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(Radio)Fluoro-Click Reaction Enabled by a Hydrogen Bonding Cluster

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Abstract

We have developed a widely applicable nucleophilic (radio)fluoro-click reaction of ynamides with readily available and easy handling $\text{KF}(^{18}\text{F})$. The reactions exhibited high functional group tolerance and needed only ambient atmosphere. Most importantly, this is the first ^{18}F addition protocol to C-C unsaturated bonds with extraordinarily high radiochemical yields.

Keywords

alkali fluoride; hydrogen bonding network; fluorination; radio-fluorination; HFIP

Due to fluorine's unique properties such as a small size and a metabolically resistant C-F bond, the selective substitution of hydrogen by fluorine constitutes a key strategy in drug discovery and material research.^{[1],[2]} More specifically, positron emission tomography (PET) based on the radioactive fluorine isotope (^{18}F) has become increasingly important in diagnosis and drug discovery.^[3] But common fluorination reagents, including nucleophilic fluorination reagents (e.g., HF-based reagents, DAST) and electrophilic fluorination reagents (e.g., NFSI and Selectfluor) are expensive, corrosive or toxic, and corresponding fluorination processes often have very poor atom-economy. Among fluorination reagents, alkali metal fluorides (MF), such as KF, are inexpensive and easy to handle. Especially for radioactive fluorine isotope introduction, the primary source of ^{18}F is the alkali metal salt of

$^{18}\text{F}^-$. For the use of MF as fluorination reagent,^[4] especially in the introduction of ^{18}F to organic molecules,^[5] the most common method is the nucleophilic displacement of alkyl or aryl halides, pseudo halides, ammonium or iodonium salts (Scheme 1a). In recent years, there has been great progress in transition metal catalyzed (radio)fluorinations using MF (Scheme 1b).^{[6], [7]} However, these metal catalyzed processes need more sophisticated conditions and are usually limited to the synthesis of aryl fluorides. Clearly, there is a need and a market for expanding the use of alkali metal fluorides to other types of fluorination reactions, such as addition reactions. We believe that the introduction of readily available MF (^{18}F) to an alkyne, under simple conditions and with great efficiency, could pave the way to applications in medicine and other fields in a manner not too dissimilar to the click reaction (copper-catalyzed reaction of an organo azide with an alkyne).^[8] Thus, we have named this transformation a fluoro-click reaction.

We propose that a hydrogen-bonding network can activate alkali metal fluorides such as KF. Due to σ -cooperativity or non-additivity (hydrogen bond energy of a chain of H-bonds can be greater than the total energies of the individual links),^[9] strong hydrogen bonding donors such as HFIP (hexafluoro-2-propanol) could form a H-bond network or aggregation (Scheme 1c).^[10] This hydrogen-bonding network is a better H-bond donor than a single HFIP, activating the electrophile *via* strong hydrogen bonding interaction (Scheme 1c). Indeed, hydrogen bonding donor solvents like HFIP have been shown to provide significant rate enhancements in many reactions,^[10a-c, 10f] and kinetic data suggest that hydrogen-bonding solvent aggregates play an important role.^[10d]

Another problem of MF salts is their poor solubility in most organic solvents. Since fluoride itself is a good hydrogen bonding acceptor, a H-bond network could complex with MF and make it highly soluble. Indeed, alkali fluorides such as KF have good solubility in HFIP at room temperature. Also, it has been reported that F^- is a better nucleophile than other halides (Br^-/I^-) in hydrogen-bonding donor solvents like *t*-BuOH, and *t*-BuOH due to their positive effect on the 'effective fluoride nucleophilicity'.^[11] Because HFIP is a stronger H-bond donor than those alcohols, we expect it will have an even stronger effect in the modulation of the nucleophilicity of fluoride. Lastly, a H-bond network generated from HFIP could also act as a proton source in hydrofluorination (Scheme 1c), as shown by Doyle and coworkers in their copper-catalyzed H-F insertion into α -diazocarbonyl compounds using HFIP as proton source.^[12] We are now glad to report the first ^{18}F addition protocol to an alkyne via a nucleophilic (radio)fluoro-click reaction, enabled by a hydrogen bonding cluster and using the readily available $\text{KF}(^{18}\text{F})$ (Scheme 1d).

We used the hydrofluorination of ynamide **1a** as our model reaction (Table 1). Ynamides are readily available compounds that have found wide applications in organic synthesis.^[13] Although the hydrofluorination of ynamides have been reported,^[14] these methods are based on hydrogen fluoride or silver fluoride as fluorination reagents, all of which are not environmentally friendly. More importantly, the introduction of ^{18}F is difficult using these methods. Initially, we chose HFIP as our hydrogen bonding activator and proton source. Screening of various alkali metal fluorides indicated that metal fluorides with bulkier counterions gave better results (Table 1, entries 1-4, efficiency $\text{LiF} < \text{NaF} < \text{KF} \sim \text{CsF}$). Because KF and CsF gave similarly good results, and KF is more inexpensive, we chose KF

as our fluorination reagent. Also, a higher temperature promoted the formation of HFIP addition by-product **2a'** (Table 1, entry 5). We investigated the effect of solvents (Table 1, entries 5-7). Reducing the amount of HFIP (Table 1, entry 6) or using the weaker hydrogen-bonding donor solvent trifluoroethanol (TFE) diminished the reactivity (Table 1, entry 7). The amount of HFIP addition by-product **2a'** was effectively reduced by increasing the number of equivalents of KF (Table 1, entry 8).

Having found the optimized conditions, we then explored the scope and functional group tolerance of our hydrofluorination protocol (Table 2). First, we evaluated the effect of R² substitution in ynamides **1** (Table 2, **2a-2g**). The structure of R² (alkyl groups, aryl groups and allyl group, benzyl group, heterocyclic groups) played only a minor role good yields of **2** were obtained regardless (Table 2, **2a-2g**). We evaluated the effect of R¹ substitution (Table 2, **2h-2u**). When R¹ was a benzylic group, substitution patterns (*ortho*, *meta*, *para*) and the presence of electron donating groups or electron withdrawing groups on R¹ exerted little influence on the efficiency of the reaction (Table 2, **2h-2s**). This reaction also tolerated a wide variety of other R¹ variations: simple alkyl group (Table 2, **2t**), fused aromatic (Table 2, **2u**), or even heteroaromatics, such as thiophene and pyridine (Table 2, **2v-2w**). To demonstrate the applicability of our method, we synthesized ynamides tethered to activated ester and azido functionalities (Table 2, **2x-2y**) or complex natural products (Table 2, **2z**, **2aa**); in all these cases our reaction worked very well.

We were quite pleased to find that our protocol could be used in the radio fluorination of ynamides **1** (Table 3). In all cases, we got excellent radiochemical yields (RCY). Various functional groups, including halogen, ester, nitrile, and nitro did not affect the efficiency of the reaction, and heterocycles such as thiophene and pyridine were well tolerated. To demonstrate the applicability of our method in biological applications, we prepared ynamide **2x**, an organoazide (Table 3, **[F18]2aa**) and a biologically active compound (Table 3, **[F18]2z**) with great efficiency. In principle, an activated ester could be tethered to biomolecules such as peptides or proteins easily in radiochemistry *via* formation of amide linkage.^[15] And the azide linker could be easily attached to bioactive compounds *via* click-chemistry.^[16] It should be noted that our method does not require the use of expensive polycyclic multidentate cation ligands such as K₂₂₂, which has been commonly used in other radiofluorination protocols to increase the nucleophilicity of ¹⁸F⁻.

Our system was also extended to iodofluorinations^[14a] (Table 4). When the iodination reagent NIS was incorporated to our fluorination system (KF/HFIP), we obtained the iodofluorination product **3** (Table 4a). The yields were only moderate, possibly due to the relatively instability of the resulting vinyl-iodides. To our delight, the corresponding radio-iodo fluorination was very efficient: close to 80% RCY yield was obtained (Table 4b).

We also investigated the serum stability of our synthesized ¹⁸F-tracer in fetal bovine serum (incubated at 37 °C for 2 h, see section 7 of SI). Our results, based on three radiotracers (**2b**, **2w**, **2y**) showed that they were stable for up to 2 h in serum.

Our methodology is scalable (Scheme 2a) and the reaction products could be further utilized in transition metal catalyzed cross-coupling reactions. As shown in Scheme 2b and 2c, the

Suzuki coupling of **2m** with phenyl boronic acid gave moderate yield of the coupling product **4a**, and the Sonogashira coupling of **2m** only furnished the aromatic substitution product **4b**.

The proposed mechanism is shown in Scheme 3. The hydrogen-bonding network generated from HFIP facilitates the rate-determining proton transfer step, which produces the key intermediate--keteniminium **A**.^[17] Ketiminium **A** possesses a linear geometry,^[17] with its upper face being sterically hindered by the R¹ group, thus favoring the nucleophile (fluoride) *syn* approach (formation of the *syn*-addition product) (Scheme 3., top).^[18] On the other hand, in the presence of NIS, an iododinium **B** forms instead because NIS is a strong electrophile; ring-opening of **B** by fluoride yields the *anti*-addition product **3** (Scheme 3., bottom).

In summary, we have developed a widely applicable synthesis of α -fluoroenamides using KF(¹⁸F). The reactions exhibited high functional groups tolerance and needed only ambient atmosphere. Most importantly, this is the first ¹⁸F addition protocol to C-C unsaturated bonds with extraordinary high radiochemical yields. Other (radio)fluorination systems based on KF/HFIP system are currently being investigated in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Common usage of MF or M¹⁸F

a) Nucleophilic displacements

R = alkyl or electron deficient aryl groups

X = halides, -OTs, -OTf, -NR₃⁺, -IR₂⁺...

b) Transition metal catalyzed (radio)fluorinations

X = halides, -OTs, -OTf, -NR₃⁺, -IR₂⁺...M = -SnR₃, -BR₂...

c) Multiple functions of H-bond networks

d) This work - the first ¹⁸F addition protocol to C-C unsaturated bonds

Scheme 1.

Nucleophilic (radio)fluoro-click reaction using alkali fluorides.

Scheme 2.

Gram scale reaction and further synthetic manipulations.

Scheme 3.
Proposed mechanism.

Table 1.

Screening of reaction conditions.^[a]

Entry	MF	Temp / °C	Solvent	Yield (%) 2a:2a':1a
1	LiF	rt	HFIP	3/4/93
2	NaF	rt	HFIP	6/4/90
3	KF	rt	HFIP	64/31/4
4	CsF	rt	HFIP	62/33/5
5	KF	70	HFIP	32/59/9
6	KF	70	HFIP/DCE (1:1)	33/34/32
7	KF	rt	TFE	2/0/98
8	KF ^C	rt	HFIP	84/14/1

^[a] Reaction conditions: **1a** (0.2 mmol), MF (0.6 mmol), solvent (0.4 mL), 8 h.^[b] Determined by GC-MS analysis.^[c] 6 equiv of KF was used.

Table 2.

Scope for the synthesis of α -fluoroenamides **3**.^a

^aReaction conditions: **1** (0.2 mmol), KF (1.2 mmol), HFIP (0.5 mL), rt. All yields are isolated yields.

^bRun at 60 °C.

Table 3.

Radio fluorination of ynamides **1**.^a

^aReaction conditions: **1** (0.015 mmol) in HFIP (100 µl) was mixed with ¹⁸F (~ 0.3 mCi, in 50 µL HFIP), 60 °C, 1 h. Reactions were performed 3 times; radiochemical yields were determined by radio-HPLC and are given in the form mean ± standard deviation.

Table 4.

Iodofluorination^a and radio iodofluorination^b of ynamides **1**. ^aReaction conditions: **1** (0.2 mmol), KF (1.2 mmol), NIS (0.24 mmol) HFIP (0.4 mL), DCM (0.1 mL), rt, 8 h.^bReaction conditions: **1** (0.015 mmol), NIS (2.7 mg) in HFIP (100 µl) was mixed with ¹⁸F (~0.3 mCi, in 50 µl HFIP), 60°C, 1 h. Reactions were performed 3 times; radiochemical yields were determined by radio-HPLC and are given in the form mean ± standard deviation.