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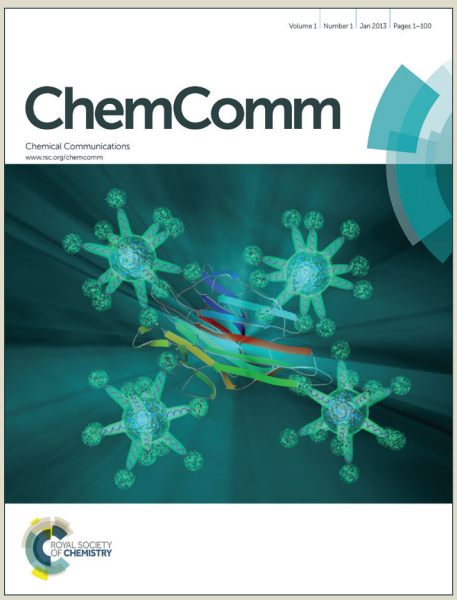

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Green Approaches to Late-stage Fluorination: Radiosyntheses of ^{18}F-Labelled Radiopharmaceuticals in Ethanol and Water

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Green strategies for late-stage fluorination with ^{18}F, in which ethanol and water are the only solvents used throughout the entire radiolabeling process (azeotropic drying, nucleophilic fluorination, purification and formulation), have been developed and applied to the radiosyntheses of a range of radiopharmaceuticals commonly employed in clinical PET imaging.

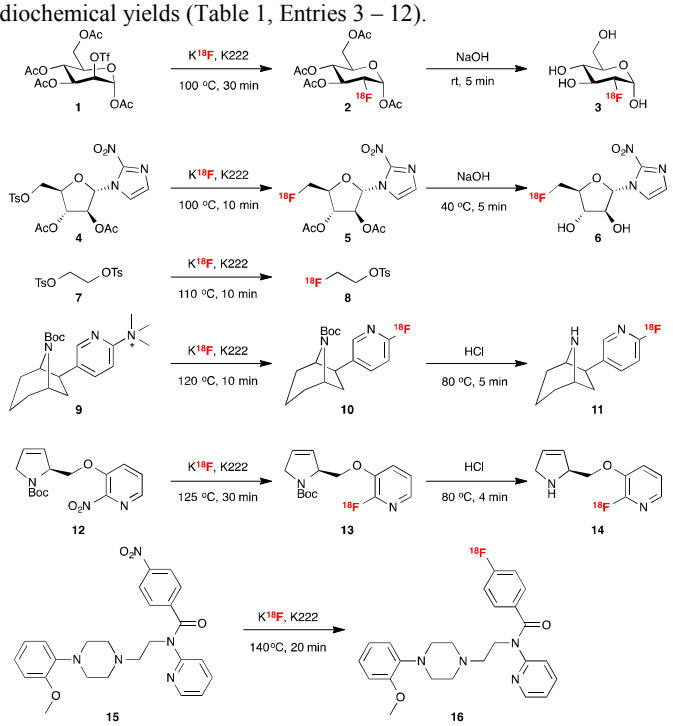
Positron emission tomography (PET) imaging is a powerful non-invasive molecular imaging technique that has had enormous impact on patient diagnosis and management around the world, as well as supporting pharmaceutical companies drug discovery programs.[1] PET utilizes radiotracers (bioactive molecules tagged with short-lived positron-emitting radionuclides such as ^{18}F ($t_{1/2}$ = 110 min) or ^{11}C ($t_{1/2}$ = 20 min)) to quantify biochemical processes in patients.[2] The limited shelf-life of such radiotracers (typically only a few hours) necessitates dose-on-demand production at manufacturing sites in close proximity to the PET scanners. Thus the synthesis of PET radiotracers does not fit the typical drug manufacturing paradigm and, to address this, regulations specifically governing PET radiotracer current Good Manufacturing Practice have been developed in recent years (e.g. 21CFR212 in the United States).[3] In our move to compliance with these new regulations, we have been working to implement pharmaceutical quality by design (QbD)[4] in our PET Center. Under QbD, we have focussed upon designing robust radiotracer manufacturing processes that will consistently deliver doses of the desired quality. One element of our QbD approach has been to eliminate the risk of doses failing quality control (QC) testing because of contamination with residual solvents used during radiotracer manufacturing (e.g. MeCN, DMF), by removing such solvents from the manufacturing process and replacing them with safer alternatives (water, EtOH, DMSO). Concomitant with these efforts, we have also been an early adopter of campus-wide sustainability efforts on-going at our institution. As part of this sustainability initiative, we began exploring how we might apply the principles of green chemistry[5] to PET radiochemistry. Given the overlap between the ideas underlying QbD and green chemistry, we expected elimination of hazardous solvents from our reactions to impact both of these priority areas. We first investigated this in the context of our carbon-11 manufacturing program, and recently reported new methods for conducting carbon-11 radiochemistry using only ethanol and water.[6] However, it is estimated that 1.5 million clinical PET scans occur annually and by far most of these are conducted with [^{18}F]fludeoxyglucose ([^{18}F]FDG).[7] Therefore, the goal of the present work is to apply QbD and develop green approaches for working with fluorine-18. While each given synthesis might only use a few millilitres – litres of such solvents, as one of the most widely used PET radionuclides, hundreds of thousands of fluorine-18 radiosyntheses are run around the world every year, and so greener approaches to such chemistry can be expected to have noticeable impact on global sustainability efforts.

[^{18}F]Fluoride is cyclotron produced *via* the ^{18}O(p,n)^{18}F nuclear reaction by bombarding [^{18}O]water with a high energy proton beam, and then delivered to the radiochemistry laboratory in a solution of [^{18}O]water to conduct radiochemical reactions. For thirty or so years, the method of choice for conducting reactions with [^{18}F]fluoride has involved three key components: i) trapping of the [^{18}F]fluoride on an ion exchange cartridge to recover [^{18}O]water; ii) elution of the [^{18}F]fluoride into a reactor with aq. base (K_2CO_3, Cs_2CO_3, Bu_4NHCO_3 etc.) followed by addition of a phase transfer catalyst (e.g. kryptofix-222; K222) in MeCN, and azeotropic drying of the resulting [^{18}F]fluoride complex; and iii) [^{18}F]nucleophilic fluorination of an appropriate precursor in an aprotic solvent (MeCN, DMSO, DMF etc.).[2] While this approach is effective for synthesizing many fluorine-18 labelled radiotracers, the process is cumbersome; azeotropic drying is time consuming (especially for a short-lived radionuclide like ^{18}F) and the use of MeCN during drying and other hazardous solvents during fluorination mandates residual

solvent analysis (RSA) during radiotracer quality control testing. Despite the fact that fluorine-18 radiochemistry has seen spectacular growth in recent years, with new transformations often now grouped under the banner of "late-stage fluorination",[2de,8] there have been few attempts to change this general reaction format. This limitation grew out of the idea that [^{18}F]fluoride is strongly hydrated and inactivated for nucleophilic reactions when in polar protic solvents. Therefore almost all [^{18}F]fluoride is dried and nucleophilic fluorination reactions are carried out under basic conditions in polar aprotic solvents, with the phase transfer catalyst included to improve solubility. However, green approaches to fluorine chemistry have been explored,[9] and there are notable exceptions that challenge the need for rigorously dried fluoride for fluorination reactions in the literature.[10-12] Chi and co-workers were able to conduct S_N2 [^{18}F]fluorination reactions with [^{18}F]TBAF in the presence of protic solvents (e.g. tBuOH-MeCN mixtures),[10] while Sergeev and colleagues have shown that titanium nanoparticles can promote radiofluorination of tosylate precursors in aq. media (MeCN – *tert*-hexanol (thexOH) – H_2O).[11] More surprisingly, in a 2013 report Lu *et al*. showed that more challenging S_NAr fluorination reactions can also proceed in aq. media, demonstrating [^{18}F]fluorination of diaryliodonium tosylates in DMF-water mixtures without the need for a phase transfer catalyst.[12]

When taken with other reports of nucleophilic fluorination reactions in aq. media from the mainstream ^{19}F-fluorine chemistry literature,[13] these remarkable results suggest the generally accepted incompatibility of fluoride with polar protic solvents does not hold up. However, all of the reports described above have limitations for clinical radiopharmaceutical production previously described, including the need to purify out and confirm removal of residual solvents (MeCN, DMF, thexOH), tetrabutylammonium cations and/or catalysts (TiO_2). While these components can be used in clinical radiopharmaceutical syntheses if needed, it is better to avoid them whenever possible. We therefore initiated a program to carefully explore the fundamental reactivity of [^{18}F]fluoride in polar protic solvents compatible with both our QbD program and our research efforts developing green radiochemistry[6] and new approaches to late-stage fluorination with ^{18}F.[14] In marked contrast to the previous reports of [^{18}F]fluorination reactions in polar protic solvents described above, our efforts have focussed upon conducting [^{18}F]fluorination reactions in ethanol or ethanol/water mixtures, without the need for hazardous solvents or metal catalysts.

Development of green fluorine-18 radiochemistry required i) replacement of MeCN in the azeotropic drying of the [^{18}F]fluoride step and ii) use of green solvents for nucleophilic fluorination reactions. We have explored both of these aspects for a range of fluorine-18 labelled radiopharmaceuticals commonly prepared at our PET Center (Scheme 1). ^{18}F is traditionally eluted from a quaternary methylammonium (QMA) sep-pak using aq. K_2CO_3 (3.5 mg in 0.5 mL water) to generate K^{18}F. A solution of K222 (15 mg in 1 mL MeCN) is added; K^{18}F is dried by azeotropic evaporation and used in subsequent nucleophilic radiofluorination reactions.[15] Initially we attempted a simple switch of the MeCN for EtOH when making up the kryptofix solution (Table 1). Given that the boiling points of MeCN-H_2O and EtOH-H_2O azeotropes are 76.5 ºC and 78.17 ºC, respectively,[16] we reasoned that this would be a straightforward switch. This proved to be the case in initial tests with the synthesis of [^{18}F]FDG. Typical radiochemical conversions (RCC) to [^{18}F]FDG (**3**) were 74±12% when MeCN was used to dry the fluoride (Table 1, Entry 1). Comparable RCC of 70±10% was achieved when MeCN was replaced with EtOH (Table 1, Entry 2), and ^{18}F was subjected to the same azeotropic drying conditions (see Electronic Supporting Information (ESI) for azeotropic drying conditions). Encouraged by these results, we switched the solvent for azeotropic drying of fluoride to EtOH for a range of radiotracers prepared by aliphatic ([^{18}F]fluoroazomycin arabinoside (FAZA, **6**), ([^{18}F]fluoroethyl tosylate (FET, **8**)) and aromatic (flubatine **11**, nifene **14**, and [^{18}F]2'-methoxyphenyl-(*N*-2'-pyridinyl)-*p*-fluoro-benzamidoethyipiperazine, MPPF **16**) fluorination without any detrimental effect on radiochemical yields (Table 1, Entries 3 – 12).



Scheme 1: Green Radiosynthesis of [^{18}F]Radiotracers

Table 1: Comparison of MeCN-H_2O and EtOH-H_2O azeotropic drying[a]

	Product	Azeotrope	Reaction Solvent	% RCY
1	**3**	H_2O-MeCN	MeCN	74±12 (n=3)[b]
2	**3**	H_2O-EtOH	MeCN	70±10 (n=3)[b]
3	**6**	H_2O-MeCN	DMSO	6±1 (n=3)[c]
4	**6**	H_2O-EtOH	DMSO	5±1 (n=3)[c]
5	**8**	H_2O-MeCN	MeCN	70±10 (n=3)[d]
6	**8**	H_2O-EtOH	MeCN	68±4 (n=2)[d]
7	**11**	H_2O-MeCN	DMSO	25±10 (n=3)[c]
8	**11**	H_2O-EtOH	DMSO	15±10 (n=20)[c]
9	**13**	H_2O-MeCN	DMSO	50 (n=1)[d]
10	**13**	H_2O-EtOH	DMSO	83 (n=1)[d]
11	**16**	H_2O-MeCN	DMSO	70±10 (n=3)[d]
12	**16**	H_2O-EtOH	DMSO	78±18 (n = 3)[d]

a) see ESI for detailed description of reaction conditions; b) radiochemical conversion (RCC) determined by radio-TLC; c) isolated radiochemical yield; d) RCC determined by radio-HPLC.

Confident that replacing MeCN with EtOH had no negative impact on the fluoride-drying step, the next phase of the work was to investigate the possibility of conducting nucleophilic fluorination reactions in EtOH. FDG was again selected as the initial test substrate, and our first reactions were conducted using EtOH for azeotropic drying of the fluoride followed by radiofluorination of mannose triflate **1** in neat ethanol (Table 2, Entry 1). Remarkably, this provided 23±10% RCC to [^{18}F]acetyl-protected FDG **2** ([^{18}F]FDG-Ac4, n = 3), which although lower than the analogous reactions in MeCN (Table 1, Entries 1 and 2), did demonstrate proof-of-concept. We next tested addition of water to the reaction solvent to see if the reaction could be improved since, in preliminary studies, VanBrocklin has shown that small amounts of water can have a positive affect on fluorination reactions.[17]

We screened a range of water concentrations from 3 to 100% (Figure 1) to explore the tolerance of the reaction to water. The optimal reaction solvent in these studies was found to be H_2O : EtOH / 15 : 85 (Figure 1 and Table 2, Entry 2) and RCC to [^{18}F]FDG-Ac4 **2** was 37±5% (n = 3). When water content was increased above 15% there was a steady drop off in RCC although, remarkably, fluorination was still possible in neat water, albeit in low RCC (2 –3%).

This tolerance for water gave us pause to reconsider our experimental design. All of the above reactions were conducted using dried [^{18}F]fluoride. However, while the role of water in improving reaction yields is not clear, fluoride drying would appear to be unnecessary if fluorination reactions can proceed in water : ethanol mixtures. We were curious if we could eliminate the trap and release of the [^{18}F]fluoride on the QMA cartridge, and subsequent azeotropic drying step, by simply adding a solution of [^{18}F]fluoride in [^{18}O]water (0.15 mL) to a solution of K_2CO_3, K222 and mannose triflate in EtOH (0.85 mL) to give a final reaction solvent concentration of 15% H_2O in EtOH. This proved ineffective however, resulting in only 3±1% RCC to [^{18}F]FDG-Ac4 (Table 2, Entry 3, n = 3), and we attribute this to the presence of other impurities in the target water (e.g. metal ions capable of sequestering [^{18}F]fluoride). To test this, [^{18}F]fluoride was next trapped on a QMA cartridge and eluted into the reactor using a mixture of K_2CO_3 / K222 in 15% water in ethanol (0.5 mL). The mannose triflate precursor was dissolved in 15% water in ethanol (0.5 mL) and added to the [^{18}F]fluoride / K_2CO_3 / K222 mixture. The total reaction (1 mL) was then heated to 100 ^{o}C for 30 mins to yield [^{18}F]FDG-Ac4 in 58±5% RCC (Table 2, Entry 4, n = 3). Increasing the reaction volume to 2 mL had a detrimental effect on yield and only 16±4% RCC to [^{18}F]FDG-Ac4 was observed (Table 2, Entry 5, n = 3). The need for inclusion of K222 as a phase transfer catalyst was also investigated. We reasoned that the aqueous reaction conditions could negate the need for a phase transfer catalyst. However, this was not the case as RCC of [^{18}F]FDG-Ac4 dropped to 4±1% when kryptofix was not included in the reaction cocktail (Table 2, Entry 6, n = 3). This was likely not due to the phase transfer properties of K222, but rather the enhanced nucleophilicity of [^{18}F]fluoride resulting from K222 complexing the potassium counter ion.

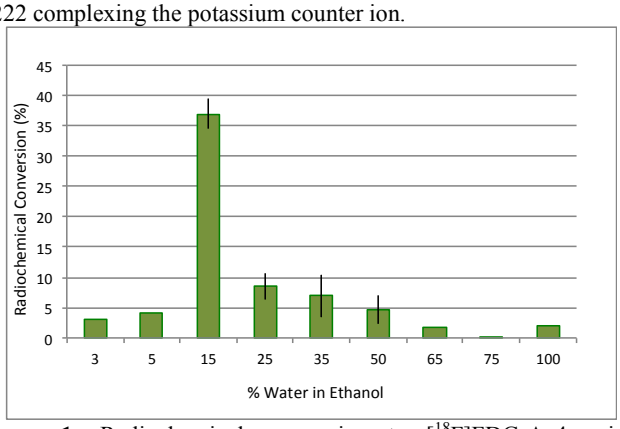


Figure 1: Radiochemical conversion to [^{18}F]FDG-Ac4 using different EtOH-H_2O Mixtures as reaction solvent

Having demonstrated that [^{18}F]FDG can be accessed via this methodology, the radiofluorination of the other radiopharmaceuticals of clinical relevance listed in Table 1 was investigated. The methodology was found to be applicable to the synthesis of [^{18}F]FAZA **6** (Table 2, Entry 7 – a drop of DMSO was added to the reaction solvent to help solubilize precursor **4**) and [^{18}F]FET (Table 2, Entry 8), giving comparable yields to the traditional synthesis of the radiotracers conducted in DMSO (Table 1, Entries 3 and 4) and MeCN (Table 1, Entries 5 and 6), respectively. Unfortunately, the aq. reaction solvent was not compatible with the aromatic fluorination reactions used to synthesize flubatine (Table 2, Entry 9), nifene (Table 2, Entry 10) or MPPF (Table 2, Entry 11) and no product was obtained from any of these reactions. In the case of MPPF, we primarily attribute this to precursor solubility issues, but attempts at using DMSO as a co-solvent with EtOH unfortunately did not improve the reaction. Moreover, for the S_NAr reactions, the boiling point of the water-ethanol reaction solvents (~70 – 80 ºC) may simply be incompatible with the higher temperatures necessary for conducting aromatic fluorination reactions (we typically conduct such reactions in DMSO at 120 – 150 ºC for 15 – 30 min), although we recognize that S_NAr at lower temperatures is known.[18] Therefore further studies into the scope of this green fluorine chemistry are warranted. With that being said, each of the fluoro(hetero)arene-containing products can be prepared in DMSO (Table 1). DMSO is bio-innocuous and one of the least toxic organic chemicals known, making it a green solvent.[19] The combination of azeotropic drying in EtOH-water and fluorination in DMSO does also eliminate the need for residual solvent analysis during QC testing according to recent updates to the US Pharmacopeia.[20]

Table 2: Conducting Nucleophilic Fluorination Reactions in EtOH-H_2O Mixtures[a]

	Product	QMA/Azeotrope	Reaction Solvent	% RCC
1	**2**	QMA/H_2O-EtOH	EtOH	23±10 (n=3)
2	**2**	QMA/H_2O-EtOH	15%H_2O : 85% EtOH	37±5 (n=3)
3	**2**	No QMA/None	15%H_2O : 85% EtOH	3±1 (n=3)
4	**2**	QMA/None	15%H_2O : 85% EtOH	58±5 (n=3)
5	**2**	QMA/None	15%H_2O : 85% EtOH[b]	16±4 (n=3)
6	**2**	QMA/None	15%H_2O : 85% EtOH[c]	4±1 (n=3)
7	**6**	QMA/None	15%H_2O : 85% EtOH	3 (n=1)
8	**8**	QMA/None	EtOH+1 drop DMSO[d]	52 (n=1)
9	**10**	QMA/None	15%H_2O : 85% EtOH	0 (n=3)
10	**13**	QMA/None	15%H_2O : 85% EtOH	0 (n=1)
11	**16**	QMA/None	EtOH	0 (n=3)
			EtOH+DMSO[d]	0 (n=3)

a) see ESI for detailed description of reaction conditions; b) 2 mL reaction volume; c) reaction conducted in the absence of kryptofix; d) DMSO added as a co-solvent to improve precursor solubility.

Finally, for routine clinical use, a radiopharmaceutical synthesis should ideally be fully automated using a remote-controlled synthesis unit. A General Electric TRACERLab FX_{FN} synthesis module was programmed to synthesize [^{18}F]FDG using the optimized conditions described above. Following the fluorination reaction, the acetate protecting groups of [^{18}F]FDG-Ac4 **2** were removed during a deprotection step by treatment with 1M NaOH at room temperature using standard procedures.[21] Neutralization (1M HCl) and formulation yielded [^{18}F]FDG **3** in 33±2% isolated and formulated radiochemical yield (decay-corrected, n = 3), which compares to 68±1% isolated and formulated yields of [^{18}F]FDG obtained using the traditional acetonitrile reaction solvent (decay-corrected, n = 3). While the yields in green solvents are lower than the traditional method, and may currently be too low for use by large commercial producers of [^{18}F]FDG, they do demonstrate proof-of-concept for using water- and ethanol-based reaction solvents in automated production of radiopharmaceuticals for clinical use. It should also be noted that these are preliminary studies that have not benefited from the decades of optimization work that have gone into the traditional synthesis to date. Moreover, in certain cases, the sacrifice in yield might be offset by the benefits of eliminating hazardous solvents and associated QC testing. For example, the move towards developing single automated modules for conducting QC testing,[22] with the aim of simplifying radiopharmaceutical production in remote/developing markets that only need to produce a few doses a day (or week), could benefit immensely from

eliminating residual solvent analysis from the required battery of QC tests.

In summary, green approaches to late-stage fluorination have been developed. The standard water-MeCN azeotrope for drying [^{18}F]fluoride can be readily replaced with an ethanol-water azeotrope without detrimental affect on radiochemical yields. Aliphatic fluorination reactions can also be conducted in ethanol and water mixtures, with 15% water : 85% ethanol being the optimal ratio. Although reaction yields are lower than when polar aprotic solvents are employed for fluorination, this work further challenges the notion that nucleophilic fluoride is completely incompatible with polar protic solvents, paving the way for further studies into the scope of green fluorine chemistry.

Financial support from the University of Michigan (College of Pharmacy, Rackham Graduate School and the Michigan Memorial Phoenix Project) is gratefully acknowledged. We also thank Ms. Merissa Zeman, Ms. Alexandra Sowa and Dr. Melissa Rodnick for assistance with routine radiotracer production.

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Electronic Supplementary Information (ESI) available: experimental procedures and radio-TLC/radio-HPLC chromatograms for reported reactions. See DOI: 10.1039/c000000x/

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