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Microwave accelerated three-component fluoroalkylations: expeditious routes to fluoropharmaceuticals and PET ligands

Michael Placzek, Paul LaBeaume, Luke Harris, Patrick Ng, Mathew Daniels, Amy Kallmerten [†], Graham B. Jones [*]

Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115, United States

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ABSTRACT

One-pot three-component coupling methods have been developed to allow in situ preparation of fluoroalkylated arenes and hydrocarbon chain analogs. The methods, which are accelerated under microwave irradiation gives access to ω-fluorinated alkyl, alkenyl, and alkynyl substituted arenes from readily available precursors. The methods involve late stage introduction of the fluorine and are well suited to application in the synthesis of ^{18}F labeled PET imaging agents.

1. Introduction

Fluorination methods are important aspects of contemporary medicinal chemistry due to the often striking physicochemical and metabolic properties of fluorinated drug candidates.[1] In addition to the growing number of fluorinated blockbuster drugs,[2] development of fluorination methodologies has been bolstered by the use of ^{18}F labeled ligands in positron emission tomography (PET) imaging (e.g., Fluorodeoxyglucose—'FDG').[3] Given the ^{18}F $t_{1/2}$ (119 min) to be generally useful, fluorination methods need to be robust, efficient in terms of chemical and radiochemical yield, and allow effortless purification of the end product.[4] We recently demonstrated a microwave accelerated fluorodenitration process, and applied the methodology to the synthesis of a number of fluorinated CNS agents.[5] Though a number of aryl fluorination methods are available, they are far more restricted for fluoroalkanes, typically limited to late stage nucleophilic displacement of tosyloxy groups.[4] Expanding the repertoire of available methods would be of benefit, as a growing number of pre-clinical and investigation agents for PET imaging possess (^{18}F) fluoroalkyl chains. These include the mitochondrial complex 1 (MC-1), inhibitors RP1005, and BMS747158-02, which were developed for myocardial perfusion imaging,[6] the α4β2 nicotinic receptor targeted nifrolidine and the dopamine receptor targeting agent fallypride,[7] both of which are used in Alzheimers disease (AD) PET imaging studies.[8] A key to developing CNS targeted imaging agents is optimizing lipophilicity of the drug to maximize blood brain barrier penetration (and, conversely for cardiovascular agents) and this typically requires re-synthesis, as the addition of even a single methylene spacer can have a profound impact on transport properties.[6] With this backdrop we have been investigating means to develop efficient coupling methods, which (1) allow effective coupling of functionalized hydrocarbon chains onto readily available arenes (2) where chain length and hybridization can be modified at ease and (3) where the ^{18}F can be introduced in situ at the final stage of the process.

We were initially drawn to reports from the Fu laboratories wherein conditions for Pd/phosphine mediated Hiyama cross-couplings of trialkoxysilanes are effective with alkyl halides but alkyl tosylates are poor electrophiles.[9] Given that fluoride can be used to catalyze the Hiyama reactions, we envisioned that α–ω bromo tosylates would be excellent substrates for a three component coupling, involving in situ fluoride exchange on the coupled aryl-alkyl tosylate as a final step. Additionally routes to ^{18}F TBAF and its functional equivalents are available,[10] as is a route to the powerfully nucleophilic anhydrous TBAF.[11] Initial results using test substrates

* Corresponding author. Fax: +1 617 373 8795.
E-mail address: gr.jones@neu.edu (G.B. Jones).
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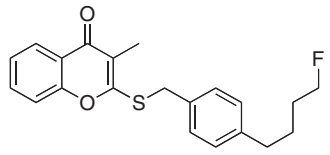
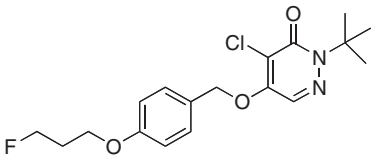
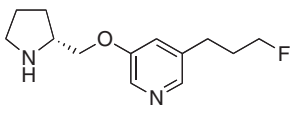


RP 1005



BMS 747158-02



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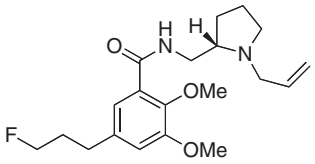
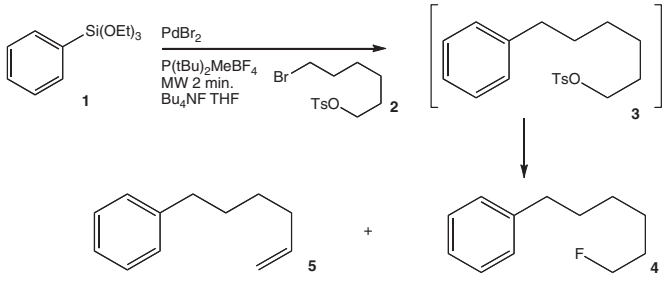


Fallypride

triethoxysilane (**1**) with tosyloxy 6-bromohexanol (**2**) were promising (Scheme 1) providing proof of principle for the strategy which, under pressing conditions were giving appreciable yields of product **4** (Table 1).[12] Traces of byproduct (<5%) stemming from elimination to form **5** were observed at extended reaction times (>5 min), and the coupled tosylate **3** at lower reaction times (<2 min.), but the major product in all cases was the desired fluoroalkane **4**. Control reactions using conventional thermal heating underscored the microwave effect—for example, entry 1, whose counterpart thermal reactions take >12 h to achieve comparable yield at room temperature.[9]

Optimal temperature was 80 °C (entry 3) and increasing catalyst loading led to yet higher conversions (cf. entries 6–7). As expected, reactions were equally effective using 6-fluoro-1-bromohexane as the substrate. Though encouraging, practical considerations stemming from the need to introduce the trialkoxysilane group in late stage syntheses and the air sensitivity of the catalytic cycle led us to pursue variants (vide infra).

We next turned attention to vinyl linked fluoroalkyls and investigated conditions for Heck type coupling (Scheme 2).[13] Iodoben-



Scheme 1. Tandem Hiyama coupling route to aryl fluoroalkanes.

Table 1
Tandem Hiyama cross-coupling fluoroalkylations[a]

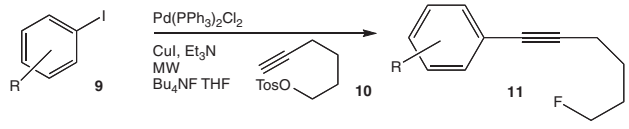
Entry	% Pd cat	Time (min)	Temp (°C)	%Yield **4**
1	10	2	60	51
2	10	2	70	55
3	**10**	**2**	**80**	**61**
4	10	2	90	45
5	10	2	110	14
6	20	2	80	76
7	**30**	**2**	**80**	**87**
8	30	5	80	85

[a] Reactions used 2 equiv TBAF in THF with 2.5 equiv phosphine.

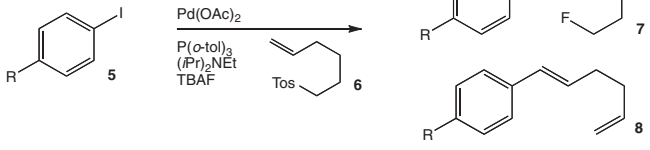
Table 2
Heck cross-coupling fluorinations[a]

Entry	**5** (R)	Temp (°C)	Time (min)	Yield 7%	Yield 8%
1	H	100	15	35	9
2	2-MeO	90	5	52	4
3	3-MeO	90	5	48	5
4	**4-MeO**	**90**	**5**	**56**	**5**
5	2-MeCO	100	40	24	12
6	3-MeCO	100	40	0	10
7	4-MeCO	100	40	22	9
8	2-NH_2	100	15	47	13
9	3-NH_2	100	15	45	11
10	4-NH_2	100	15	43	9

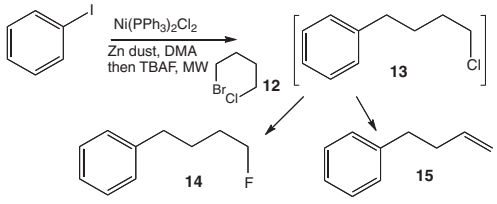
[a] Reactions used 2 equiv TBAF and **6** in 1,4-dioxane, 0.05 equiv Pd cat and 0.1 equiv phosphine. *E*/*Z* ratios of **7**–8:1.



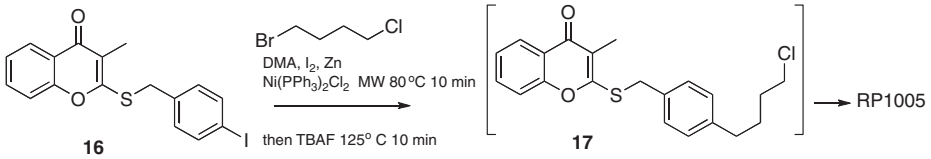
Scheme 3. Tandem Sonogashira coupling route to aryl fluoroalkynes.



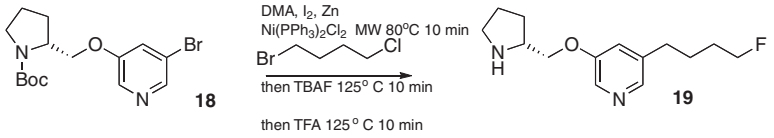
Scheme 2. Tandem Heck coupling route to aryl fluoroalkenes.



Scheme 4. Tandem Negishi coupling-fluorination.



Scheme 5. Negishi coupling route to RP 1005.



Scheme 6. Negishi coupling route to nifrolidine homolog.

Table 3
Sonogashira cross-coupling fluorinations[a]

Entry	**9**	Temp	Time	Yield **11**
1	H	50	10	86
2	**2-CH_3CO**	**70**	**10**	**93**
3	3-CH_3CO	70	10	88
4	4-CH_3CO	70	10	91
5	4-CH_3CO	90	10	62
6	4-CH_3CO	70	15	86
7	2-MeO	70	10	79
8	3-MeO	70	10	82
9	4-MeO	70	10	73
10	**2-iodopyridine**	**70**	**10**	**90**
11	3-iodopyridine	70	10	91
12	4-iodopyridine	70	10	89

[a] Reactions used 2 equiv TBAF, 1.1 equiv **10** (9:1 THF/Et_3N) with 0.05 equiv Pd and Cu cat.

Table 4
Tandem Negishi cross-coupling fluorinations[a]

Entry	Temp (°C)	Time (min)	TBAF (equiv)	%Yield **14**	%Yield **15**
1	70	15	2	63	10
2	80	5	2	54	8
3	**80**	**10**	**2**	**62**	**11**
4	80	15	2	65	11
5	80	20	2	55	18
6	90	5	2	52	15
7	90	10	2	53	14
8	90	15	2	59	17
9	100	15	2	56	15
10	100	10	3.5	22	25

[a] Reactions used 2 equiv **12**, 0.1 equiv I_2, 3 equiv Zn in DMA, with 0.05 equiv Ni cat.

zene was effective under forcing conditions but moving to an activated substrate led to appreciable conversion to the fluorinated product **7** (Table 2, entries 2–4). Elevated temperatures and reaction times led to increased formation on elimination product **8**, but in most cases the balance of material was recovered. Arene **5**, which for subsequent radiolabeling purposes (using ^{18}F TBAF) can be easily separated from the desired product chromatographically. Electron deficient substrates were inferior substrates and anilines moderately effective at higher temperatures and extended reaction times (entries 5–10) warranting additional investigation.

Finally a series of Sonogashira couplings were developed (Scheme 3).[14] Various iodoarenes **9** were coupled with tosyloxy substrate **10**, giving appreciable conversion to products **11** (Table 3). The scope, using this initial screening, suggests that this could develop into a widely applicable strategy for a range of arene and heteroarene substrates, and is worthy of fuller optimization, though it is evident that subtle variations in reactions temperature or reaction time have a marked impact on product yield (entries 4–6). Given the initial success of the tandem coupling procedures, we became interested in application of the technology to synthesis of fluorinated medicinal agents. Using RP1005 and nifrolidine as benchmarks, in order to form fluoroalkyl derivatives it is evident that re-tooling of the original syntheses is required in order to install the requisite siloxane for the Hiyama coupling. Given the availability of halogenated intermediates in the synthesis of these agents, an alternate coupling in the form of the Negishi process was investigated (Scheme 4).[15] In this, a bromo-chloroalkane would be coupled and subjected to in situ halogen exchange via microwave irradiation.

Using iodobenzene as the test substrate under standard conditions, within 10–15 min 4-chloro-1-bromobutane coupled to form intermediate **13**, which was subjected to in situ fluorination to give **14** with appreciable conversion, together with varying quantities of elimination product **15** (Table 4). Elevated temperatures resulted in increase in elimination, optimal conditions being 80 °C with 2 equiv of TBAF. Direct halex displacement from isolated intermediate **13** was effective and the tandem one pot sequence proved comparable to the Hiyama process, and could be conducted without the need for glove box handling.[16]

With the conditions developed, we were able to apply immediately to the synthesis of RP 1005. Iodoarene intermediate **16** underwent Negishi coupling to give **17** and was followed by in situ halex fluorination to give the desired product in moderate yield (~20% over two steps) in a one pot process (Scheme 5).[6] Though substantially higher yields are attainable through optimization with these substrates (cf. Table 4) we were motivated to identify conditions that minimize the formation of alkene (elimination) byproducts, to make the process more amenable to an ^{18}F labeled variant for PET imaging, sequential introduction of TBAF for example minimizing elimination products. In a similar vein, an advanced intermediate in the synthesis of nifrolidine, the readily available pyridyl *bromide* **18**, was coupled successfully to give, following fluorination and in situ deprotection, the four carbon chain nifrolidine analog **19** in good yield (35% over three steps based on **18**) as shown in Scheme 6.[7]

In summary, methods have been developed for in situ fluoroalkylation, fluorovinylation, and fluoroalkynylation of arenes. The methods, which exploit microwave heating,[17] give good yields with short reaction times, and provides a potentially attractive route for the preparation of ^{18}F labeled radiopharmaceuticals.[4] To this end, one of the methods has been applied to two classes of PET image contrast agents of current interest.

Acknowledgment

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