Radiosynthesis of [^{18}F]fluoromethyl tosylate for ^{18}F-fluoromethylation

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Objectives: [^{18}F]Fluoromethyl tosylate is particularly suitable for ^{18}F-fluoromethylation of radiopharmaceuticals, but labelling of *bis*(tosyloxy)methane with [^{18}F]F$^-$ in general gives tosyl [^{18}F]fluoride as a by-product. Addition of small amounts of water resulted in poor radiochemical yields in contrast to previous reports[1]. Therefore, optimization of the RCY and the [^{18}F]fluoromethyl tosylate-to-tosyl [^{18}F]fluoride-ratio was the aim of our work.

Methods: As common radiolabelling strategies, using [^{18}F]KF/K_{222}, seem to lead to degradation of the *bis*(tosyloxy) methane precursor[2], in this work the reaction was carried out in MeCN/tBuOH using tetrabutylammonium bicarbonate (TBABC) instead of K_2CO_3. Diverse stoichiometric compositions of solvents, varying amounts of TBABC and 2 different precursors, *bis*(tosyloxy) methane and *bis*(tosyloxy) d_2-methane, were examined. The use of 10mg of precursor, 15mg of TBABC and 800µl of MeCN/tBuOH 3/1 gave promising results. [^{18}F]Fluoromethyl phenolate was prepared using sodium phenolate in DMSO at a reaction temperature of 120°C with 20-50 MBq d_2-[^{18}F]fluoromethyl tosylate in DMSO were added. The reaction mixture was quenched with water and analyzed by TLC and analytical HPLC. *O*-[^{18}F]fluoromethyl harmol was prepared at 120 °C within 20 min from harmol and d_2-[^{18}F]fluoromethyl tosylate in DMSO.

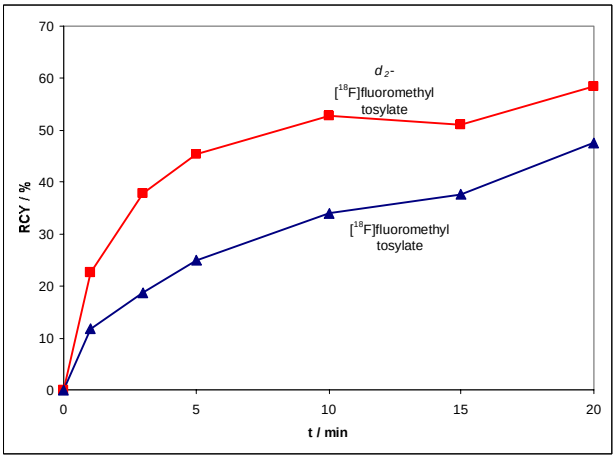

Figure 1: RCY of d_2-[^{18}F]fluoromethyl- and [^{18}F]fluoromethyl tosylate from ^{18}F-fluorination in MeCN/tBuOH 3/1 at 85 °C.

Results: Radiofluorination of *bis*(tosyloxy) methane in MeCN/tBuOH 3/1 at 85 °C resulted in a significant increase in the formation of [^{18}F]fluoromethyl tosylate compared to radiosynthesis in MeCN with small amounts of water. In addition, for the formation of d_2-[^{18}F]fluoromethyl tosylate higher yields could be observed. The two products were analyzed by TLC and analytical HPLC and purified by semi-preparative HPLC with a decay-corrected yield of 36±8% (n=8) and 42±4% (n=5) for the deuterated analogue. The reaction of d_2-[^{18}F]fluoromethyl tosylate with sodium phenolate as a model compound was examined and reaction temperatures were varied. Only poor RCYs could be observed at 100 °C and 110 °C. Increased yields were obtained at 120 °C, while higher temperatures (130°C) led to decomposition and defluorination of d_2-[^{18}F]fluoromethyl tosylate.

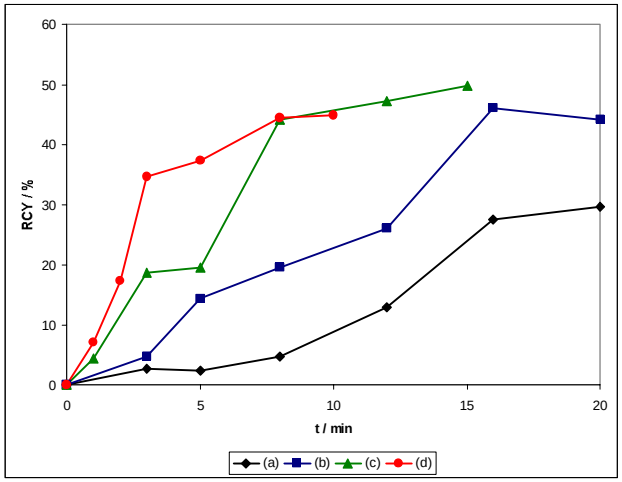

Figure 2: RCYs of [^{18}F]fluoromethyl phenolate at (a) 100°C, (b) 110°C, (c) 120°C, (d) 130°C

Conclusions: [^{18}F]Fluoromethyl tosylate and d_2-[^{18}F]fluoromethyl tosylate were labelled in reproducible yields by nucleophilic radiofluorination in MeCN/tBuOH and successfully separated from by-products. The reaction of d_2-[^{18}F]fluoromethyl tosylate with sodium phenolate lead to the formation of [^{18}F]fluoromethyl phenolate in 50% after 15 minutes, the reaction with harmol resulted in the formation of *O*-[^{18}F]fluoromethyl harmol. According to a lack of reactivity of d_2-[^{18}F]fluoromethyl tosylate compared to [^{18}F]fluoromethyl iodide, higher reaction temperatures (120°C) and reaction times (20 min) were required.

References

[1] Neal TR et al., J Label Compd Radiopharm 48, 557 (2005)
[2] Smith G et al., Nuclear Medicine and Biology 38, 39 (2011)