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No carrier-added nucleophilic aromatic radiofluorination using solid phase supported arenediazonium sulfonates and 1-(aryldiazenyl)piperazines

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ABSTRACT

This Letter concerns the investigation of a solid phase based method for no carrier-added nucleophilic [^{18}F]fluorination of aromatic compounds via de-diazofluorination. Initial screening of reaction conditions was conducted using soluble analogues, that is, substituted benzenediazonium tosylates and 1-(phenyldiazenyl)piperazines in solution. This was followed by translation of the principle conditions to solid phase bound analogues. A variety of substituted aryldiazonium cations were immobilised using a sulfonate functionalised ion exchange resin and labelled with [^{18}F]fluoride ion by Balz–Schiemann like thermal decomposition in the presence of no carrier-added [^{18}F]fluoride ion. Likewise, a chloromethyl-bearing (Merrifield-) resin was modified using piperazine to provide the means for covalent immobilisation of diazonium ions. The resin bound 1-(aryldiazenyl)piperazines obtained were used as substrates for a Wallach reaction with hydrogen [^{18}F]fluoride.

No carrier-added (NCA) nucleophilic aromatic radiofluorination of electron rich aromatic compounds with [^{18}F]fluoride ion is a highly challenging task in radiopharmaceutical chemistry.[1] There is a need to develop novel methods to access a wider range of products or improve the radiosynthesis of key radiopharmaceuticals. Still required are straightforward methods for the PET-tracers, 2-[^{18}F]fluoro-L-DOPA and 6-[^{18}F]fluoro-*meta*-tyrosine which are clinically relevant radiotracers for neurodegenerative diseases, to be produced with high specific radioactivity and high yield. Moreover, a traceless, direct nucleophilic labelling method which does not require the use of toxic metals and catalysts would ease quality control and validation in radiotracer productions for human application significantly.[1]

Recent reports of very stable solid-supported aryldiazonium sulfonates and resin-bound triazenes[2] motivated our effort to re-investigate de-diazofluorination in NCA nucleophilic radiofluorination using solid phase bound substrates. In both cases, only the labelled product would be cleaved off the resin upon the formation of a C–F bond with [^{18}F]fluoride ion whereas the unlabelled precursor would remain on the resin. Thereby, the purification of the product is simplified remarkably.

Despite the high interest in a simple and straightforward methodology for ^{18}F-labelling of aromatic substrates, solid phase methods have not been investigated in aromatic ^{18}F-labelling reactions. Fluorination of aromatic compounds by Balz–Schiemann and Wallach reactions has been reported in good yields, however their translation into ^{18}F-radiochemistry has been hampered by low radiochemical yields (RCY), low specific radioactivity and extensive by-product formation.[3]

Our initial experiments were focussed on the investigation of the utility of aryldiazonium tosylates as precursors for ^{18}F-labelling. A set of diversely functionalised model substrates were prepared using a modification of previously published methods[2a] (Scheme 1).

In our laboratory, diazonium salts were obtained under mild conditions by using solid-supported nitrite ions and toluenesulfonic acid as a proton source in 30–60% yields.

Immobilisation on a solid phase was achieved by stirring the commercially available cation exchange resin Amberlyst A15 (Na^+-form) in a solution of the desired aryldiazonium tosylate in methanol. To maximise the loading of the resin, this step was repeated three times to allow for a maximum loading of 1–1.5 mmol/g.[4]

We chose the conditions elaborated by Knöchel and Zwernemann[5] as the starting point for labelling experiments. Precursors **1a–e** were reacted with either Cs[^{18}F]F or [Na^+/18-C-6][^{18}F]F^- at 120 °C in toluene for 30 min. The commonly used polyether [K^+/18-C-6]$^{18}F^-$ and the cryptate [K^+/K222]$^{18}F^-$ were largely omitted due to low radiochemical yields being obtained, supposedly due to host–guest interactions between the diazonium cation and the larger complexing agents 18-crown-6 and K222[4,6a] which are not possible with the smaller analogue 15-crown-5.[6b] Under these conditions radiolabelled fluoroarenes were obtained in 0.5–7% yields after 30 min at 120 °C in toluene (Table 1). Precursor-loaded Amberlyst A15 resins **2a,b** were then used under essentially the same conditions to obtain ^{18}F-labelled products in a radiochemical yield of 6% (Table 1).

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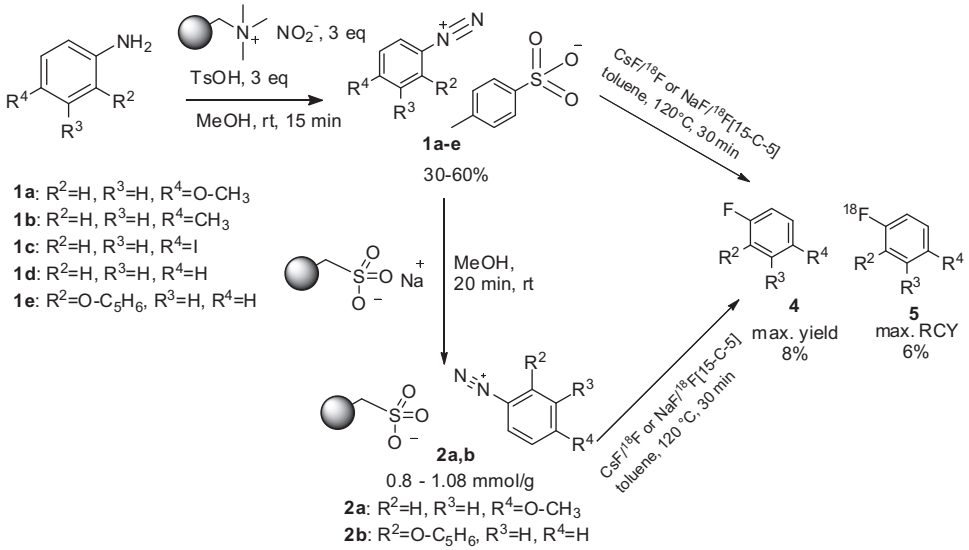


Scheme 1. Synthesis and radiosynthesis of fluoroarenes from aryl tosylates and solid-supported arenediazonium ions.

At this point we attempted to improve the radiochemical yields by screening a variety of solvents, metal additives, temperatures and reaction times.[4] However, this effort did not give any significant improvement in the labelling outcome. A detailed radioactivity balance furthermore revealed that after removal of the reaction mixture followed by three subsequent washing steps (2.5 ml) more than 90% of the ^{18}F-radioactivity was irreversibly bound to the solid phase containing the resin.[4] We concluded that dediazo[^{18}F]fluorination of resin-bound diazonium sulfonates is feasible but does not give sufficient yields for further investigation.

We therefore turned our interest to triazene analogues which can be readily decomposed in the presence of strong acids to yield diazonium ions.[3d]

Prior to the use of a solid phase bound precursor, the reaction conditions were investigated using 1-(aryldiazenyl)piperazines **3a** and **3b**.

Compounds **3a** and **3b** (Fig. 1) were synthesised by a standard method[8] and radiofluorinated by a method similar to that of Pages et al.[3f] The strong acids methanesulfonic acid, sulfuric acid and triflic acid were used for acid-induced decomposition of **3a** and **3b** in the presence of Cs[^{18}F]F or [Na$^+$/15-C-5]^{18}F$^-$ (Table 2). Carbon tetrachloride was used as the solvent. Up to 23% RCYs were obtained for substrate **3b** using [Na$^+$/15-C-5]^{18}F$^-$ and triflic acid after heating for 30 min.

Similar conditions were used to synthesise the non-radioactive reference compound **7**, however only trace amounts (0.3%) of fluorinated product were isolated (Scheme 2).

Table 1
[^{18}F]Fluorination of aryldiazonium tosylates **1a**–**e** and solid-supported aryldiazonium sulfonates **2a**,**b** after 30 min

Substrate	Reaction conditions	RCY[7]
1a	Cs^{18}F, toluene, 120 °C	1%
1a	[Na$^+$/15-C-5] ^{18}F$^-$, toluene, 120 °C	Trace
1c	[Na$^+$/15-C-5] ^{18}F$^-$, toluene, 120 °C	1%
1e	Cs^{18}F, toluene, 120 °C	7%
1e	[Na$^+$/15-C-5] ^{18}F$^-$, toluene, 120 °C	1%
1a	[K$^+$/18-C-6] ^{18}F$^-$, toluene, 120 °C	Trace
1a	[K$^+$/K222] ^{18}F$^-$, toluene, 120 °C	Trace
2a	[Na$^+$/15-C-5] ^{18}F$^-$, toluene, 120 °C	trace
2b	[Na$^+$/15-C-5] ^{18}F$^-$, toluene, 120 °C	6%
2b	Cs^{18}F, toluene, 120 °C	6%

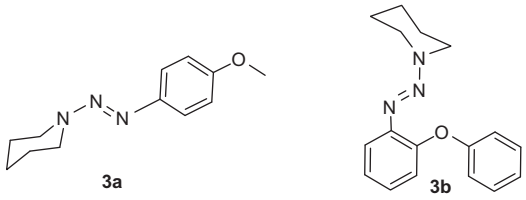
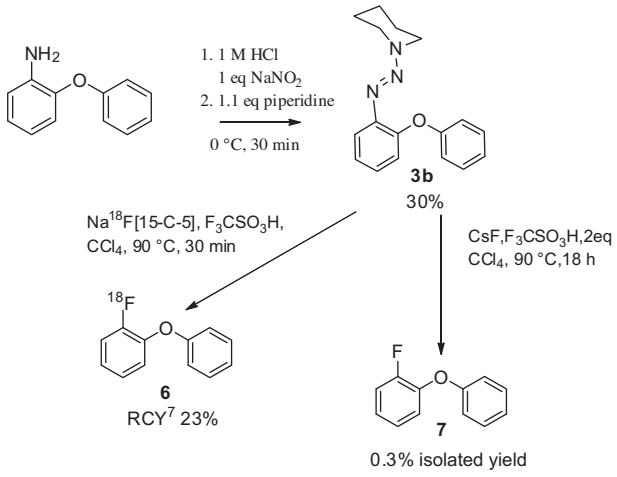


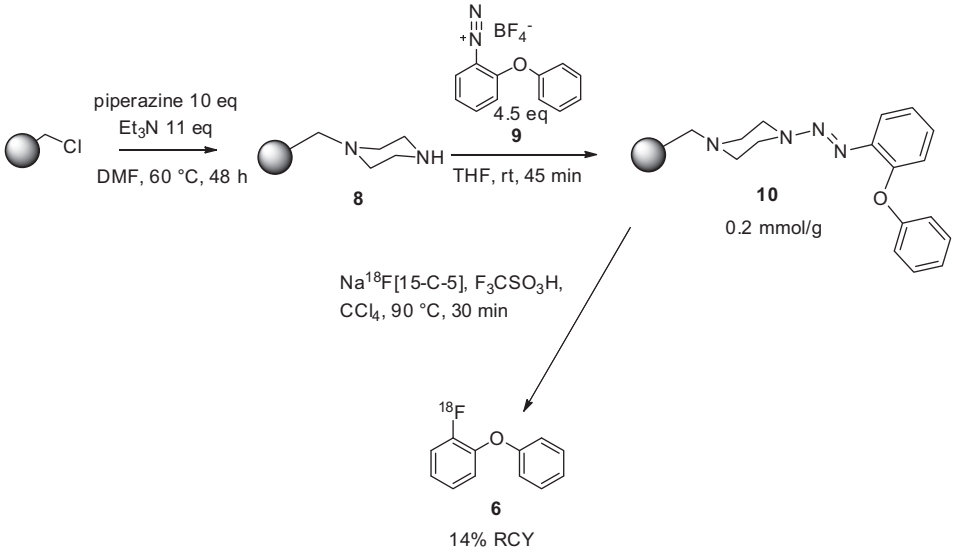
Figure 1. 1-(Aryldiazenyl)piperazines.

Table 2
[^{18}F]Fluorination of 1-(aryldiazenyl)piperazines **3a**,**b** under different reaction conditions in CCl_4 at 90 °C

Substrate	Reaction conditions	RCY[7]
3a	C^{18}F, H_3CSO_3H (5 equiv)	3%
3a	C^{18}F, F_3CSO_3H (5 equiv)	3%
3a	[Na$^+$/15-C-5]^{18}F$^-$, H_3CSO_3H (5 equiv)	2%
3a	[Na$^+$/15-C-5]^{18}F$^-$, F_3CSO_3H (5 equiv)	5%
3b	Cs^{18}F, H_2SO_4 (5 equiv)	Trace
3b	Cs^{18}F, H_3CSO_3H (5 equiv)	3%
3b	Cs^{18}F, F_3CSO_3H (5 equiv)	6%
3b	[Na$^+$/15-C-5]^{18}F$^-$, H_3CSO_3H (5 equiv)	3%
3b	[Na$^+$/15-C-5]^{18}F$^-$, F_3CSO_3H (5 equiv)	23%



Scheme 2. Synthesis and fluorination of **3b**.



Scheme 3. Synthesis and [^{18}F]fluorination of polymer functionalised triazene **10.**

In addition, about 10% of diphenyl ether was formed in the reaction, with 20% of the triazene recovered from the reaction mixture even after a prolonged reaction time of 18 h under reflux. We therefore synthesised this non-commercially available reference compound from 2-fluorophenol and diphenyliodonium tosylate.[4]

A commercially available 'Merrifield'-type polymer resin bearing chloromethylene functional groups for covalent attachment was modified with piperazine according to a published procedure in order to establish an anchoring point, that is, secondary amine functionalised resin **8**, to allow for triazene formation on the resin.[8]

Polymer functionalised triazene **10** was synthesised using **8** and diazonium tetrafluoroborate **9** (Scheme 3) following the procedure of Bräse et al.[9]

The triazene bound polymer was obtained with a maximum loading of 0.2 mmol/g.[4]

Resin **10** was reacted using the optimised conditions from Table 2. Within 30 min at 90 °C, ^{18}F-labelled ether **6** was obtained in up to 14% RCY.[4,10]

Contrary to the ion exchange resin, the activity balance of this reaction has shown that more than 60% of the ^{18}F-radioactivity can be recovered by filtering the resin. Only 18% of the radioactivity was still adsorbed on the resin and the reaction vessel after three subsequent washing steps (2.5 ml).[4]

We conclude that solid phase supported de-diazofluorination using arenediazonium cations ionically bound to a sulfonate functionalised ion exchange resin is not suitable for nucleophilic ^{18}F-labelling of aromatic compounds. Very low RCYs due to poor conversion are further augmented by extensive adsorption of ^{18}F-radioactivity to the resin. This methodology does not promise utility in radiotracer synthesis.

On the other hand, 1-(phenyldiazenyl)piperazines **3a** and **3b** were radiofluorinated within 30 min at 90 °C using [Na^+/15-C-5]$^{18}F^-$ in CCl_4 in the presence of trifluoromethanesulfonic acid with up to 23% RCY. The analogous reaction using solid supported triazene **10** afforded the ^{18}F-labelled product **6** in a reasonable radiochemical yield. This novel solid phase method has proven to be suitable for ^{18}F-radiolabelling of aromatic compounds, in particular since no electron-withdrawing group was necessary in order to facilitate the synthesis of [^{18}F]**6**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.082.

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10. An aliquot of [^{18}F]fluoride ion in H_2O (10–20 MBq) was added to a solution of $CsCO_3$ or a mixture of Na_2CO_3 and 2.5 equiv 15-C-5 (100 µl, 0.08 mmol/ml) in a V-shaped reaction vessel (Wheaton 5 ml reactivial®) and heated to 90 °C in a stream of nitrogen to evaporate the liquid. Residual traces of H_2O were removed by co-evaporation with MeCN (3 × 0.8 ml).
Resin **10** was allowed to swell in CCl_4 for 1.5 h prior to the labelling reaction. An aliquot (equivalent to a dry mass of 100 mg) was added to the dried [Na^+/15-C-5]$^{18}F^-$ and then anhydrous CCl4 (500 µl) was added. The vessel was cooled in an ice bath to 0 °C prior to the addition of trifluoromethanesulfonic acid (10 µl). The reaction vessel was briefly vortexed and heated to 90 °C for 30 min. Radiochemical yields were determined by radioTLC on silica gel (hexanes–EtOAc, 19:1).