A Step Towards New, Cyclopropane-Based Reagents for Positron Emission Tomography

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[18F]-Cyclopropanes are of great interest as potential compounds for diagnostic of tumor, numerous brain and heart diseases, for investigation of pharmacokinetics of drugs or natural compounds by PET. However, known methods of fluorocyclopropane synthesis are not suitable for synthesis of molecules labeled with 18F isotope. Due to its short half-life, 18F can only be introduced by a fast and quantitative fluorination reaction on the last step of synthesis. We have developed a method for preparation of gem-difluorocyclopropane carboxylic acid derivatives using a fluoride anion as fluorine source. The method includes dichloro- or dibromocyclopropanation of a,b-unsaturated carbonyl compounds followed by substitution of chlorine or bromine atoms by fluorine. The one-step dihalocyclopropanation process uses a novel approach involving Michael addition of CX3Li (X = Cl, Br) followed by cyclization of the forming enolate. CX3Li reagents are generated by deprotonation of the corresponding haloform with a strong amide base at –95°C in ethereal solvents. This method gives moderate yields of dihalocyclopropanes with high stereoselectivity. For the fluoride substitution of gem-dichlorocyclopropane carboxylic acid and its derivatives (esters, amides and ketones) we have tested various conditions including protic and aprotic solvents, different fluorine sources, additional bases or phase transfer catalysts, and found that corresponding gem-difluorocyclopropanes are formed in presence of TBAF in DMF after 1–2 hours at r.t. in high to quantitative yields. The structures of obtained products have been confirmed by 1H, 19F, 13C-NMR spectroscopy and MS, as well as elemental analysis or HRMS for unpublished compounds.

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