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Communication

Radiolabeled Synthons

Seyferth–Gilbert Homologation as a Route to ^{18}F-Labeled Building Blocks: Preparation of Radiofluorinated Phenylacetylenes and Their Application in PET Chemistry

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Abstract: A convenient method for the preparation of hitherto unknown ([^{18}F]fluorophenyl)acetylenes ([^{18}F]FPAs) using the Seyferth–Gilbert homologation is reported. The novel building blocks were efficiently prepared from easily accessible [^{18}F]fluorobenzaldehydes by using the Bestmann–Ohira reagent. High radiochemical yields and excellent radiochemical purities were achieved within only 20 min of reaction time; 2- and 4-[^{18}F]FPAs were applied to prepare radiofluorinated heterocycles by using different cycloaddition and cross-coupling reactions. Additionally, these building blocks were used to prepare three novel PET tracers. Thus, an artificial radiofluorinated protected amino acid [^{18}F]**10**, a COX-2-specific ligand [^{18}F]**14**, and a PSMA-selective inhibitor [^{18}F]**16** were obtained in high radiochemical yields.

Introduction

Positron emission tomography (PET) is an important non-invasive imaging modality widely used in clinical diagnostics. PET allows the real-time visualization of physiological and pathological processes on the molecular level by using in vivo tracing of biologically active molecules labeled with β^+-emitting nuclides. Among them, fluorine-18 represents the most popular PET radionuclide since no carrier added (n.c.a.) ^{18}F in the form of [^{18}F]fluoride is readily accessible in multi-Curie amounts by the high-yielding ^{18}O(p,n)^{18}F nuclear reaction at low-energy cyclotrons. Furthermore, it exhibits favorable decay properties. Thus, the energy of the emitted β^+-particles is low [$E(\beta^+)$ = 630 keV] resulting in PET scans with high intrinsic resolution due to the short range of the emitted particles in tissue. Furthermore, the half-life of ^{18}F (109.8 min) is well-suited for the majority of PET applications. Moreover, this relatively long half-life enables sophisticated multistep radiochemical syntheses and monitoring of biological processes in the range of hours. Additionally, the half-life of ^{18}F facilitates "satellite" distribution of ^{18}F-labeled radiopharmaceuticals to distant clinical centers.

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A broad spectrum of direct and indirect methods for ^{18}F-labeling has been developed.[1] Among them, the (3+2) azide-alkyne Huisgen cycloaddition (azide-alkyne click reaction),[2] originally transferred to radiochemistry by Marik et al.[2d] became a widely used method for the preparation of PET tracers. In particular, sensitive biomolecules including biopolymers could be efficiently radiofluorinated by using this method. The main advantages of this approach are: chemical and enzymatic stability of the resulting 1,2,3-triazoles, regioselectivity of radiolabeling, excellent compatibility with different functional groups, and fast reaction kinetics under mild reaction conditions. (3+2) Cycloadditions of radiofluorinated nitrile oxides and nitrones with unsaturated compounds have also been explored for radiolabeling.[2f] Furthermore, the Kinugasa reaction has been shown to provide easy access to radiofluorinated β-lactams starting from ^{18}F-labeled nitrones and alkynes.[2h]

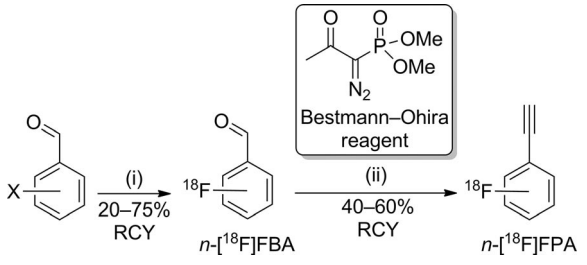
Several radiofluorinated alkynes have been synthesized and applied as radiolabeled synthons for click chemistry.[3] However, compared to the plethora of alkynes applied for nonradioactive applications only a few radiofluorinated alkynes have been developed for PET chemistry. Furthermore, their preparation often requires multiple reaction steps and time-consuming purification procedures, resulting in low radiochemical yields (RCY).

Radiofluorinated arylacetylenes represent potentially very useful building blocks, which could provide access to numerous novel radiolabeled compounds of high interest. Their radiosynthesis has not been reported yet, albeit a rapid development of radiofluorination methods has taken place in recent years.[4,5] Herein we describe the efficient preparation of hitherto unknown ([^{18}F]fluorophenyl)acetylenes ([^{18}F]FPAs). These synthons were synthesized from the corresponding [^{18}F]fluorobenzaldehydes ([^{18}F]FBAs) by using the Seyferth–Gilbert homologation with the Bestmann–Ohira reagent.[6] The application of 2- and

4-[^{18}F]FPAs as building blocks to produce various radiolabeled compounds was studied. The latter were prepared by (3+2) cycloaddition reactions, the radio-Kinugasa reaction, the copper-free Sonogashira coupling and the Rh-catalyzed (2+2+2) cycloaddition. Furthermore, these building blocks were used to produce PET tracers. Thereby, ^{18}F-labeled variants of an amino acid [^{18}F]**10**, a COX-2- ([^{18}F]**14**) and a PSMA-specific ([^{18}F]**16**) ligand were prepared.

Results and Discussion

[^{18}F]Fluorobenzaldehydes were produced according to the recently reported "minimalist" radiofluorination protocol.[7] Shortly, [^{18}F]fluoride was eluted from an anion exchange resin with the appropriate onium salt precursor in MeOH. MeOH was evaporated, the residual [^{18}F]fluoride salt was redissolved in DMSO and heated for 10 min to give *n*-[^{18}F]FBAs in 20–75 % radiochemical yields (RCYs; not corrected for decay) after purification by solid-phase extraction (SPE) within 20–25 min (Scheme 1). [Radiochemical yield (RCY) refers to the isolated yield of the radiochemically and chemically pure radiolabeled compound.]



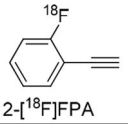
Scheme 1. Synthesis of *n*-[^{18}F]FPAs. (i) Preparation of *n*-[^{18}F]FBAs: 2-[^{18}F]FBA: X = $Me_3N^+ClO_4^-$, DMSO, 150 °C, 10 min (50–65 %); 3-[^{18}F]FBA: X = (4-$MeOC_6H_4$)I^+I^-, DMSO, 130 °C, 10 min (20–25 %); 4-[^{18}F]FBA: X = $Me_3N^+ClO_4^-$, DMSO, 150 °C, 10 min (65–75 %); (ii) Synthesis of *n*-[^{18}F]FPAs: dimethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann–Ohira reagent) solution (10 % in MeCN), K_2CO_3, 120 °C for 15 min. Therafter, distillation at 80 °C under a gentle stream of helium was carried out {in the case of 4-[^{18}F]FPA, $NaBH_4$ (1–2 mg) was added before distillation}.

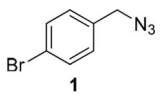
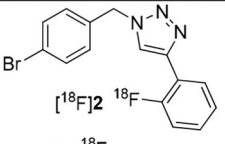
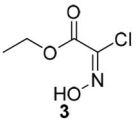
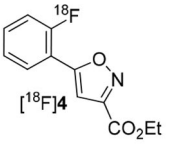
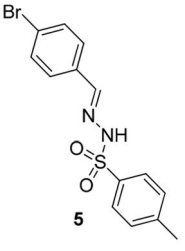
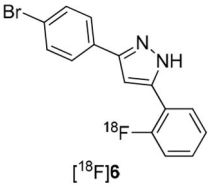
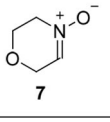
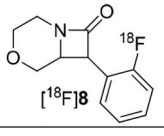
The radiolabeled benzaldehydes were allowed to react with the Bestmann–Ohira reagent [dimethyl (1-diazo-2-oxopropyl)-phosphonate] in the presence of K_2CO_3 in MeOH/MeCN at 120 °C for 15 min to afford the desired radiofluorinated alkynes in > 90 % radiochemical conversions (RCCs). [Radiochemical conversion yield (RCC) refers to the amount of [^{18}F]fluoride or another immediate radiolabeled precursor, which was transformed into the desired ^{18}F-labeled compound; it was determined by radio-HPLC.] The radiolabeled synthons were isolated by distillation in 40–60 % RCY (not corrected for decay; $n > 20$) and with more than 98 % radiochemical purity (RP) within 20 min. In the case of 4-[^{18}F]FPA, $NaBH_4$ was added to the reaction mixture before distillation to avoid contamination of the product with traces (< 5 %) of 4-[^{18}F]fluorobenzaldehyde. Notably, this preparation method was insensitive to electronic and steric effects of substituents and worked equally well for all three [^{18}F]FBAs.

Once a reliable and simple method for the efficient preparation of [^{18}F]FPAs had been established, their versatility as synthons for radiolabeling was evaluated.

Initially, the utility of 2-[^{18}F]FPA for click labeling was studied. Accordingly, 2-[^{18}F]FPA was allowed to react with a model azide **1** (Entry 1, Table 1) in the presence of $CuSO_4$, sodium ascorbate, and histidine in aqueous MeOH at ambient temperature. The corresponding radiolabeled triazole [^{18}F]**2** was formed in an RCC of 53 % already after 10 min of reaction time. In following experiments the cycloaddition reactivity of 2-[^{18}F]FPA with 1,3-dipoles other than azides was examined (Entries 2–4, Table 1). Thus, 2-[^{18}F]FPA was allowed to react with nitrile oxide generated in situ from the corresponding *N*-hydroxyimidoyl chloride **3** by base-promoted elimination of HCl to afford the ^{18}F-labeled 3,5-substituted isoxazole [^{18}F]**4** in 52 % RCC.

Table 1. (3+2) Cycloadditions between 2-[^{18}F]FPA and different 1,3-dipoles.



Entry[a]	Precursor	Product	RCC±SD [%]
1[b]	 **1**	 [^{18}F]**2**	53±5
2[c]	 **3**	 [^{18}F]**4**	52±6
3[d]	 **5**	 [^{18}F]**6**	20±8
4[e]	 **7**	 [^{18}F]**8**	52±5

[a] All syntheses were carried out manually. Before being analyzed, the reaction mixtures were cooled to ambient temperature and diluted with water (2 mL). Unless otherwise stated, each experiment was carried out at least in triplicate ($n \geq 3$). [b] 2-[^{18}F]FPA (50–500 MBq) in MeOH (50 µL), $CuSO_4$ (2.5 mg), histidine (3.8 mg), sodium ascorbate (9.8 mg) and **1** (5 mg) in H_2O (200 µL), 25 °C, 10 min. [c] 2-[^{18}F]FPA (50–500 MBq) in EtOH (200 µL), **3** (10 mg), Et_3N (10 µL), 120 °C, 30 min. [d] 2-[^{18}F]FPA (50–500 MBq) in dioxane (400 µL), **5** (10.5 mg), K_2CO_3 (8 mg), 150 °C, 30 min. [e] **7** (5 mg), CuI (9.8 mg), Et_3N (28 µL), MeCN (200 µL), 2 min, ambient temp. Then 2-[^{18}F]FPA (50–500 MBq) in MeOH (150 µL), 1,10-phenanthroline (18 mg) in MeCN (100 µL), 90 °C, 10 min.

Next the feasibility of the building block for the preparation of radiolabeled pyrazoles was studied. To this end, 2-[^{18}F]FPA was allowed to react with (4-bromophenyl)diazomethane generated in situ from the respective *N*-tosylhydrazone **5** (Entry 3, Table 1) at 150 °C for 30 min to give the radiolabeled 3,5-substi-

tuted pyrazole [^{18}F]**6** in 20 % RCC. Radiolabeled isoxazoles and pyrazoles could be of potential use as imaging agents targeting, i.e., HDAC 3 and 8,[8] αvβ3 integrins,[9] 20-HETE synthase[10] and COX1/COX2.[11]

Radiofluorinated β-lactams are potentially applicable in PET for the detection of bacterial and viral infections as well as thrombosis, emphysema, and tumors.[12] Consequently, the suitability of ([^{18}F]fluorophenyl)acetylenes for the preparation of ^{18}F-labeled bicyclic β-lactams by the radio-Kinugasa reaction[2h] using cyclic nitrone **7** and 2-[^{18}F]FPA was investigated (Entry 4, Table 1). In the presence of CuI as Cu^{I} source and 1,10-phenanthroline as Cu^{I}-stabilizing ligand this reaction provided the corresponding radiofluorinated fused β-lactam [^{18}F]**8** in an RCC of 52 % within 10 min.

Next, the ability of the radiofluorinated fluoroacetylenes to participate in late transition metal mediated transformations was studied.

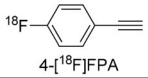
The Sonogashira reaction represents a powerful tool for the preparation of arylalkynes and conjugated enynes.[13] It has been extensively used for the synthesis of different materials, pharmaceuticals and natural products.[7] However, Sonogashira cross-coupling with radiofluorinated alkynes has not been reported yet. Only 4-[^{18}F]fluoroiodobenzene has been used as a building block for the radio-Sonogashira coupling.[14] We studied the Sonogashira reaction between 4-[^{18}F]FPA and protected (4-iodophenyl)alanine **9** (Table 2). Usually, radio-Sonogashira cross-couplings were carried out by using Pd complexes with triarylphosphine ligands and CuI as a metal co-catalyst. We applied the protocol of Yang et al.,[15] which eliminates the need of any co-catalyst and ligands. Accordingly, the radio-Sonogashira reaction was performed under air in water by using only $PdCl_2$ as a catalyst and pyrrolidine as a base. Under these conditions the protected radiofluorinated artificial amino acid [^{18}F]**10** was obtained in an RCC of 83 % after 10 min at 120 °C.

Alkyne trimerization represents a powerful tool for the de novo construction of polysubstituted heteroaromatic and aromatic systems. This reaction is widely used in the total synthesis of complex natural products.[16] Transfer of this method into radiochemistry could provide a fast access to otherwise hardly available ^{18}F-labeled polycyclic compounds.[17]

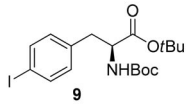
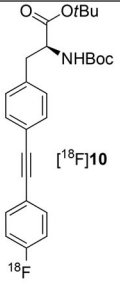
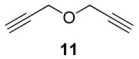
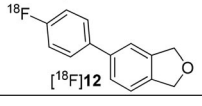
As a proof of principle, model 4-[^{18}F]fluorophenyl-substituted 1,2-dihydrobenzofuran [^{18}F]**12** was prepared by the reaction of propargyl ether (**11**) with 4-[^{18}F]FPA in the presence of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] in unoptimized 18 % RCC.

Finally, [^{18}F]**14** and [^{18}F]**16** were prepared to illustrate the potential of the novel labeling synthons for tracer production and development. [^{18}F]**14** represents a probe potentially suitable for the visualization of cyclooxygenase 2 (COX-2), an enzyme associated with inflammatory processes and tumor progression.[18] On the other hand [^{18}F]**16** containing the Lys-ureido-Glu fragment could be applied for imaging of the prostate-specific membrane antigen (PSMA),[19] e.g., in prostate carcinoma,[20] breast cancer[21] and tumor-associated neovasculature.[22] Both molecular probes were afforded in > 70 % RCCs by the azide-alkyne "click" cycloaddition between 2-[^{18}F]FPA and the corresponding azide precursors **13** and **15** under standard conditions (Table 3). [^{18}F]**14** and [^{18}F]**16** were isolated by semipreparative HPLC in RCYs of 25 % and 30 % (corrected for decay; starting from ^{18}F-fluoride), respectively, within an overall synthesis time of 60 min. The specific activity of [^{18}F]**14** and

Table 2. Late transition metal mediated reactions of 4-[^{18}F]FPA.

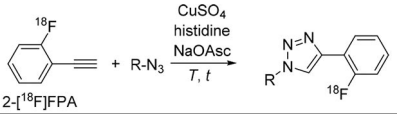


4-[^{18}F]FPA

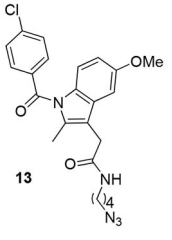
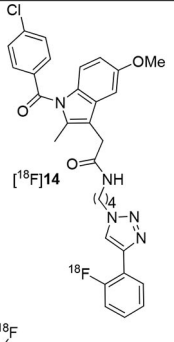
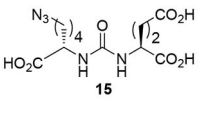
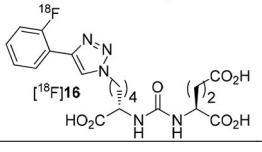
Entry[a]	Metal	Precursor	Product	RCC±SD [%]
1[b]	Pd	 **9**	 [^{18}F]**10**	83±2
2[c,d]	Rh	 **11**	 [^{18}F]**12**	18

[a] All syntheses were carried out manually. Before being analyzed, the reaction mixtures were cooled to ambient temperature and diluted with water (2 mL). Unless otherwise stated, each experiment was carried out at least in triplicate ($n \geq 3$). [b] **9** (35 mg), $PdCl_2$ (0.35 mg), pyrrolidine (100 μL) in H_2O (250 μL), 50 °C, 5 min. Then 4-[^{18}F]FPA (50–500 MBq) in MeCN (150 μL), 120 °C, 10 min. [c] 4-[^{18}F]FPA (50–500 MBq) in EtOH (150 μL), $Rh(PPh_3)_3Cl$ (1 mg), 40 °C, 5 min. Thereafter, **11** (20 μL), 120 °C, 15 min. [d] The synthesis of [^{18}F]**12** was carried out one time ($n = 1$).

Table 3. Preparation of [^{18}F]**14** and [^{18}F]**16**.



2-[^{18}F]FPA

Entry[a]	Precursor	Product	RCC±SD [%]
1[b]	 **13**	 [^{18}F]**14**	75±4
2[c]	 **15**	 [^{18}F]**16**	84±3

[a] All syntheses were carried out manually. Before being analyzed, the reaction mixtures were cooled to ambient temperature and diluted with water (2 mL). Unless otherwise stated, each experiment was carried out at least in triplicate ($n \geq 3$). [b] $CuSO_4$ (2.5 mg), 2-[^{18}F]FPA (50–500 MBq) in MeOH (50 μL), histidine (3.8 mg, 50 μL), sodium ascorbate (9.8 mg) and **13** (15 mg) in H_2O (150 μL), 25 °C, 10 min. [c] 2-[^{18}F]FPA (50–500 MBq) in MeOH (50 μL), $CuSO_4$ (2.5 mg), histidine (3.8 mg), sodium ascorbate (9.8 mg) and **15** (4 mg) in H_2O (150 μL), 50 °C, 20 min.

[^{18}F]**16** was 140 GBq/μmol and 232 GBq/μmol, respectively. The biological evaluation of [^{18}F]**14** and [^{18}F]**16** is in progress and will be reported in due course.

Conclusions

The first application of the Seyferth–Gilbert homologation in PET chemistry is reported. This approach enables the fast and simple access to radiofluorinated phenylacetylenes. A wide application scope of the novel synthons was demonstrated by the preparation of various radiolabeled model compounds and PET tracers using (3+2) cycloadditions and cross-coupling reactions.

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Keywords: Radiopharmaceuticals · Fluorine-18 · Click chemistry · Seyferth-Gilbert homologation · Alkynes

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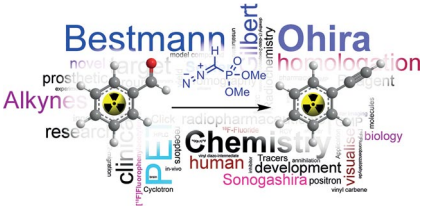
Radiolabeled Synthons



A convenient method for the preparation of hitherto unknown ([^{18}F]fluorophenyl)acetylenes ([^{18}F]FPAs) utilizing the Seyferth–Gilbert homologation is reported. The novel building blocks were applied to prepare radiofluorinated heterocycles and PET tracers utilizing different cycloaddition and cross-coupling reactions.

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