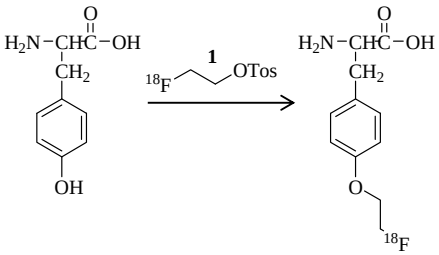
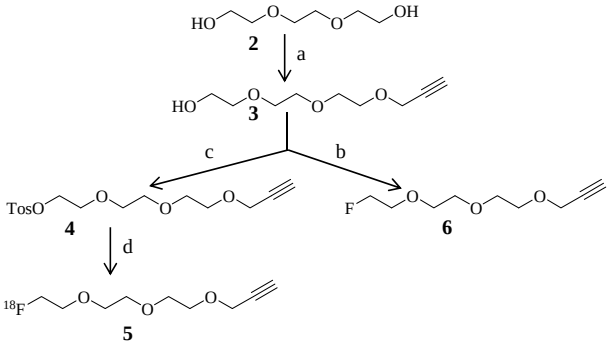
Introduction: Direct ^{18}F-fluorinations are often difficult and give only low yields due to deactivated systems or instable precursor molecules under the harsh conditions of direct labeling. Therefore, prosthetic groups were developed to circumvent a direct [^{18}F]fluorination approach. Prosthetic groups are small molecules, which are easy to label with [^{18}F]fluoride. Subsequently these molecules are reacted with the actual compound. The most common used prosthetic group is [^{18}F]fluoroethyl tosylate (**1**) e.g. to label *O*-[^{18}F]fluoroethyltyrosine (*Scheme 1*) [1]. In the last decade, the development of such synthons increased and several of them were transferred to automated modules. Moreover, the so called "click" reactions became more and more popular. So, we were looking for a prosthetic group which is able to participate in a "click" reaction on the one hand and is not as lipophilic as normal alkyl-chains. [2] For this reason, we decided to use 3-(2-(2-(2-[^{18}F]fluoroethoxy)-ethoxy)ethoxy)prop-1-yne (**5**) as the prosthetic group of choice.



Scheme 1: Labeling tyrosine with [^{18}F]FETos

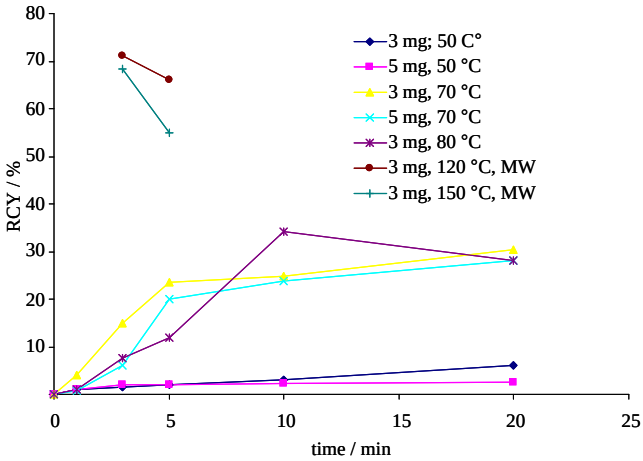
Methods and Materials: The precursor 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**4**) was synthesized in a two-step reaction. During the first step, triethylene glycol (**2**) was coupled to propagyl alcohol using sodium hydride as base in DMF to give 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethanol (**3**). To **3**, tosylchloride and DABCO were added to provide **4**. Moreover, **3** was reacted with DAST to generate the inactive reference compound (**6**).
The ^{18}F-labeling of **4** was performed under microwave support in acetonitrile with tetra-*n*-butyl ammomium hydroxide as base (*Scheme 2*). Purification of **5** was carried out with a DIONEX HPLC-system using a Phemomenex LUNA-C18 column. The labeled synthon showed a retention time of 8 min. The separated fraction was diluted with water (20:1) and fixed on a Strata-X cartridge. Elution of the cartridge was performed with ethanol.

Results and Discussion: The synthesis of the precursor and cold reference was carried out under conventional conditions. The fluorination of **3** with DAST was successful under mild conditions. **6** has to be stored under light exclusion to avoid degradation.



Scheme 2: a) Propagyl alcohol, NaH, DMF, 24 h. b) DCM, DAST, 12 h. c) Tosyl chloride, DCM, DABCO. d) [^{18}F]F$^-$, MeCN, TBA-solution, 3 min, microwave.

The synthesis of **4** proceeded with good yields. The radiochemical labeling was performed under conventional conditions and solvents, bases and amount of precursor were optimized. We obtained RCY of over 30% using 3 mg of **4** at 80 °C, TBA, and MeCN. Subsequently, a microwave supported synthesis were tested and yielded excellent RCY of 72% within 5 min (*Scheme 3)*.



Scheme 3: Temperature and reaction time screening under conventional and microwave heating. All experiments were performed with TBA as base.

Outlook: Due to the availability of this prosthetic group, we are now able to perform "click"-reactions to label biomolecules carrying the corresponding azide functionality. This will be carried out using a "clickable" azido-folate (folic acid derivative).

References

[1] A. Baumann *et al.*, *Tetrahedron Lett.*, 44, 2003, 9165-9167.
[2] N. K. Neal *et al.*, *Bioconj. Chem.*, 20, 2009, 397-401.