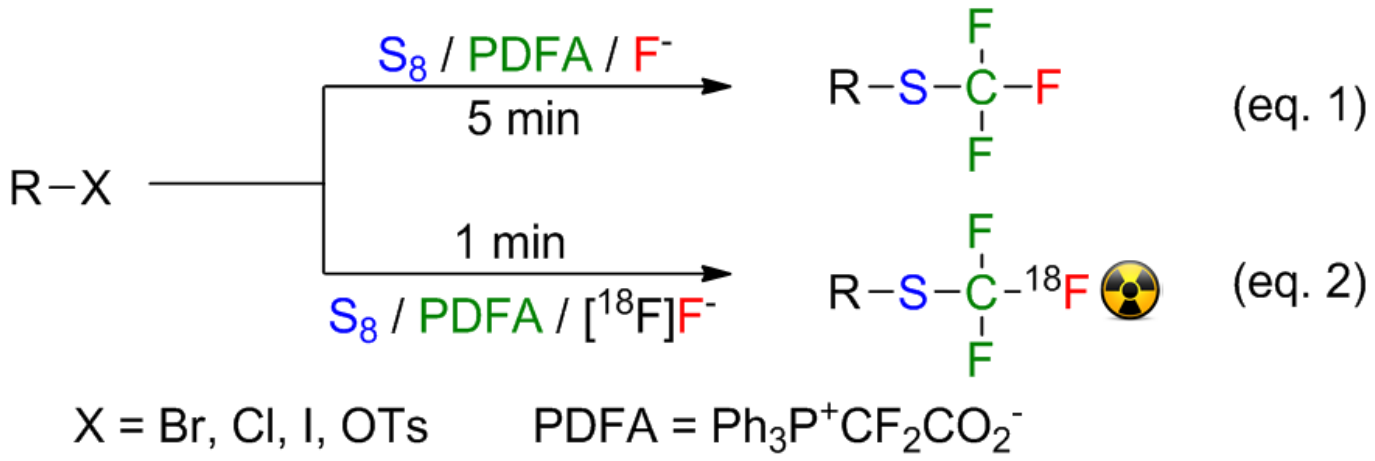
Trifluoromethylthiolation of aliphatic electrophiles

As one of the most advanced technologies currently available for studying *in vivo* molecular interactions, positron emission tomography (PET) is a functional imaging technique that can produce a three-dimensional image of functional processes in the body. It has served as a powerful medical tool and has been heavily used in clinical oncology, clinical diagnosis of certain diffuse brain diseases, and so on. Since PET imaging requires the preparation of a positron-emitting radiolabelled probe or radiotracer, the selection of a proper positron-emitting isotope is quite important. Fluorine-18 (^{18}F) has proved to be a nice choice due to its relatively long half-life of 109.7 min, high-yielding production and high specific activity, importance of fluorine substitution as isotopologue in drug discovery, and extensive clinical use of [^{18}F]FDG (2-[18F]fluoro-2-deoxy-D-glucose). Therefore, significant efforts have been devoted to the exploration of novel and efficient methodologies for ^{18}F-incorporation into small or biological molecules.



Trifluoromethylthio group (CF_3S) is a valuable pharmacophore in medicinal chemistry and drug discovery, but the formation of [^{18}F]CF_3S moiety has never been realized and thus remains a significant challenge. Given that half-life of ^{18}F is short and [^{18}F]F^- is a good ^{18}F source, it can be speculated that the best protocol for the installation of [^{18}F]CF_3S functionality is a fast reaction involving the use of [^{18}F]F^-. Although outstanding accomplishments have been recently made for the incorporation of CF_3S group via non-radioactive trifluoromethylthiolation methods, the CF_3S scaffold are derived from CF_3S- or CF_3-containing reagents without the involvement of external fluoride, which makes it not applicable or difficult for translation into ^{18}F-radiolabeling.

We have developed an efficient method for trifluoromethylthiolation of aliphatic electrophiles based on the reaction between difluorocarbene, elemental sulfur and fluoride ion (eq. 1). This strategy has been successfully applied to the first ^{18}F-labelled [^{18}F]trifluoromethylthiolation reaction (eq. 2). The present discovery is also significant given the short reaction time (?1 min) and operational simplicity for [^{18}F]trifluoromethylthiolation, which is ideal for short-lived radionuclide ^{18}F and automated radiosynthesis. This approach also requires no participation of transition metals and

thus eliminates the risk of introducing toxic metals into final formulation for injection. All of these advantages make this method suitable for the preparation of [^{18}F]CF_3S-labeled pharmaceuticals and subsequent PET imaging studies.

Publication

Difluorocarbene-Derived Trifluoromethylthiolation and [18 F]Trifluoromethylthiolation of Aliphatic Electrophiles.
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