Minimalist approach meets green chemistry: Synthesis of ^{18}F-labeled (hetero)aromatics in pure ethanol

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Abstract: The application of toxic solvents and additives is inevitable for most of the described protocols for ^{18}F-labeling. Herein, a novel "green" procedure for nucleophilic aromatic radiofluorination of highly activated (hetero)aromatic substrates in pure EtOH is described. Using this method a series of ^{18}F-labeled (hetero)arenes have been synthesized in radiochemical yields (RCYs) of up to 97%.

Introduction

Positron emission tomography (PET) and related hybrid methods (like PET/CT and PET/MR) have become indispensable methods in patient diagnostics, therapy monitoring as well as in drug development. These methods are distinguished by their high sensitivity allowing to detect slightest biochemical changes during disease development. PET utilizes molecular probes tagged with short-lived β^+-emitting radionuclides. Owing to the good accessibility of [^{18}F]fluoride in aqueous solution as well as the favorable nuclear decay properties of ^{18}F with regard to β^+ energy and half-life, ^{18}F is the most frequently used radionuclide in PET-chemistry. The outcome of PET examinations highly depends on the development of PET tracers which selectively address molecular targets of high clinical relevance. The development of specific probes requires the application of high-yielding and simple radiofluorination techniques. However, in comparison to fluorination methods in organic chemistry, techniques to introduce ^{18}F into target molecules are limited. This can be mainly ascribed to the relatively short half-life and the minute amounts of ^{18}F used for tracer preparation. Moreover, radiofluorination procedures should be amenable to automation. The latter reduces radiation exposure of the personnel and at the same time simplifies cGMP PET tracer production. Nevertheless, in recent years several novel fluorination techniques for the preparation of radiofluorinated compounds have been reported.[1] In particular, several efficient transition metal-mediated radiofluorination protocols have been published.[2]

However, these methods apply phase transfer catalysts like Kryptofix-222 (K222) and 18-crown-6, quaternary ammonium salts and toxic aprotic solvents (e.g. DMF, MeCN or DMSO). The residual content of these hazardous substances in pharmaceutical preparations must be carefully examined and is an integral part of the quality control (QC) of radiopharmaceuticals.[3] Minimizing or completely avoiding hazardous reagents/solvents in protocols for the production of radiopharmaceuticals or their replacement by safer and more sustainable alternatives will further eliminate the need of such time- and cost-intensive analyses and significantly decrease the possibility of QC failure. Remarkably, these requirements are fully consistent with four of the most important of the twelve principles of green chemistry declared by Anastas *et al*:[4] prevention of waste, atom economy, safer reagents, and safer solvents and auxiliaries.

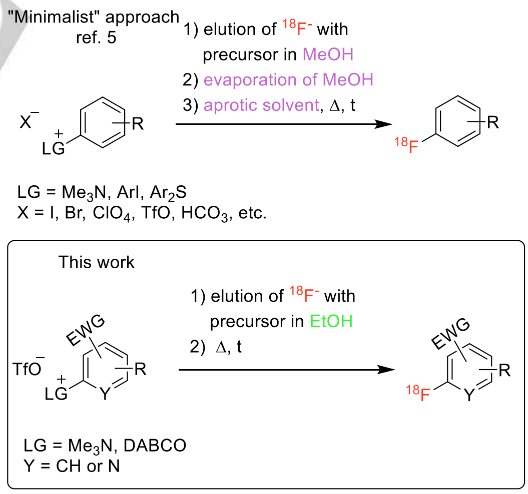

Figure 1: Comparison between "minimalist" and "green" radiofluorination approaches..

A first ^{18}F-radiolabeling protocol which implemented some of the green chemistry principles (atom economy, preventing wastes and energy efficiency) was the "minimalist" approach published recently by our group.[5] Accordingly, ^{18}F-labeling was carried out by using only radiolabeling precursor and ^{18}F$^-$. This obviated time-consuming azeotropic drying and application of any other additives. Furthermore, this procedure was successfully adapted

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Supporting information for this article is given via a link at the end of the document to Cu-mediated radiofluorination of (aryl)(mesityl)iodonium salts.[2i, 2j] Moreover, we demonstrated radiofluorination of aryl boronic acids in pure EtOH applying the alcohol-enhanced protocol for Cu-mediated radiofluorination.[2h] $^{18}F^-$ was eluted with an ethanolic solution of an appropriate salt directly into a mixture of the corresponding precursor and Cu source in DMA and the resulting solution was briefly heated under air affording radiolabeled arenes in moderate radiochemical yields (determined by HPLC).[6]

Recently, Scott et al. described ^{18}F-labeling in aqueous ethanol in the presence of K_2CO_3 and K2.2.2:[7] $^{18}F^-$ was eluted from an anion exchange resin with a solution of K_2CO_3 and K2.2.2 in 85% EtOH into a solution of the radiolabeling substrate in the same solvent and the resulting mixture was heated at 100 °C for 30 min furnishing the corresponding radiofluorinated compounds in fair to moderate RCYs. However, this simple and innovative procedure is limited to aliphatic ^{18}F-fluorinations and not applicable for radiolabeling of (hetero)aromatics. In addition, polar protic solvents can stabilize carbocations and consequently promote a shift from SN2 to SN1 ^{18}F-fluorination leading to a partial racemization at the secondary carbon, e.g. in the case of [^{18}F]FDG or [^{18}F]FLT. To elucidate if racemization occurs, we prepared [^{18}F]FDG according to reaction conditions reported.[7] In contrast to the reported results no ^{18}F-incorporation was observed in 85% EtOH. However, using pure EtOH as a reaction solvent afforded tetracetylated [^{18}F]FDG in RCYs of up to 55%. Subsequent hydrolysis with aqueous NaOH afforded [^{18}F]FDG together with 2-deoxy-2-[^{18}F]fluoro-D-mannose (20%). This formation of mannose showed that a partial shift to SN1 radiofluorination indeed took place.

Herein, we describe the first green protocol for metal-free SNAr radiofluorination in pure EtOH using only $^{18}F^-$ and *N,N,N*-trimethylammonium or 1,4-diazabicyclo[2.2.2]octane (DABCO)-derived precursors. In contrast to the "minimalist" radiofluorination procedure, the novel protocol does not require any evaporation step and completely avoids application of toxic MeOH as well as potentially hazardous aprotic solvents like DMF, DMSO or MeCN. This protocol was used for the synthesis of several labeled aldehydes and protected PSMA-selective ligands.[8]

Results and Discussion

Initially, 4-[^{18}F]fluorobenzaldehyde ([^{18}F]**1**),[9] a versatile radiolabeled building block,[9] was selected as a model compound. Radiolabeling was carried out as follows. [^{18}F]Fluoride was loaded onto an anion exchange resin. The resin was washed with EtOH before $^{18}F^-$ was eluted with an ethanolic solution of the corresponding *N,N,N*-trimethylanilinium triflate precursor. The reaction mixture was heated at 150 °C for 20 min. At such high temperature EtOH was completely in the gas phase and radiolabeling took place in the film on the reactor walls affording [^{18}F]**1** in 32% RCY. This yield, however, was significantly lower than RCYs obtained from the same precursor using the convenient "minimalist" protocol.[5] We reasoned that, while EtOH was obviously a suboptimal solvent for aromatic nucleophilic radiofluorination, the use of more activated substrates for radiolabeling could improve RCYs. Therefore, we turned to the preparation of 6-[^{18}F]fluoronicotinaldehyde ([^{18}F]**2**), a prosthetic group first described by Kügler et al..[10] Whereas the preparation of [^{18}F]**2** using trimethylamine as a leaving group had already been described,[11] we decided to evaluate 1,4-diazabicyclo[2.2.2]octane (DABCO) as an alternative leaving group in order to avoid handling of toxic and malodorous Me_3N. The corresponding triflate precursor was conveniently prepared by the direct reaction between 6-chloronicotine and DABCO followed by anion metathesis with TMSOTf. Radiofluorination of both precursors in pure EtOH proceeded smoothly to render the desired radiolabeled aldehyde in 65 and 44% RCY from the Me_3N- or DABCO-substituted precursor, respectively. For comparison, we produced [^{18}F]**2** using the on-cartridge protocol described by Basuli et al..[11] This procedure is a further development of the "minimalist" approach and allowed to prepare ^{18}F-labeled pyridines with electron-withdrawing substituent(s) like [^{18}F]**2** simply by slow elution of $^{18}F^-$ from a Cromafix PS-HCO_3 anion exchange cartridge, with a solution of the corresponding *N,N,N*-trimethylammonium precursor in MeCN/*t*BuOH (1/4). Using this protocol [^{18}F]**2** was prepared in RCYs of 55–70%. However, in contrast to previously published results, 40–50% [^{18}F]fluoride remained on the anion exchange cartridge. Moreover, although [^{18}F]**2** could be efficiently prepared, due to its low lipophilicity, its retention on a C18 or polymer reverse phase cartridge was insufficient for an efficient RP SPE purification. To increase the lipophilicity of the ^{18}F-labeled product a methoxy group was introduced in 2-position of the pyridine ring. This additional substituent allowed to easily purify 6-[^{18}F]fluoro-2-methoxynicotinaldehyde ([^{18}F]**3**) by convenient RP-SPE purification. Furthermore, radiolabeling of the appropriate Me_3N- and DABCO-substituted precursors afforded the novel radiolabeled building block, in high RCYs of 94 and 80%, respectively.

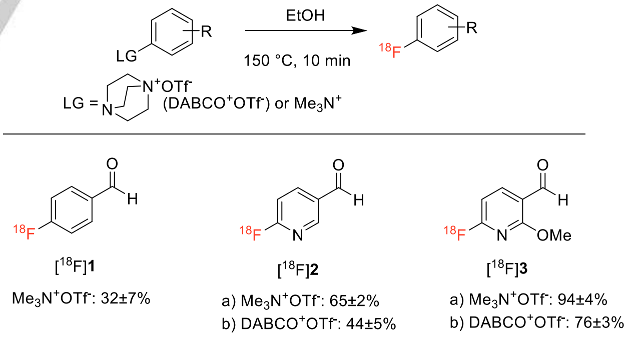

Figure 2: Preparation of 4-[^{18}F]fluorobenzaldehyde, 6-[^{18}F]fluoronicotinaldehyde, and 6-[^{18}F]fluoro-2-methoxy-nicotinaldehyde using "green" conditions. Conditions: $^{18}F^-$ (50–200 MBq) was eluted from an anion exchange resin with a solution of the appropriate precursor (5 mg) in anhydrous EtOH (500 µL) into a V-vial (5 mL) and the resulting solution was heated at 150 °C for 10 min. The reaction mixture was cooled to ambient temperature diluted with H_2O (1 mL) and analyzed by HPLC. Each experiment was carried out at least in triplicate.

Next the applicability of the novel protocol for the preparation of clinically relevant tracers was tested. First protected [^{18}F]DCFPyL was prepared. [^{18}F]DCFPyL was recently described as a PET probe for the visualization of the prostate specific membrane antigen which is overexpressed in e.g. prostate cancer.[12] The radiolabeled intermediate [^{18}F]**4** was prepared in 47% RCY from the appropriate Me_3N-substituted precursor.[13] Similarly, protected [^{18}F]JK-PSMA-7[8] which contains an additional methoxy group in the pyridine ring was prepared in 89% RCY from the Me_3N-substituted precursor. For the DABCO-substituted precursor a RCY of 31% was observed. Notably, protected [^{18}F]JK-PSMA-8[8] which differs from [^{18}F]JK-PSMA-7 only in the position of the methoxy group (in 4- instead of 2-position of the pyridine ring) could be prepared only in 15% RCY. [^{18}F]**7**[8] was prepared in > 97% RCY. This high RCY was enabled by the electron poor nature of the pyridazine ring.

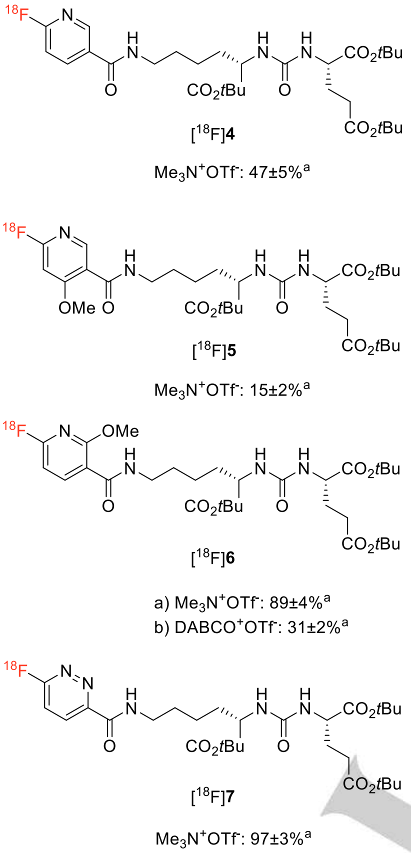

Figure 3: Radiolabelled protected PSMA ligands. a) Conditions: $^{18}F^-$ (50–500 MBq) was eluted from an anion exchange resin with a solution of the appropriate precursor (5 mg) in anhydrous EtOH (500 µL) into a V-vial (5 mL) and the resulting solution was heated at 150 °C for 20 min. The reaction mixture was cooled to ambient temperature diluted with H_2O (1 mL) and analyzed by HPLC. Each experiment was carried out at least in triplicate.

Conclusions

The described „minimalist green" approach to S_NAr ^{18}F-fluorination enables the efficient preparation of radiolabeled highly activated (hetero)aromatics in environmentally benign and non-toxic EtOH from only $^{18}F^-$ and the appropriate radiolabeling precursor without any evaporation steps. This procedure eliminates the need for time- and cost-intensive analytical determination of residual solvents and reagents. In summary the described method represents an important step towards green radiochemistry.

Experimental Section

General chemistry

Commercially available reagents and solvents were purchased from Alpha Aesar, VWR-International and Sigma-Aldrich and used without further purification. Sep-Pak Accell Plus QMA carbonate plus light cartridges, 40 mg sorbent per cartridge were purchased from Waters GmbH (Eschborn, Germany). HPLC analyses and purifications were carried out on Dionex Ultimate 3000 System with Ultimate 3000 Diode Array Detector coupled in series with Berthold NaI detector. Chromolith® SpeedROD RP-18e column (Merck, Darmstadt Germany), 50×4.6 mm, was used for analyses of the radiofluorinated products. ^{18}F-Labeled compounds were identified by co-injection of with the corresponding ^{19}F-reference compounds and analyzed using the following gradient: 0–2 min: 5% MeCN, 2–2.5 min: 5→70% MeCN, 2.5–7 min: 70% MeCN, 7–8 min: 70→5% MeCN, 8–9 min: 5% MeCN; flow rate: 3.0 ml/min.

Nuclear magnetic resonance spectroscopy (NMR)

Bruker Avance Neo (400 MHz) was used for ^{1}H-NMR measurements. ^{1}H chemical shifts are reported in ppm and calibrated against residual peaks of deuterated solvents. Higher-order NMR spectra were approximately interpreted as first-order spectra, where possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, and br = broad. Coupling constants (J) were reported in Hertz (Hz).

Bruker Avance Neo (400 MHz) was used for measurement of ^{13}C-NMR-ATP (attached proton test) spectra. ^{13}C chemical shifts are reported in ppm and calibrated against residual peaks of deuterated solvents.

Bruker Avance Neo (400 MHz) was used for measurement of ^{19}F-NMR. ^{19}F chemical shifts are reported in ppm. No calibration was carried out.

Thin layer chromatography (TLC)

For TLC Merck precoated aluminum sheets, 0.25 mm Sil G/UV254 were used and viewed under UV light and/or stained by 10% phosphomolybdic acid in EtOH.

All reactions were carried out with magnetic stirring and all air- or moisture-sensitive substrates and/or reagents, were handled in oven-dried glassware under argon.

1-(5-Formylpyridin-2-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate

A solution of 6-chloronicotinaldehyde (1.25 g, 8.83 mmol, 1.00 eq.) and DABCO (2.97 g, 26.50 mmol, 3.00 eq.) in toluene (30 mL) was stirred for

2.5 h. The resulting suspension was filtered; the solid was washed with CH_2Cl_2, Et_2O and EtOAc (20 mL of each) and dried under reduced pressure affording 1-(5-Formylpyridin-2- yl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (1.90 g, 7.50 mmol, 84%) as an off-white solid.

TMSOTf (4.00 mL, 22.10 mmol, 3.71 eq.) was added to a suspension of 1-(5-Formylpyridin-2-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (1.50 g, 5.92 mmol, 1.00 eq.) in CH_2Cl_2 (20 mL) and stirred for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O and filtered. The filter cake was washed with Et_2O and EtOAc (20 mL of each) and dried under reduced pressure To give the title compound (2.98 g, 5.77 mmol, 97%) as a colorless solid.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (ppm) = 10.22 (s, 1H, H3), 9.20 (d, *J* = 2.1 Hz, 1H, H-4), 8.72 (d, *J* = 6.4 Hz, 1H, H-2), 8.27 (d, *J* = 8.6 Hz, 1H, H-1), 4.32 – 4.15 (m, 6H, H-6, H-6', H-6''), 3.79 – 3.59 (m, 6H, H-5, H-5', H-5'').

^{13}C NMR [101 MHz, $(CD_3)_2SO$] δ (ppm) = 191.00, 157.57, 150.45, 141.50, 133.16, 117.16, 52.91, 43.97.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{12}H1_6N_3O^+$: 218.12285; found: 218.12867.

HRMS (ESI): *m/z* $[M]^-$ calcd for $CO_3F_3S^-$: 148.95258; found: 148.95234

5-Formyl-6-methoxy-*N,N,N*-trimethylpyridin-2-aminium triflate

To 6-chloro-2-methoxynicotinaldehyde (3.03 g, 17.65 mmol, 1.00 eq.) a 2 M Me_3N in THF (30.80 mL, 61.78 mmol, 3.50 eq.) was added and the resulting mixture was stirred for 2 h. The precipitate was filtered, washed with CH_2Cl_2 and Et_2O (20 mL of each) and dried under reduced pressure affording 5-formyl-6-methoxy-*N,N,N*-trimethylpyridin-2-aminium chloride (3.34 g, 14.48 mmol, 82%) as a colorless solid.

TMSOTf (6.47 mL, 35.64 mmol, 3.00 eq.) was added to a suspension of 5-formyl-6-methoxy-*N,N,N*-trimethylpyridin-2-aminium chloride (2.74 g, 11.88 mmol, 1.00 eq.) in CH_2Cl_2 (20 mL) and the resulting mixture was stirred for 16 h. The precipitant was filtered off, the filter cake was washed with Et_2O (20 mL) furnishing the title compound (2.92 g, 8.49 mmol, 71%) as a colorless solid.

^{1}H NMR [400 MHz, $(CD_3)_2SO + CDCl_3$] δ (ppm) = 10.26 (s, 1H, H-3), 8.38 (d, *J* = 8.0 Hz, 1H, H-2), 7.73 (d, *J* = 8.0 Hz, 1H, H-1), 4.12 (s, 3H, H-4), 3.65 (s, 9H, H-5, H- 5', H-5'').

^{13}C NMR [101 MHz, $(CD_3)_2SO + CDCl_3$] δ (ppm) = 186.54, 162.42, 157.23, 142.29, 119.87, 54.72, 54.32.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{10}H_{15}N_2O_2^+$: 195.11282; found: 195.11279.

1-(5-Formyl-6-methoxypyridin-2-yl)-1,4-diazabicyclo[2.2.2]octan-1- ium triflate

A solution of 6-chloro-2-methoxy-nicotinaldehyde (1.50 g, 8.77 mmol, 1.00 eq.) and DABCO (2.95 g, 26.30 mmol, 3.00 eq.) in toluene (30 mL) was stirred for 1 h. The resulting suspension was filtered, the solid was washed with CH_2Cl_2, Et_2O and pentane (20 mL of each) and dried under reduced pressure furnishing 1-(5-formyl-6-methoxypyridin-2-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (1.86 g, 6.56 mmol, 75%) an off-white solid.

TMSOTf (4.00 mL, 22.10 mmol, 4.19 eq.) was added to a suspension of 1-(5-formyl-6-methoxypyridin-2-yl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (1.50 g, 5.28 mmol, 1.00 eq.) in CH_2Cl_2 (20 mL) DCM and the reaction mixture was stirred for 2 h. The suspension was filtered, the precipitate was washed with Et_2O and EtOAc (20 mL of each) and dried under reduced pressure affording the title compound (1.55 g, 2.84 mmol, 53%) as an off-white solid.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (ppm) = 10.22 (s, 1H, H-3), 8.46 (d, *J* = 8.2 Hz, 1H, H-1), 7.74 (d, *J* = 8.1 Hz, 1H, H-2), 4.10 (s, 3H, H-4), 3.97 – 3.87 (m, 6H, H-6, H-6', H-6''), 3.25 – 3.16 (m, 6H, H-5, H-5', H-5'').

^{13}C NMR [101 MHz, $(CD_3)_2SO$] δ (ppm) = 187.79, 162.17, 156.63, 143.04, 119.97, 109.32, 55.08, 53.62, 45.06.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{12}H_{20}N_3O_2^+$: 238.15501; found: 238.15497.

HRMS (ESI): *m/z* $[M]^-$ calcd for $CO_3F_3S^-$: 148.95258; found: 148.95225.

6-Fluoro-2-methoxynicotinaldehyde

MeCN (2 mL) was added to 5-formyl-6-methoxy-*N,N,N*-trimethylpyridin-2-aminium triflate (0.47 g, 1.37 mmol, 1.00 eq.) and TBAF×4 *t*BuOH (0.91 g, 1.63 mmol, 1.2 eq.) and the resulting suspension was stirred by the bubbling of argon for 15 min. After that, the resulting solution was diluted with Et_2O (20 mL) and was washed with H_2O and brine (10 mL of each ×3), dried and concentrated under reduced pressure. The residue was purified by low temperature crystallization followed by bulb-to-bulb destillation affording the title compound as a colorless solid (72 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 4.07 (s, 3H) 6.59 (ddd, *J* = 8.2, 2.6, 0.6 Hz, 1H) 8.24 (t, *J* = 8.2 Hz, 1H) 10.28 (d, *J* = 0.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 187.23, 166.36 , 166.40 (*J* = 251.5 Hz), 142.90 (*J* = 10.0 Hz), 116.59 (J = 5.0 Hz), 101.77 (*J* = 36.2 Hz).

^{19}F NMR (376.5 MHz, $CDCl_3$) δ (ppm) = -56.81.

Radiochemistry

All radiosyntheses were carried out under ambient air using anhydrous EtOH stored over molecular sieves (available from "Acros" or "Aldrich").[^{18}F]Fluoride was produced by the $p^{18}O(p,n)^{18}F$ nuclear reaction by bombardment of enriched [^{18}O]water with 16.5 MeV protons using a BC1710 cyclotron (The Japan Steel Works Ltd., Shinagawa, Japan) at the INM-5 (Forschungszentrum Jülich). Each radiochemical experiment was carried out at least in triplicate.

Radiofluorination – General Procedure

[^{18}F]F$^-$ (50–500 MBq) was loaded from the male side on a QMA cartridge, preconditioned with water (1 mL). Afterwards the resin was flushed with EtOH (1 mL) again from the male side. Next, [^{18}F]fluoride was eluted with a solution of the corresponding precursor (5 mg) in EtOH (500 µL) from the female side into a reaction vessel. The vessel was sealed and the reaction mixture was heated at 150 °C for 10–20 min. The reaction mixture was cooled to room temperature, diluted with H_2O (1 mL) and analyzed by HPLC.

Acknowledgements

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Keywords: radiofluorination • green chemistry • sustainability • (hetero)aromatics • minimalist approach • PSMA

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Minimalist approach meets green chemistry: Synthesis of ^{18}F- labeled (hetero)aromatics in pure ethanol