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Reactivity of Iodine Monofluoride on Sub-Micromolar Scale with Arenes

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Abstract: *In situ* generated iodine monofluoride (IF) has for the first time been used on sub-micromolar scale for iodination of model arenes. Reactivity and selectivity of the reagent have been determined by the radiotracer method using $[^{123,131}I]IF$.

Iodine monofluoride (IF) has been known on molar scale since the early 1960s[1]; however, its use as iodination reagent for aromatic compounds on this scale has only been reported in recent years[2]. We have used *in situ* generated $[^{123,131}I]IF$ on sub-micromolar scale for radioiodination experiments with benzene, anisole, phenol, and toluene as indicated by the equations.

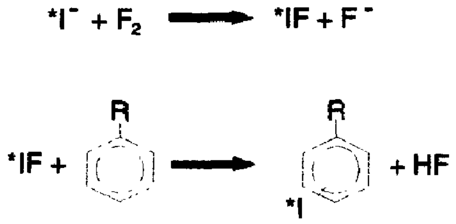

Fig. 1 R = -H, $-CH_3$, $-OCH_3$, -OH.

A 10% mixture of elemental fluorine and neon was handled in a monel apparatus. CAUTION: elemental fluorine is highly corrosive[3]. The reagent *IF was generated by passing fluorine through a solution of no-carrier-added radioiodide. Afterwards a solution of the arene in the same solvent was added, with a final arene concentration of $8 \cdot 10^{-7}$M. Various solvents like water, trifluoroacetic anhydride and trifluoroacetic acid (TFA) have been tested, with TFA being most successful. After 10 minutes at a selected temperature between -70°C and +60°C the reaction was stopped by evaporation of the solvent and addition of 1 ml of HPLC solvent containing 1 mg/ml sodium sulfite. Product analysis was carried out against "macroscopic" reference substances using HPLC with radioactivity- and UV-detection.

As expected, the reactivity of iodine monofluoride proved to be very high, thus leading to high chemical yields of monoiodo compounds in the case of medium-activated anisole and to high yields of by-products in the case of more activated compounds. Even less activated compounds can be iodinated successfully where other iodine monohalides (ICl, IBr) fail, while no yield was observed with benzene.

Table 1. Radiochemical yields of iodination of arenes with IF.

Arene	Radiochemical yield monoiodoarenes [%]	Radiochemical yield by-products [%]
Toluene	11±2	0
Anisole	66±4	30±3
Phenole	27±3	41±5

Conditions: 15 μmol F_2, room temperature, 10 min reaction time, arene concentration $8{\cdot}10^{-7}$M

The relative reactivity with a para-to-ortho ratio (per position) of about 45 for anisole and 3.5 for phenol (at 20°C in TFA) exhibits a high selectivity for the para-position which is in contrast to direct electrophilic iodination in aqueous solutions. Iodine monofluoride on sub-micromolar scale proved to be stable even at 60°C (radiochemical yield of monoiodoanisoles: 68±5% at +60°C) although a decomposition temperature of -14°C has been reported[4] (yield of monoiodoanisoles 45±3% at -15°C). This might be attributed to a stabilizing effect of TFA. Different to other radioactive iodine monohalides, generally obtained by equilibration of radioiodide and iodine monohalide, the generation of *IF without addition of stable iodide allows preparation of products of high specific activity. This is especially important in synthesis of radiotracers for studies in life sciences. The consecutive generation of *IF in TFA and subsequent addition and reaction of the arene might also prove successful for preparative monoiodination on an equimolar scale of radioiodide and oxidation agent F_2 in contrast to previously used in situ oxidation in presence of the arene, thus avoiding fluorination side reactions.

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