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# Microwave-accelerated fluorodenitrations and nitrodehalogenations: expeditious routes to labeled PET ligands and fluoropharmaceuticals

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ABSTRACT

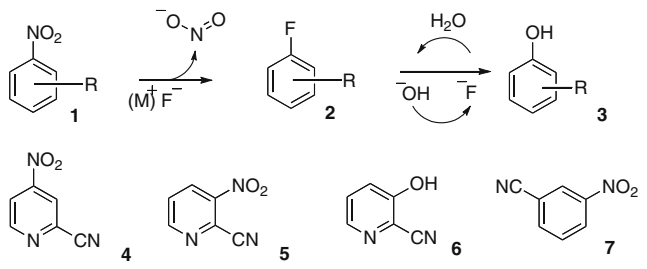
Methods for the expeditious fluorination of arenes have been investigated, using readily available fluoride sources. An optimized procedure for microwave-accelerated fluorodenitration has been developed, giving good to excellent yields in less than 10 min, rendering it practical for use in the preparation of $F^{18}$ labeled ligands for PET imaging. Application of the method in the synthesis of CNS agents is demonstrated, and a practical method for the preparation of substrates is also presented.



## 1. Introduction

Methods for the introduction of fluorine into arenes and heteroarenes are significant components of contemporary medicinal chemistry due to its often striking physicochemical and metabolic impact on drug candidates.[1] A large number of blockbuster agents possess the fluoroarene motif ranging from antimicrobials (e.g., Ciprofloxacin), antifungals (e.g., Diflucan), CNS agents (e.g., Haloperidol, Risperidone) to antimetabolites (e.g., Fludarabine), and statins (e.g., Lipitor).[2] Interest in the development of fluorination methodologies has been bolstered with the advent of positron emission tomography (PET) imaging, and the attractiveness of $F^{18}$ labeled ligands (e.g., Fluorodeoxyglucose—'FDG').[3]

Given the $F^{18}$ $t_{1/2}$ (119 min) efficient synthetic methodologies are required, which has served to limit the scope of ligand development.[4] We became interested in developing expeditious methodology for fluorodenitration of arenes using microwave-accelerated processes, a field which has grown considerably in recent years,[5] and which we have enjoyed success with a variety of transformations.[6] To be generally useful for the preparation of $F^{18}$ labeled ligands, methodology needs to be robust, efficient in terms of chemical and radiochemical yield, and allow effortless purification of end product. Cyclotron chemistry makes $^{18}F^-$ available routinely, so we opted to investigate microwave-mediated fluorodenitration of substrates using commonly available fluoride sources under a variety of conditions. Fluorodenitration of **1** and heterocyclic variants has been reported using a range of different conditions, principal limitations being the need for highly activated substrates and degradation of desired products **2** into the phenols **3** (Scheme 1).[7] Kuduk reported facile fluorodenitration of cyanopyridine **4** using a reagent grade TBAF but in the case of **5**, using dry TBAF observed conversion to phenol **6**.[8] In a series of reports, DiMagno describes remedy in the use of specially prepared anhydrous (as opposed to spray dried) TBAF, which promotes facile fluorodenitration of a range of substrates including unactivated arenes such as **7**.[9] Prior to this work, a traditionally exploited route




**Scheme 1.** Fluorodenitration pathways using nucleophilic fluoride sources.

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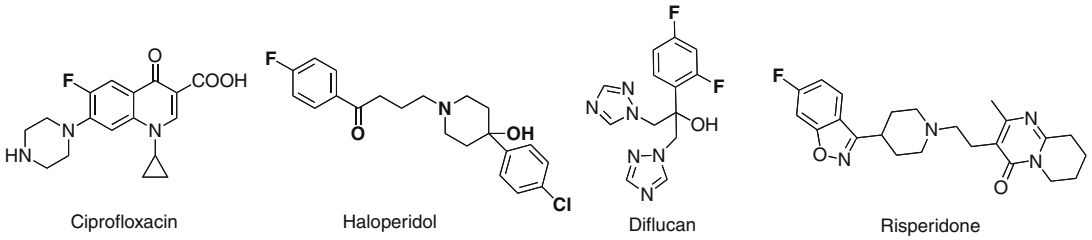
involved the use of dried KF in combination with $K_2CO_3$ and the phase transfer agent 4,7,13,16,21,24-hexa-oxa-1,10-diazabicyclo[8.8.8]-hexacosane (Kryptofix 222).[7] In an attempt to achieve a degree of consistency, and with a view to developing microwave-based protocols for the production of radiolabeled variants (which might be subsequently amenable to automated production methods) we studied a number of substrates using three representative conditions (Chart 1).[10]

experiments using cyclotron generated $^{18}F^-/K_{222}$ a radiochemical yield of >75% was attained with substrate **11** on a preparative scale. In cases where low yields of fluorinated product **2** were obtained using method B, the balance of material (up to 95%) was the derived phenols **3**, advocating the need for specially prepared anhydrous TBAF (method C).

With economic and expeditious routes to fluoroarenes secured, we wished to highlight application of the method with a synthesis




A series of activated heteroarene and bicyclic arene substrates were assessed to evaluate and compare reaction times, in most cases resulting in smooth conversion to the fluorinated product in less than 10 min (cf. up to ~4 h using conventional heating) as shown in Chart 1. Though the ready availability of KF in $^{18}F$ labeled form is to be noted (relevant to method A), the most reproducible results were with anhydrous TBAF (method C) and the availability of conventionally prepared $^{18}F$ TBAF bodes well for cases where methods B and C are comparable.[11] Reactions are routinely conducted on 100 mg scale, however the scalability of the process was confirmed with preparative scale versions using substrates 10–15 giving equivalent yields.[12] Additionally, in preliminary

of an $F^{19}$-substituted CNS agent, and selected Haloperidol® (Scheme 2). The original Janssen route to this commonly prescribed anti-psychotic involves late-stage coupling of a substituted piperidine onto an ω-chlorinated flouroarene.[13] For the demonstration of proof of concept, the corresponding nitroacylarene **35** was prepared by Pd-mediated alkyl coupling followed by deprotection of the TBS-protected iodoalkane, which was then subjected to amination with **37** via mesylate **36** (Scheme 2).[14] Finally, the key microwave-mediated fluorodenitration of **38** was investigated. Using the KF/$K_{222}$ in DMF, ether linked side products were formed contributing to the moderate yields of product attained (~25%).

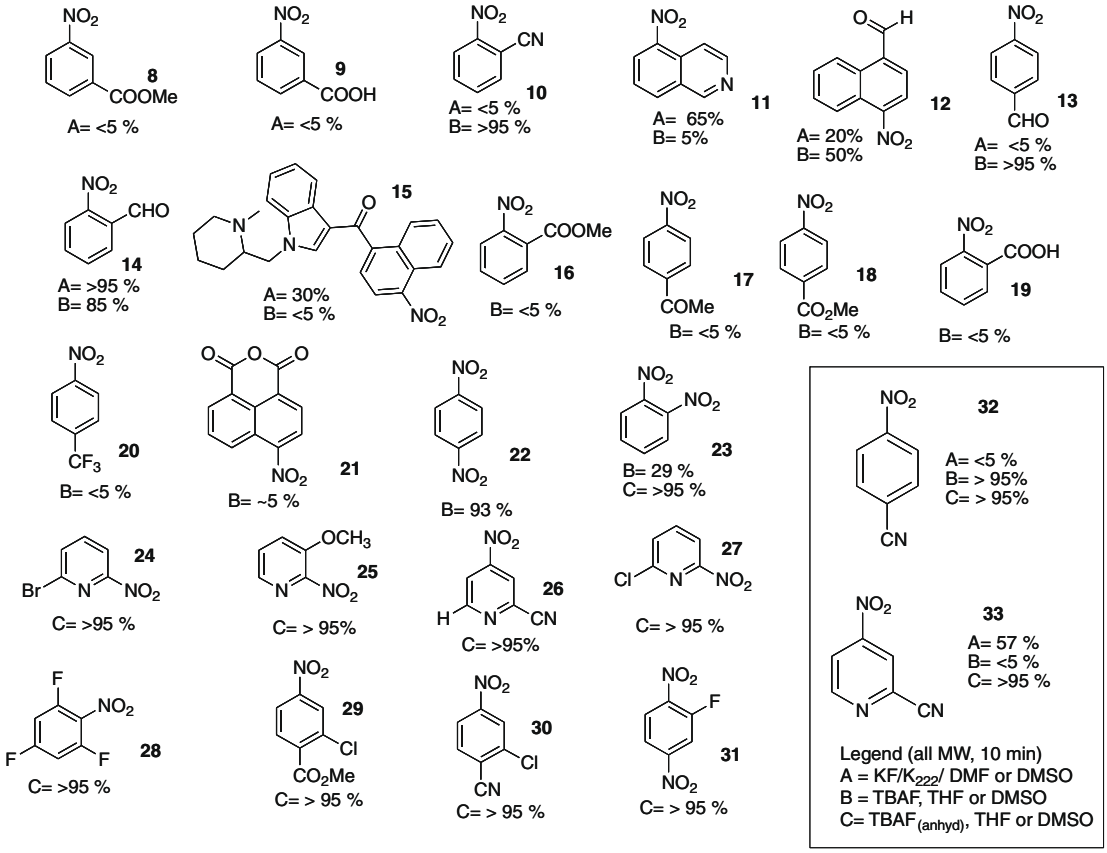
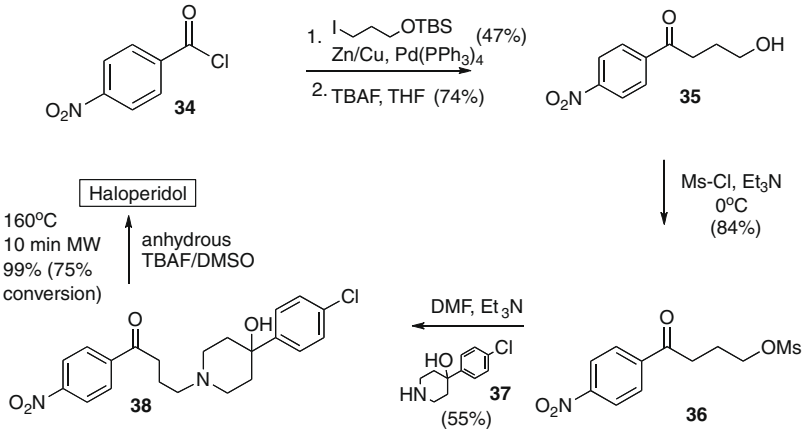
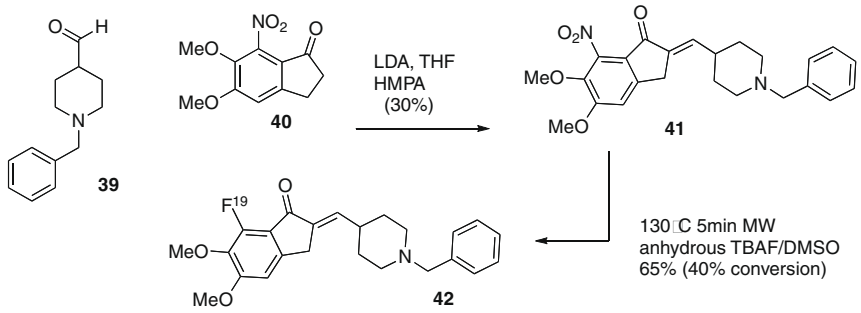



**Chart 1.** Comparative fluorodenitrations.



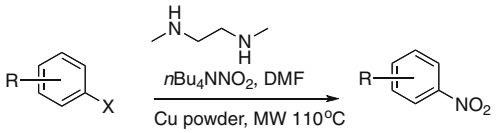

**Scheme 2.** Synthesis of haloperidol through microwave halodenitration.




**Scheme 3.** Microwave-accelerated denitration route to fluorinated donepezil analogues.

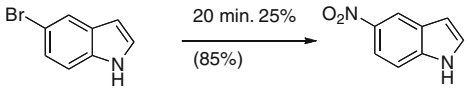
With the conventional TBAF in THF yields of up to 30% could be obtained on prolonged heating (2 min heat/2 min pause cycles over a 30-min period). However, using anhydrous TBAF very clean conversion to the desired product was effected within minutes, with 30% conversion within 3 min and 75% within 10 min (2 min heat/2 min pause cycles). Given the importance of this agent, it is thus expected that a route to the corresponding $F^{18}$ labeled PET ligand can be developed using the methodology outlined herein. Though instructive, we also wished to demonstrate fluorodenitration in a non-activated substrate and developed a synthesis of a fluorinated analogue of the acetyl cholinesterase inhibitor donepezil (Scheme 3).[15] Coupling of the enolate derived from **40** with **39** afforded advanced intermediate **41**, which underwent fluorodenitration using anhydrous TBAF to give analogue **42** in good yield within 5 min (followed by 5-min pause cycle).

With the microwave-mediated fluorodenitration process established, we have also begun to investigate methods for the introduction of the key leaving group. Based on observed leaving group patterns of I > F > $NO_2$, we were motivated to investigate microwave-accelerated nitro de-iodination, and have subsequently identified conditions which are far superior to the conventional thermolyses in terms of both time and conversion efficiency (Scheme 4).[16] Using a range of substrates, the process is effective in <20 min (all uninterrupted heating cycles) to give a variety of useful building blocks (Table 1), which makes the prospect of transformations of I > F feasible in labeling studies. This is especially relevant in cases where one needs to study under SPECT and PET imaging methods, where the $^{123}I/125I$ and $^{18}F$ counterparts are obvious choices. The conditions are also applicable for the preparation of 5-nitroindoles, key building blocks for CNS agents, from the corresponding *bromo* substrate. The yield based on recovered substrate (85% at 20 min) suggests considerable optimization may be possible, making the sequence Ar-Br→Ar-F a practical, two-step possibility.




**Scheme 4.** Microwave-accelerated nitrodeiodinations.

**Table 1**
Microwave-accelerated Cu-catalyzed nitrodehalogenations




| X | R | Time (min) | Yield (%) | Conventional (21–27 h) (%) |
|---|---|---|---|---|
| I | 4-MeO | 17 | 88 | 81 |
| I | 4-Me | 20 | 50 | 25 |
| I | 3-MeO | 20 | 84 | 65 |
| I | H | 16 | 85 | 65 |
| I | 3-Me | 20 | 84 | 69 |
| I | H | 1 | 58 | 65 |
| I | 3-Me | 1 | 49 | 69 |
| I | 4-$CF_3$ | 15 | 10 | ~5 |
| I | 2-Pyridine | 10 | 15 | ~5 |

## 2. Representative procedures

### 2.1. 4-Nitroanisole

4-Iodoanisole (0.0581 g, 0.25 mmol), copper powder (0.0095 g, 0.15 mmol), and tetrabutylammonium nitrite (0.1442 g, 0.50 mmol) were added to a flame-dried 14 × 86 mm (OD) glass microwave tube

and charged with argon. Freshly distilled DMF (0.5 mL) was added followed by *N*,*N*′-dimethyl ethylenediamine (0.0265 g, 0.30 mmol). The vial was capped with a CEM Corp. PL cap (SP1318A) and stirred in the cavity of a CEM Discover® Lab Mate reactor at 110 °C for 17 min (200 W, 300 psi). The residue was purified by silica gel column chromatography (9:1 hexanes/ethyl acetate) and concentrated in vacuo to yield the title compound (0.0330 g, 88%) as a yellow oil.

### 2.2. 4-Fluoro-2-pyridinecarbonitrile

4-Nitro-2-pyridinecarbonitrile (0.0298 g, 0.2 mmol) was added to a flame-dried 14 × 86 mm (OD) glass microwave tube and charged with argon. Anhydrous TBAF (0.5 mL of a 1 M solution in DMSO, 0.5 mmol) was then added at 25 °C. The vial was capped with a CEM Corp. PL cap (SP1318A) and stirred in the cavity of a CEM Discover® Lab Mate reactor set at 25 °C for 2 min (300 W, 250 psi). The reaction mixture was diluted with water (5 mL), extracted with diethyl ether (2 × 5 mL), washed with brine (1 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by filtration through a plug of silica gel to yield the title compound (0.024 g, 99%) as a white solid mp 72–74 °C;[9] TLC (hexanes/ethyl acetate = 4:1); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28–7.33 (m, 1H), 7.47 (dd, $J$ = 2.5, 8 Hz, 1H), 8.72 (dd, $J$ = 5.5, 8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 115.4, 117.2, 136.2, 153.9, 167.4, 169.6.

## Acknowledgments

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