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Synthesis of [^{18}F]-Labeled EF3 [2-(2-Nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)-acetamide], a Marker for PET Detection of Hypoxia

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Abstract—[^{18}F]-2-(2-Nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)-acetamide ([^{18}F]-EF3) has been prepared, in 65% chemical yield and 5% radiochemical yield, by coupling 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate **1** with [^{18}F]-3,3,3-trifluoropropylamine **7**. This original radiolabelled key-synthon was obtained in 40% overall chemical yield by oxidative [^{18}F]-fluorodesulfurization of ethyl *N*-phthalimido-3-aminopropane dithioate **4**, followed by deprotection with hydrazine of the resulting [^{18}F]-*N*-phthalimido-3,3,3-trifluoropropylamine **5**. All the process was performed within 90 min, from the [^{18}F]-HF production in the cyclotron to the purification of the final target.

Introduction

A low oxygen concentration in solid tumor cells inevitably increases the resistance to radiotherapy.[1] Therefore, the development of clinically useful methods for measuring tissue hypoxia has been a focus of intensive research,[2] in view to provide prognostic information, and indication to select for alternative therapies. Recent progress in microelectrode techniques permitted to measure the oxygen partial pressure in tumors;[3,4] however, this method is invasive and has important limitations considering its sensitivity and specificity. An alternative method is based on the use of hypoxia markers (chemical radiosensitizers)[5,6] and detection by medical imaging techniques, as recently reviewed.[7–9] 2-Nitroimidazole derivatives constitute an important class of such markers, exemplified with misonidazole, etanidazole, and erythronitroimidazole (Scheme 1); their particular reductive metabolism in hypoxic cells (with cytochrome P450 reductase) leads to the formation of intermediates which can covalently bind to cellular macromolecules.[10–13] Consequently, the bioreduction of 2-nitroimidazoles provides an unrivalled way of labelling hypoxic cells in vivo.[14] In this case, the marked cells can be detected by immunofluorescence on tissue sections or by flow cytometry, using for both techniques specific antibodies.

Tagged with an appropriate radioactive isotope, the cell-bound metabolites of 2-nitroimidazoles could also be detected by nuclear medicine techniques. Thus, [^{18}F]-labelled 2-nitroimidazoles have been proposed to visualize hypoxic cells by positron emission tomography (PET), a non-invasive, highly sensitive, and short-time consuming, medical imaging technique.[15] Accordingly, [^{18}F]-fluoromisonidazole,[16–19] [^{18}F]-fluoroetanidazole,[20] and [^{18}F]-fluoroerythronitromidazole[21,22] (Scheme 1) were prepared, and used for the localisation and quantification of hypoxia. However, these PET tracers, obtained by replacing a methoxyl or hydroxyl group of the parent radiosensitizers with [^{18}F]-fluorine, present different (bio)chemical properties regarding the corresponding unlabelled compounds.

Some years ago, tri- and pentafluorinated nitroimidazole derivatives,[23] called EF3 and EF5 respectively (Scheme 1), were synthesized. Comparatively to misonidazole, the prototype of hypoxia-binding markers, these two

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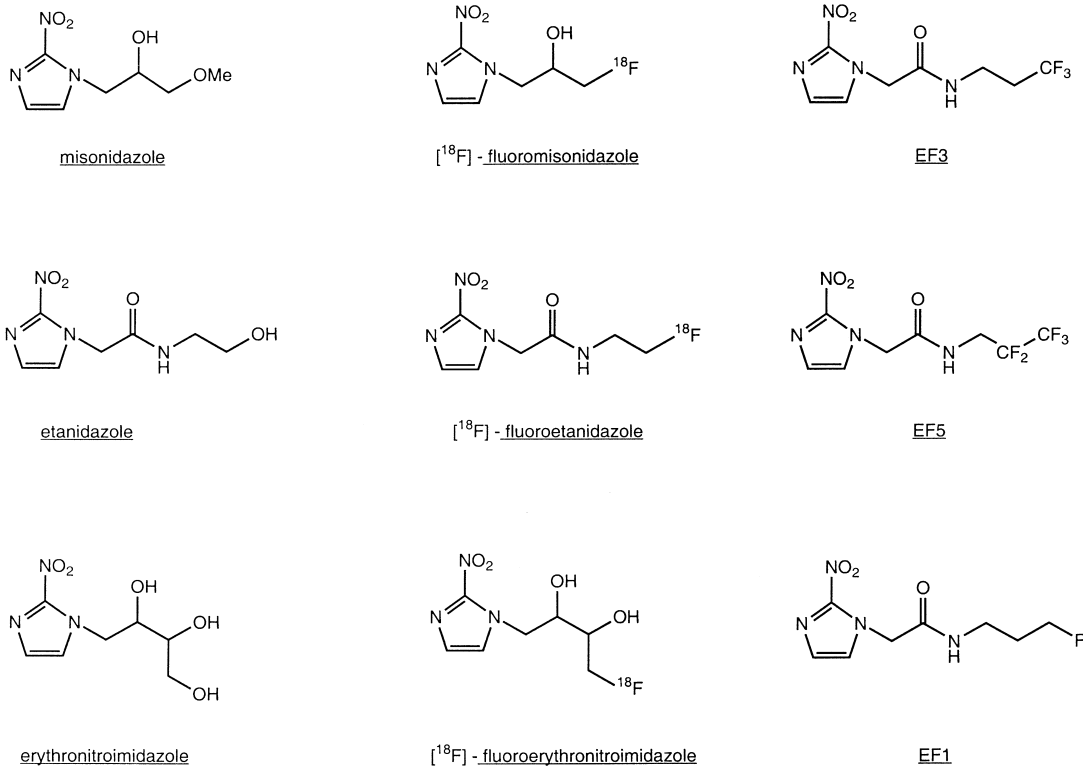


Scheme 1.

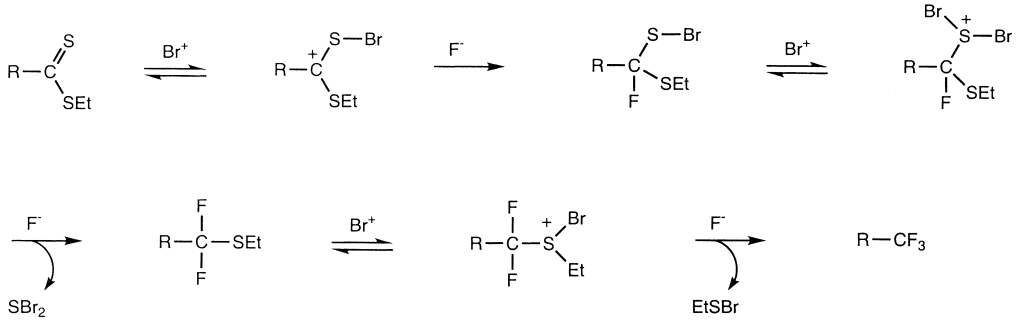
compounds offer several advantages:[24,25] they have a more specific binding to hypoxic cells,[26] their binding does not too much depend on the intracellular level of reductase systems,[27] their binding is oxygen-dependent, and they present a reduced toxicity comparatively to other chemical probes. Moreover, specific antibodies are available against EF3-EF5 only, allowing the co-existing control of hypoxia by biopsic measurements and imaging techniques. In view of the high sensitiviy and specificity of these markers, the [^{18}F]-fluorine labelling of EF3 and EF5 was examined to produce new PET tracers. Interestingly, in this case, the unlabelled and labelled compounds would have exactly the same properties.

The [^{18}F]-labelling of a perfluoroalkyl moiety is a difficult task because the classical nucleophilic displacement of a leaving group by [^{18}F]-fluoride anion (as illustrated with the synthesis of [^{18}F]-EF1[28]) cannot be readily applied. Recently, the group of Koch succeeded in labelling EF5 by electrophilic addition of [^{18}F]-F_2 to 2-(2-nitroimidazol-1-yl)-*N*-(2,3,3-trifluoroallyl)-acetamide.[29] In a parallel course, we developed the oxidative fluorodesulfurization method for the preparation of [^{18}F]-EF3.[30] The details of this original way to produce [^{18}F]-labelled trifluoromethylated compounds, in functionalized aliphatic series, are described in this article. Our work led to the preparation of an interesting labelled key-intermediate, namely [^{18}F]-3,3,3-trifluoropropylamine.

Strategy

As far as [^{18}F]-labelling is concerned, the classical methods of trifluoromethylation based on 'CF_3^-', 'CF_3^+', or 'CF_3•' synthetic equivalents could not be applied.[31] The usual reagent for [^{18}F]-labelling of radiopharmaceuticals is [^{18}F]-potassium fluoride added with [2,2,2] kriptofix.[32,33] This reagent has been used to prepare ethyl [^{18}F]-trifluoroacetate from ethyl 2-bromo-2,2-difluoroacetate,[34] and [^{18}F]-2-trifluoromethyl-4,4-dimethyl-2-oxazoline from 2-bromo-2,2-difluoromethyl-4,4-dimethyl-2-oxazoline.[35] This nucleophilic substitution on CF_2Br- precursors with [^{18}F]-F^- requires hard conditions, and is limited to specific compounds in which the competition with an elimination reaction cannot occur. To our knowledge, the two previous examples are the only ones described in the literature concerning the [^{18}F]-labelling of a trifluoromethyl group.

The direct transformation of a carboxylic acid into CF_3 normally requires sulfur tetrafluoride as the fluorinating agent,[36,37] a very strong and toxic reagent which would not be easily labelled with [^{18}F]-fluorine. Recently, an alternative solution has been brought to produce CF_3 groups from carboxyl precursors, making use of sulphurated derivatives (orthothioesters[38] and dithioesters) treated with an HF-reagent in the presence of an oxidant (halonium ions) (Scheme 2). This mild reaction, called 'oxidative desulfurization-fluorination', has been well developed by the group of Hiyama.[39–46] However the method appears to be limited to trifluoromethyl-aromatic[38,39] and conjugated[44] derivatives, and to trifluoromethyl ethers[40,45] (O-CF_3) and amines[41–43,46] (N-CF_3); no examples were disclosed in the aliphatic series, with functionalized precursors, such as *N*-protected aminoacid derivatives. Nevertheless, we speculated that this method would be well adapted for our purpose, because high selectivity could result from the specific interaction



Scheme 2.

between the sulphurated precursor (soft nucleophile) and the oxidant (soft electrophile), giving an intermediate activated towards the substitution with fluoride. Moreover, the source of soft fluoride is an HF-reagent, such as tetrabutylammonium dihydrogen trifluoride ($TBA^+ H_2F_3^-$),[47] or pyridinium poly(hydrogen fluoride)[48] (30% pyridine–70% HF); such reagents are dramatically less basic than potassium fluoride added with kriptofix, and would thus limit the occurrence of side-reactions.

Several requirements have to be fulfilled for developing the synthesis of [^{18}F]-EF_3 by oxidative fluorodesulfurization: (i) the production of the appropriate [^{18}F]-labeled HF-reagents; (ii) the preparation of the required dithioester precursors; (iii) the development of fluorination conditions in aliphatic series avoiding competitive side-reactions, such as eliminations; (iv) the application of the method to the production of [^{18}F]-EF3 in the last synthetic step, or via an advanced [^{18}F]-labeled key-intermediate; (v) the consideration of the half-life of [^{18}F]-fluorine (110 min) to design short-time syntheses (a maximum of 5 h, from the production of [^{18}F]-HF in the cyclotron to the purified final target is acceptable); (vi) the production of [^{18}F]-EF3 with good radiochemical yields and appropriate activity for PET detection.

Results

Production of the [^{18}F]-labeled HF-reagents

[^{18}F]-HF was produced at the cyclotron by irradiating [^{18}O]-enriched water with 16.5 MeV protons.[49] The [^{18}F]-fluoride was separated from the [^{18}O]-enriched water by trapping on an ion exchange resin. Organic solvents (CH_3CN and CH_2Cl_2) were passed through the resin to remove all traces of water. Then [^{18}F]-$TBA^+ H_2F_3^-$ was obtained by fluorine exchange with unlabelled[47] $TBA^+ H_2F_3^-$ (Scheme 3): the resine was eluted with a solution of $TBA^+ H_2F_3^-$ in dry dichloromethane. This process, performed within 15 min, gave a solution of $TBA^+ H_2F_3^-$ with 82% (decay corrected) of [^{18}F] incorporation at the laboratory scale.[50]

The [^{18}F]-poly(hydrogen fluoride) pyridinium was prepared by eluting the [^{18}F]-fluoride trapped on the resin with an aqueous solution of potassium carbonate. The resulting solution of [^{18}F]-KF was concentrated to dryness, then treated with unlabeled[48] $(HF)_n$. pyridinium. This process, performed within 15 min, gave pure [^{18}F]-$(HF)_n$. pyridinium (Scheme 3) with 93% (decay corrected) of [^{18}F] incorporation at the laboratory scale.[51]

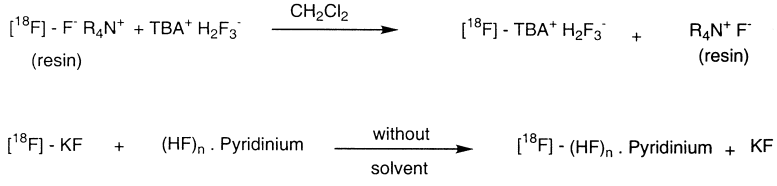
The capacity of these [^{18}F]-reagents to label CF_2 and CF_3 groups in aromatic series has been previously established.[50,51]

CF_3-Labeling of an aliphatic model compound

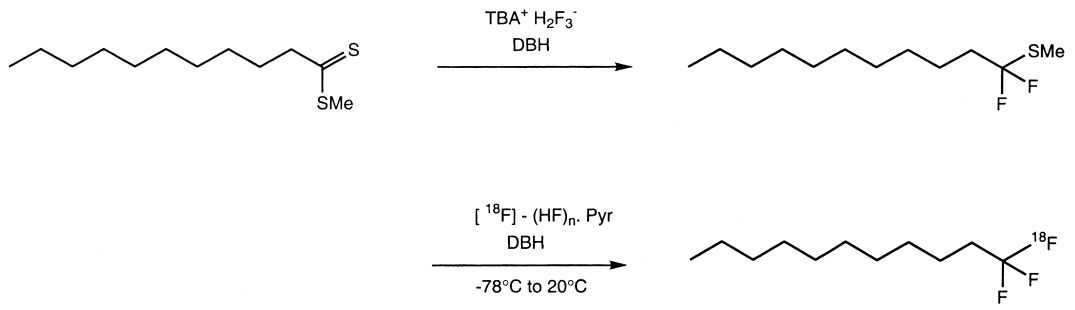
Methyl undecanedithioate (Scheme 4) was obtained by addition of carbon disulfide to 1-decylmagnesium bromide, followed by reaction with iodomethane.

Treatment of methyl undecanedithioate with tetrabutylammonium dihydrogen trifluoride in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBH) as the oxidant (CH_2Cl_2, low temperature to room temperature; excess of fluorinating agent) led to 1,1-difluoro-1-thiomethylundecane resulting from uncomplete fluorination. Similar results have been reported by Hiyama in the case of aliphatic orthothioester precursors.[52–54]

On the other hand, by using poly(hydrogen fluoride) pyridinium as the fluorinating agent, complete substitution occurred, and 1,1,1-trifluoroundecane was the major product (Scheme 4); about 80% yield of trifluoromethylated compound could be isolated (column chromatography) when the dithioester precursor was treated



Scheme 3.



Scheme 4.

with 15 equiv of $(HF)_n$. pyridinium and 3.5 equiv of DBH in CH_2Cl_2 at −78 °C. Under such conditions, electrophilic bromination of the aliphatic chain,[52,53] and elimination reactions[54] were not observed.

The process applied to $[^{18}F]$-$(HF)_n$. pyridinium gave $[^{18}F]$-1,1,1-trifluoroundecane with a radiochemical yield of 4.3% at the laboratory scale. Therefore, this method of $[^{18}F]$-perfluorination was applied to the precursor **3** of EF3.

Synthesis of $[^{18}F]$-EF3: direct route

According to our previously established strategy, the direct precursor of $[^{18}F]$-EF3 is the dithioester **3a** (R = H) (Scheme 5). This compound could be obtained by coupling the tetrafluorophenyl ester[55] **1** of 2-(2-nitro-imidazol-1-yl) acetic acid[20] with ethyl 3-aminopropane-dithioate **2a**[56] in acetonitrile at room temperature. After chromatography on silica gel, the compound **3a** was isolated in 85% yield and well characterized as usual (see Experimental).

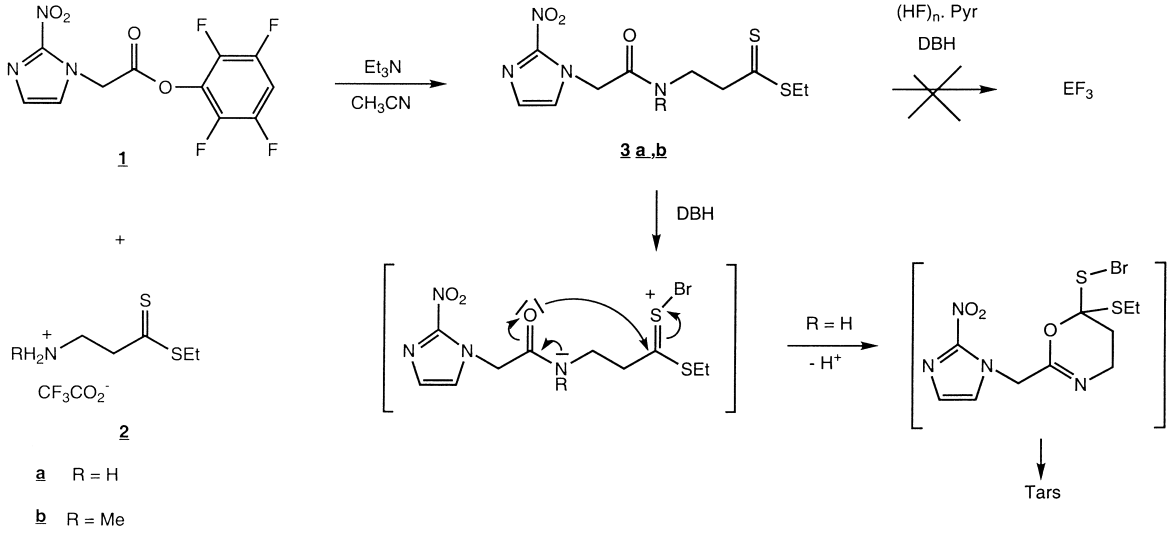
Treatment of the dithioester **3a** with an excess of $(HF)_n$. pyridinium in the presence of DBH, or *N*-iodosuccinimide (NIS) as the oxidant, gave untractable mixtures; the same disappointing results were obtained with $TBA^+ H_2F_3^-$ and DBH or NIS. This could result from intramolecular nucleophilic attack of the amide function on the activated dithioester moiety, followed by deprotonation and degradation of the resulting cyclic-1,3-iminoether (Scheme 5) under the oxidative fluorodesulfurization conditions.

The related *N*-methyl precursor **3b** has been similarly prepared (Scheme 5) from the activated ester **1** and ethyl 3-(methylamino) propanedithioate **2b**. Compound **2b** was obtained in six steps from 3-(methylamino) propionitrile, according to the procedure we established for β-alanine dithioester:[56] the method is based on the nucleophilic substitution of a thioacyl-*N*-phthalimide intermediate with ethanethiol (Scheme 6).

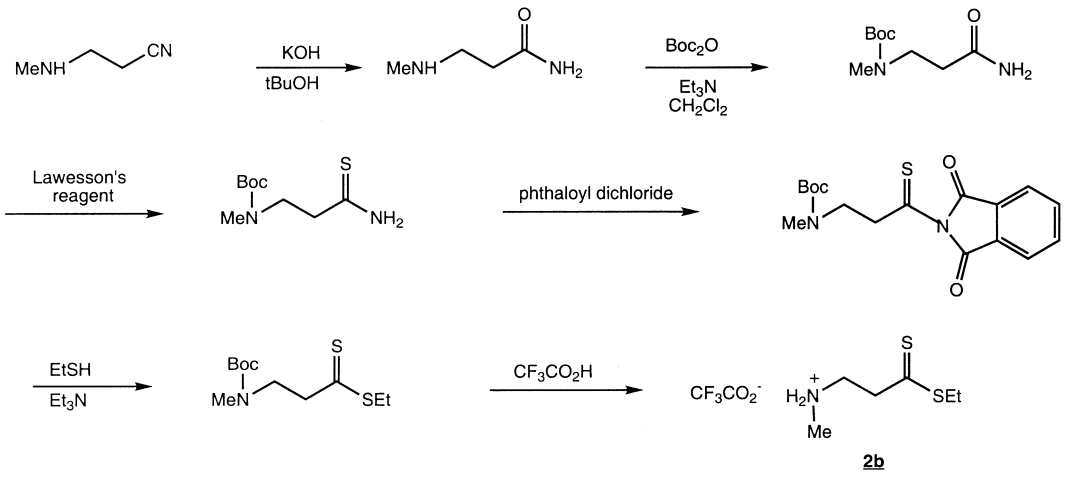
The transformation of the *N*-methyl precursor **3b** into *N*-methyl EF3 also failed, whatever the experimental conditions of fluorination could be. In both cases (precursors **3a** and **3b**), traces of $[^{18}F]$-nitroimidazole derivatives could not be detected in the crude mixtures by radio-TLC (thin layer chromatography), when using $[^{18}F]$-labeled fluorinating agents in the synthetic process. Consequently, another strategy was developed, based on the production of $[^{18}F]$-3,3,3-trifluoropropylamine as the key-intermediate.

Synthesis of $[^{18}F]$-EF3: indirect route

The reaction of ethyl 3-aminopropane dithioate **2a** (trifluoroacetate salt)[56] with $(HF)_n$. pyridinium and DBH



Scheme 5.



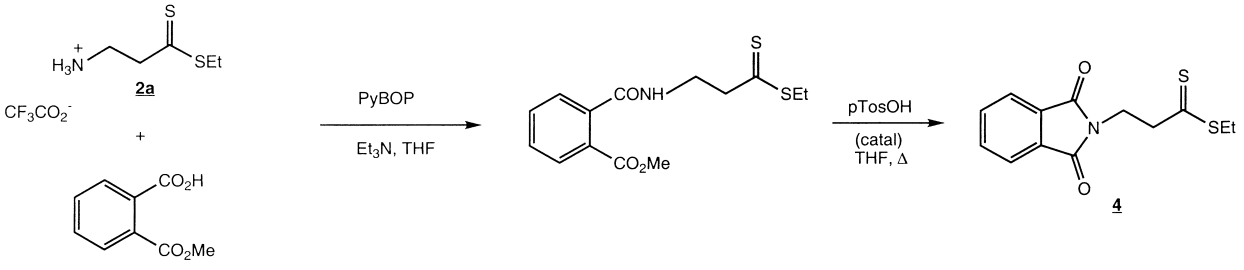
Scheme 6.

gave less than 5% yield of isolated 3,3,3-trifluoropropylamine (hydrofluoride salt). The Boc-protected precursor,[56] similarly treated, led to untractable mixtures. Therefore, we selected the phthalimido group as the protecting group susceptible to survive under the oxidative fluorodesulfurization conditions.

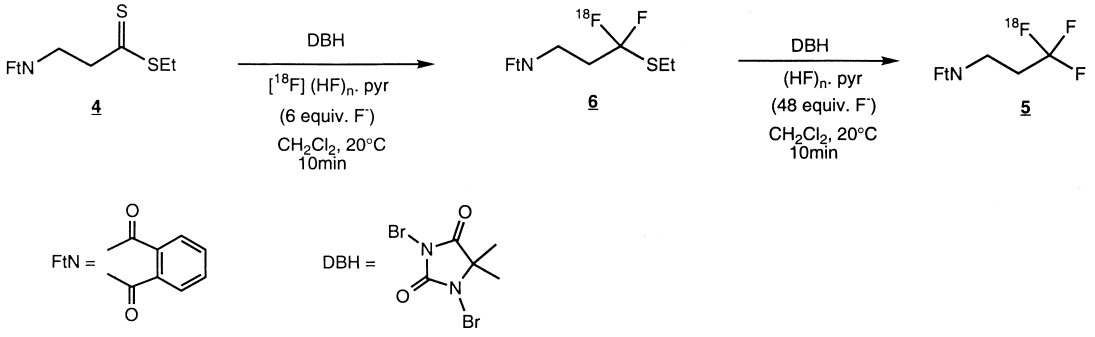
The primary amine of **2a** was readily transformed into the corresponding phthalimide **4** by reaction with 2-(methoxycarbonyl) benzoic acid activated by PyBOP, followed by acid-catalyzed cyclization of the resulting phthalamic ester[57] (Scheme 7).

Pure *N*-phthalimido-3,3,3-trifluoropropylamine **5** could be obtained in about 50% chemical yield by reacting **4** with a large excess of $(HF)_n$.pyridinium ($\geq$50 equiv) in the presence of DBH (4 equiv), in dichloromethane at room temperature (Scheme 8). In the radiolabeling process, we first used 6 equiv of [^{18}F]-$(HF)_n$.pyridinium (10 min) to produce the [^{18}F]-labeled difluoro-intermediate **6**; then addition of 48 equiv of unlabeled $(HF)_n$.pyridinium (10 min) transformed [^{18}F]-**6** into [^{18}F]-**5**. The total reaction time, from **4** to *N*-phthalimido-[^{18}F]-3,3,3-trifluoropropylamine **5**, was 30 min, including the purification by column chromatography on neutral alumina with CH_2Cl_2 and the concentration of the solution. The radiochemical yield, determined by radio-TLC was 5.6% (decay corrected) at the laboratory scale.

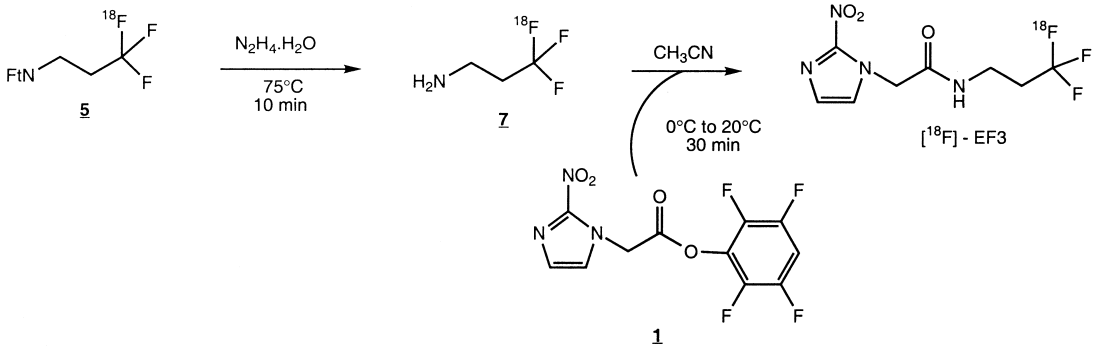
The next step was the deprotection of the phthalimido group of [^{18}F]-**5** to furnish [^{18}F]-3,3,3-trifluoropropylamine **7** (Scheme 9). Treatment of [^{18}F]-**5** with aqueous



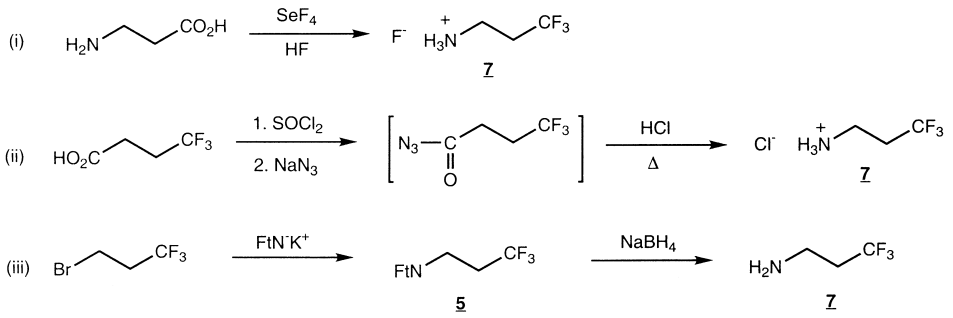
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

hydrazine at 75 °C led to the rapid formation of the free amine [^{18}F]-**7** which was removed from water by distillation under an argon stream, and condensed into an ice-cooled acetonitrile solution of 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate **1** (Scheme 9) to give [^{18}F]-EF3 ([^{18}F]-2-(2-nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl) acetamide) in about 70% chemical yield. The duration of the process, from [^{18}F]-**5** to [^{18}F]-EF3, was 40 min; 65% (decay corrected) of the initial radioactivity of **5** was recovered in the final target, as determined by radio-TLC. [^{18}F]-EF3 prepared at the 10^{-2} mmol scale was identified by comparison with an unlabeled authentic sample.

Synthesis of unlabeled EF3

'Cold' EF3 was prepared, similarly to [^{18}F]-EF3, by condensing the 'cold' amine **7** with the activated ester **1** (Scheme 9).

The preparation methods of **7** described in the literature could not be easily applied, i.e. (i) the reaction of β-alanine with SeF_4 carried out in hydrogen fluoride;[58] (ii) the Curtius rearrangement of 4,4,4-trifluorobutyryl azide obtained in situ from 4,4,4-trifluorobutyric acid.[59] In our hands, this method gave only a few percent yields of the hydrochloride salt of **7**. Thus, we developed an alternative two-step route, starting from 1-bromo-3,3,3-trifluoropropane (Scheme 10, method iii): substitution with potassium phthalimide in DMSO gave **5** which phthalimido group was deprotected by reduction with sodium borohydride in aqueous isopropanol.[60] The amine **7**, recovered in 45% overall yield (as hydrochloride salt) reacted with **1** to quantitatively furnish EF3.

Conclusion

The successful synthesis of [^{18}F]-EF3 relies upon the rapid coupling reaction of the activated ester **1** of 2-(2-nitroimidazol-1-yl)acetic acid with [^{18}F]-3,3,3-trifluoropropylamine **7**. This novel key-synthon would be useful in other radiosyntheses.

The preparation of [^{18}F]-3,3,3-trifluoropropylamine **7** was realized in three steps from ethyl *N*-phthalimido-3-aminopropane dithioate **4**, by oxidative [^{18}F]-fluorodesulfurization and hydrazinolysis of the resulting [^{18}F]-*N*-phthalimido-3,3,3-trifluoropropylamine **5**, with an overall chemical yield of about 40%, and within 60 min since the production of [^{18}F]-HF in the cyclotron (Table 1). At the laboratory scale (0.01 − 0.02 mmol; [^{18}F]-starting activity < 30 mCi), the radiochemical yield was of about 5% (Table 2, entries 1 and 2), giving a specific activity of the free amine [^{18}F]-**7** of 58 mCi/mmol. In one experiment (entry 3) using 880 μCi of [^{18}F]-HF as labeling source, we recovered 65 μCi of [^{18}F]-**5** (= 76 μCi, decay corrected), corresponding to a radiochemical yield of 8.6%, and a specific activity of 74 mCi/mmol. Comparatively to the synthesis of [^{18}F]-EF5 actually made by electrophilic perfluorination,[29] which gave a radiochemical yield of about 10%, our results, based on nucleophilic perfluorination, appear quite similar.

Extrapolation to the use of 1 Ci of [^{18}F]-HF, as it should be handled in an automatized system, would produce about 15 mCi of purified EF3 (injectable dose for one patient); this value is more than enough for practical application in detection and quantification of hypoxia.

Table 1.

[^{18}F] Compound	Activity (d.c.)[a]	mmol	Chemical yield(%)	Process duration
$(HF)_n$.pyridinium	28 mCi			20 min
Ft-amine **5**	1.24 mCi (1.5 mCi)	0.021	50	30 min
Free amine **7**	0.982 mCi (1.2 mCi)	0.017	80	10 min
EF3	0.639 mCi (0.78 mCi)	0.011	65	30 min

[a]d.c. = Decay corrected.

Table 2.

Entry	[^{18}F]-$(HF)_n$ Pyr. activity	[^{18}F]-**5** activity (d.c.)	Radiochemical yield[a]
1	28 mCi	1.30 mCi (1.58)	5.6%
2	28 mCi	1.00 mCi (1.22)	4.4%
3	880 μCi	65 μCi (76)	8.6%

[a]Activity of isolated **5**/activity of [^{18}F] fluoride introduced.

All the process for [^{18}F]-EF3 production (four steps) could be easily performed within 90 min, from [^{18}F] F^- production to final purification, giving the target molecule in 26% overall chemical yield and about 5% radiochemical yield.

Experimental

Solvents were dried before use. Reagents (from Acros, Fluka or Aldrich) were used as purchased. Melting points (uncorrected) were determined on an Electrothermal apparatus. ^{1}H (200 or 300 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on Varian Gemini 200 and 300 spectrometers; ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were recorded on Bruker AM-500 and ^{19}F (282 MHz) on Varian Gemini 300 spectrometer. Chemical shifts are reported as δ values (ppm) downfield from TMS. The mass spectra (FAB or CI modes) were obtained on a Finnigan MAT TSQ-70 instrument. IR spectra were obtained using a Biorad FTS 135 spectrometer calibrated with polystyrene. TLC were carried out using silicagel 60 F_{254} (0.2 mm, Merck) and spots were visualised by UV. Silica gel 60, mesh size 0.04–0.063 mm (Merck), was used for column chromatography. [^{18}F]-Fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction on an enriched [^{18}O]-water target (2.0 mL) using the IBA 'Cyclone 30' cyclotron. Radio-TLC were monitored with a Berthold TLC-Linear Analyser.

[^{18}F]-Tetrabutylammonium dihydrogen trifluoride. 22.4 mCi of [^{18}F]-HF in [^{18}O]-water were deposited on the ion exchange resin (BIO-RAD AG-1X8). After removal of [^{18}O]-water, the resin was rinsed with acetonitrile (200 μL) followed by dichloromethane (200 μL). Then, [^{18}F]-fluoride was eluted two times with a solution of 25 μL $TBAH_2F_3$ (wt 82% in 1,2-dichloroethane) in 200 μL dichloromethane and a third time with solution of 31 μL $TBAH_2F_3$ (wt 82% in 1,2-dichloroethane) in 200 μL dichloromethane. This process allowed the recovery of 16 mCi of [^{18}]-fluoride in the form of [^{18}F]-$TBAH_2F_3$ (0.22 mmol) (82% decay corrected, 15 min).

[^{18}F]-Poly(hydrogen fluoride)pyridinium. 96 mCi of [^{18}F]-HF in [^{18}O]-water were deposited on the ion exchange resin (BIO-RAD AG-1X8). After removal of [^{18}O]-water, the [^{18}F]-fluoride was eluted with an aqueous solution of K_2CO_3 (2.3 mg in 400 μL). The solution was then heated under argon flow to remove water and give 81 mCi of anhydrous [^{18}F]-KF. Then, 9.2 μL of $(HF)_n$.pyridinium (corresponding to 0.32 mmol of hydrogen fluoride) were added so that all the radioactivity could be incorporated in the perfluorinating agent (93% decay corrected, 15 min).

Methyl undecanedithioate.[61] To a solution of 1-decylmagnesium bromide, prepared from 1-bromodecane (0.938 mL, 4.52 mmol) and magnesium (0.115 g, 4.75 mmol) in THF (8 mL), was added, with ice cooling and stirring, carbon disulfide (0.408 mL, 6.78 mmol). The mixture was left overnight at room temperature. The excess of magnesium was filtered off and the volatiles were removed under vacuumn. The residue was dissolved in dichloromethane (30 mL) and the dithiocarboxylate was extracted with water (3×15 mL). Iodomethane (0.282 mL, 4.52 mmol) was added to the aqueous phase. After 24 h of stirring, the solution was extracted with dichloromethane (3×20 mL), dried ($MgSO_4$) and filtered on silica gel (hexane; R_f 0.06) to afford the dithioester as a yellow liquid. Yield: 0.419 g (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, 3H, J = 6.6 Hz, CH_3–$(CH_2)_9$–), 1.26 (m, 14H, CH_3–$(CH_2)_7$), 1.83 (m, 2H, C_8H_{17}–CH_2–CH_2–CS_2–), 2.62 (s, 3H, –CS_2–CH_3), 3.04 (t, 2H, J = 7.5 Hz, C_8H_{17}–CH_2CH_2–CS_2–); IR (NaCl, film: ν = 2953, 2923, 2853, 1464, 1458, 1437, 1418, 1198, 956, 937, 906, 891 cm^{-1}; MS (CI, CH_4–N_2O): m/z (%) = 233.1 ($[M+H]^+$, 100), 217.1 (19.2), 185.0 (22.4), 141.1 (7.3), 112.9 (4.9).

[^{18}F]-1,1,1-trifluoroundecane. 1,3-Dibromo-5,5-dimethylhydantoin (DBH) (73.9 mg, 0.25 mmol) was suspended in dichloromethane (0.2 mL) in a polyethylene flask and cooled to −70 °C. [^{18}F]-HF_n.pyridinium (27.8 μL, 0.97 mmol of fluoride) was added to this suspension. Then, a solution of methyl undecanedithioate (15 mg, 0.065 mmol) in dichloromethane (0.2 mL) was slowly introduced; the reaction mixture was allowed to warm to 20 °C and was stirred for 1 h. The crude mixture was filtered on neutral alumina and, after concentration, the residue was purified by flash chromatography on silica gel (hexane, R_f = 0.8) to give labeled trifluoroundecane (4.3% radiochemical yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, 3H, J = 6.3 Hz, CH_3–$(CH_2)_9$–), 1.27 (m, 14H, CH_3–$(CH_2)_7$–), 1.52 (m, 2H, C_8H_{17}–CH_2–CH_2–CF_3), 2.05 (m, 2H, C_8H_{17}–CH_2–CH_2–CF_3); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$) δ = −66.9 (t, J = 10.6 Hz); MS (CI, CH_4-N_2O): m/z (%) = 210 ($[M]^{\bullet +}$, 10), 209 (36).

2,3,5,6-Tetrafluorophenyl trifluoroacetate.[55] A solution of 2,3,5,6-tetrafluorophenol (3.045 g, 18.33 mmol), trifluoroacetic anhydride (3.400 mL, 24.07 mmol) and boron trifluoride etherate (280 μL, 2.21 mmol) was refluxed for 24 h. The volatiles were removed under vacuumn. Trifluoroacetic anhydride (3.40 mL, 24.07 mmol) and boron trifluoride etherate (280 μL, 2.21 mmol) were added and

the mixture refluxed for another 24 h. This process was repeated two times to allow a complete conversion of the starting phenol. The final mixture was concentrated under vacuumn and used as such for the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ = −74.2 (s, 3F, –CF_3), −137.4 (m, 2F), −152.6 (m, 2F).

2,3,5,6-Tetrafluorophenyl 2-(2-nitroimidazol-1-yl)acetate (1).[20] 2-(2-Nitroimidazol-1-yl)acetic acid[20](0.375 g, 2.19 mmol) in acetonitrile (5 mL) was neutralized with triethylamine (0.306 mL, 2.19 mmol) before the addition of the solution of tetrafluorophenyl trifluoroacetate (0.680 mL, 2.63 mmol). The mixture was stirred overnight at 20 °C. After concentration, the residue was purified by flash chromatography on silica gel (EtOAc-hexane, 50:50; R_f = 0.4) to yield **1** (0.489 g, 70%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.52 (s, 2H, –CH_2–), 7.07 (m, 1H, –C_6HF_4), 7.23 (d, 1H, J = 0.9 Hz, imidazol-H), 7.29 (d, 1H, J = 0.9 Hz, imidazol-H); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ = −76.4 (s, 3F, CF_3), −138.2 (m, 2F), −152.7 (m, 2F); IR (NaCl, film): ν = 3402, 1641 (C=O), 1376, 1135; MS (FAB, MNBA): m/z (%) = 320.0 ([M + H]$^+$, 19.3), 226.3 (37.5), 225.2 (44.6), 210.9 (100), 198.0 (10.0), 96.5 (26.6).

***N*-Methyl-β-alaninamide.**[62] 3-(Methylamino)-propionitrile (3.4 mL, 36.4 mmol was slowly added to a suspension of KOH (6.0 g, 107.14 mmol) in *t*-BuOH (15 mL) and heated for 60 min at 90 °C. After cooling at 20 °C, the liquid phase was separated from the solid, cooled to −15 °C and treated with water (3 mL). Distillation under vacuumn left a residue which was dissolved in acetonitrile (50 mL), dried on $MgSO_4$ and concentrated to give *N*-methyl-β-alaninamide (2.6 g, 70%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.38 (t, 2H, J = 6.0 Hz, –CH_2–$CONH_2$), 2.44 (s, 3H, N–CH_3), 2.85 (t, 2H, J = 6.0 Hz, N–CH_2–), 5.05 (br s, 1H, –CONH_2), 7.57 (*brs*, 1H, –CONH_2); IR (NaCl, film): ν = 3365, 2954, 2806, 2456, 1652 (C=O), 1457, 1236, 1143, 1108, 1035; MS (CI, CH_4–N_2O): m/z (%) = 102.9 ([M + H]$^+$, 28.7), 85.9 (5.0), 59.9 (38.3), 43.9 (100).

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-β-alaninamide.** To a solution of *N*-Methyl-β-alaninamide (2.5 g, 24.5 mmol) and $(Boc)_2O$ (5.45 g, 25.0 mmol) in dichloromethane (125 mL), was slowly added triethylamine (3.484 mL, 25.0 mmol). The mixture was refluxed for 40 h. After cooling at 20 °C, the solution was washed with water (3×20 mL) and brine (1×20 mL). After drying ($MgSO_4$) and concentration, the product was obtained as a white solid (4.2 g, 85%). Mp 109–110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.46 (s, 9H, *t*-C_4H_9), 2.49 (t, 2H, J = 6.3 Hz, –CH_2–$CONH_2$), 2.88 (s, 3H, N–CH_3) 3.53 (t, 2H, J = 6.3 Hz, N–CH_2–), 5.55 (br s, 1H, –CONH_2), 6.70 (br s, 1H, –CONH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.4 [(CH_3)$_3$C], 34.7 (–CH_2–$CONH_2$), 45.2 (N–CH_3), 79.9 [$(CH_3)_3C$], 156.2 (OCONH), 173.4 (–CONH_2); IR (NaCl, film): ν = 3364, 3200, 2974, 2932, 1668 (C=O), 1558, 1489, 1456, 1395, 1149; MS (CI, CH_4-N_2O): m/z (%) = 203.2 ([M + H]$^+$, 0.7), 147.0 (8.7), 103.0 (100), 59.9 (8.3). Anal. calcd for $C_9H_{18}N_2O_3$: C 53.45, H 8.97, N 13.85. Found: C 53.46, H 9.14, N 13.58.

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-β-thioalaninamide.** *N*-Boc-*N*-methyl-β-alaninamide (0.1 g, 0.49 mmol) and Lawesson's Reagent (0.13 g, 0.32 mmol) in THF (1 mL) were stirred at 20 °C for 21 h. After concentration, the residue was purified by flash chromatography on silica gel (EtOAc:hexane, 50:50; R_f = 0.4) to yield the thioamide (0.08 g, 80%) as a white solid. Mp 89–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.46 (s, 9H, *t*-C_4H_9), 2.88 (s, 3H, N-CH_3), 3.05 (t, 2H, J = 6.8 Hz, –CH_2–$CSNH_2$), 3.58 (t, 2H, J = 6.8 Hz, N-CH_2-), 7.55 (br s, 1H, -$CSNH_2$), 8.65 (br s, 1H, –$CSNH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.2 [(CH_3)$_3$C], 34.7 (–CH_2–$CSNH_2$), 43.7 (N-CH_3), 47.9 (N–CH_2–), 80.1 [$(CH_3)_3C$], 156.0 (OC-ONH), 207.1 (–$CSNH_2$); IR (NaCl, film): ν = 3307, 3175, 2977, 2930, 1674 (OCONH), 1483, 1456, 1429, 1396, 1365, 1165, 1136, 999; MS (CI, CH_4-N_2O): m/z (%) = 219.0 ([M + H]$^+$, 18.3), 162.8 (79.6), 119.0 (100), 88.0 (21.2), 76.0 (30.0), 44.1 (14.6). Anal. calcd for $C_9H_{18}N_2O_2S$: C 49.51, H 8.31, N 12.83, S 14.68. Found: C 49.16, H 8.32, N 12.56, S 14.81.

3-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)propanethioacyl *N*-phthalimide. To a mixture of thioamide (2.320 g, 10.64 mmol) and K_2CO_3 (1.769 g, 12.77 mmol) in THF (30 mL), cooled at 0 °C, was added dropwise (within 4 h, stirring under argon atmosphere) a solution of phthaloyl dichloride (1.84 mL, 12.7 mmol) in THF (30 mL). After the addition was complete, the mixture was further stirred for 4 h at 20 °C, then poured into water (50 mL) and extracted with EtOAc (3×20 mL). Drying over $MgSO_4$, concentration and purification by flash chromatography on silica gel (EtOAc:hexane 30:70; R_f = 0.78 for EtOAc:hexane 40:60) gave pure thioacyl phthalimide as a red solid. Yield: 2.78 g (75%). Mp 112–113 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.37 (s, 9H, *t*-C_4H_9), 2.87 (s, 3H, N-CH_3), 3.61 (*brt*, 2H, –CH_2-CSNPhth), 3.66 (*brt*, 2H, N–CH_2–), 7.86 (m, 2H$_{arom}$), 7.96 (m, 2H$_{arom}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.1 [(CH_3)$_3$C], 34.2 (–CH_2–CSNPhth), 46.7 (N–CH_2–), 47.8 (N-CH_3), 79.5 [$(CH_3)_3C$], 124.5, 130.7, 135.3, 155.8 (OCONH), 164.5 (Phth-C=O), 209.3 (-CSNPhth); IR (NaCl, film): ν = 3457, 2971, 2942, 1790, 1732 (C=O, Ft), 1668 (OCONH), 1456, 1392, 1298, 1144, 1029, 872; MS (FAB, MNBA): m/z (%) = 349.0 ([M + H]$^+$, 0.8), 274.2 (8.3), 249.1 (2.9), 218.0 (100), 206.1 (10.0), 160.2 (34.1), 148.2 (9.1). Anal. calcd for $C_{17}H_{20}N_2O_4S$: C 58.60, H 5.78, N 8.04, S 9.20. Found: C 58.39, H 5.72, N 7.92, S 9.00.

Ethyl 3-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)propanedithioate. To a cold (0 °C) solution of thioacyl phthalimide (0.522 g, 1.50 mmol) in CH_2Cl_2 (5 mL), were added dropwise successively (stirring under argon atmosphere) ethanethiol (0.560 mL, 7.50 mmol) and triethylamine (0.215 mL, 1.50 mmol). The solution was allowed to reach 20 °C within 1 h and left for another 1 h at 20 °C. After addition of 4 N NaOH (15 mL), the mixture was rapidly extracted with CH_2Cl_2 (3×15 mL). Drying over $MgSO_4$, concentration and purification by flash chromatography on silica gel (EtOAc:hexane 10:90; R_f = 0.77 for EtOAc:hexane 30:70), gave pure dithioester as a yellow oil. Yield: 0.315 g (80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.32 (t, 3H, J = 7.4 Hz), 1.46 (s, 9H, *t*–C_4H_9),

2.88 (s, 3H, N-CH_3), 3.21 (q, 2H, J = 7.4 Hz, –SCH_2 CH_3), 3.23 (t, 2H, J = 6.8 Hz, -CH_2-CS_2Et), 3.62 (*t*, 2 H, J = 6.8 Hz, N–CH_2–); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 11.9 (–SCH_2CH_3), 28.2 [(CH_3)$_3$C], 30.7 (–SCH_2 CH_3), 34.4 (–CH_2–CS_2Et), 49.8 (N–CH_2–), 50.2 (N-CH_3), 79.5 [$(CH_3)_3C$], 155.3 (O*C*ONH), 235.0 (-CS_2Et); IR (NaCl, film): ν = 2974, 2929, 1699 (OCONH), 1480, 1456, 1392, 1365, 1226, 1162, 1129, 914; MS (FAB, MNBA): m/z (%) = 264.2 ([M + H]$^+$, 2.9), 208.0 (25.8), 189.1 (9.6), 175.3 (24.0), 164.1 (100), 146.2 (14.1), 133.1 (40.8), 121.0 (19.6), 103.9 (10.5), 87.8 (19.9). Anal. calcd for $C_{11}H_{21}NO_2S_2$: C 50.16, H 8.03, N 5.32, S 24.34. Found: C 50.36, H 8.02, N 5.37, S 24.55.

Ethyl 3-(methylamino)propanedithioate (2b). The *N*-Boc precursor (0.5 g, 1.91 mmol) was dissolved in cold (0 °C) trifluoroacetic acid (3 mL) and left 1 h (under argon atmosphere). After evaporation under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and extracted with water (4×5 mL; HPLC grade). Lyophilization of the aqueous phases gave pure **2b** (trifluoroacetate salt) as a yellow oil. Yield: 0.502 g (95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.32 (t, 3H, J = 7.4 Hz), 2.73 (s, 3H, N-CH_3), 3.23 (q, 2H, J = 7.4 Hz, –SCH_2CH$_3$), 3.3–3.5 (m, 4H, N–CH_2–CH_2–CS_2Et), 9.52 (m, 2H, NH_2^+); ^{13}C NMR (50 MHz, D_2O) δ = 12.2 (–SCH_2CH_3), 31.9 (–SCH_2CH$_3$), 34.0 (–CH_2–CS_2Et), 46.5 (N–CH_2–), 49.2 (N–CH_3), 117.4 (CF_3, J_{C-F} = 290.5 Hz), 163.7 (C=O, J_{C-F} = 34.8 Hz), 235.2 (–CS_2Et); IR (NaCl, film): ν = 3025, 2797, 1674 (C=O, carboxylate salt), 1456, 1423, 1202, 1134, 912; MS (FAB, MNBA): m/z (%) = 163.9 (M$^+$, 100), 133.0 (26.0), 43.7 (41.2).

***N*-[3-(Ethylthio)-3-thioxopropyl]-2-(2-nitroimidazol-1-yl) acetamide (3a). General coupling procedure.** Triethylamine (0.022 mL, 0.16 mmol) was added slowly to a solution of **1** (0.05 g, 0.16 mmol) and **2a** (0.041 g, 0.16 mmol) in acetonitrile (1 mL). After stirring at 20 °C for 17 h, acetonitrile was removed under vacuum and the residue purified by flash chromatography on silica gel (EtOAc:hexane, 70:30; R_f = 0.26) to give pure **3a** (0.040 g, 85%) as a yellow solid. Mp 131–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.32 (t, 3H, J = 7.3 Hz, –CS_2 CH_2CH_3), 3.15 (t, 2H, J = 5.8 Hz, –CH_2CS_2Et), 3.22 (q, 2H, J = 7.3 Hz, –$CS_2CH_2CH_3$), 3.74 (dt, 2H, J = 5.8 Hz et 5.8 Hz, NH–CH_2–CH_2–), 4.99 (s, 2H, –CH_2–CONH–), 6.41 (br t, 1H, J = 5.8 Hz, –CON*H*–), 7.14 (d, 1H, J = 1.2 Hz, imidazol-H), 7.21 (d, 1H, J = 1.2 Hz, imidazol-H); ^{13}C NMR (125 MHz, $CDCl_3$) d = 11.9 (SCH_2CH_3), 30.8 (SCH_2CH_3), 39.2 (CONH–CH_2–), 49.4 (–CH_2–CS_2Et), 52.2 (–CH_2–CONH), 126.8 ($CH_{imidazol}$), 128.6 ($CH_{imidazol}$), 146.84 (C-NO_2), 164.4 (*C*ONH), 235.53 (CS_2Et); IR (NaCl, film): δ = 3318, 2987, 2930, 2872, 2431, 1662 (C=O), 1559, 1534, 1482, 1420, 1368, 1342, 1290, 1216, 1166, 923; MS (CI, CH_4-N_2O): m/z (%) = 302.1 (M$^+$, 31.6), 273.0 (100), 169.0 (5.0), 145.9 (9.1), 111.9 (18.9), 102.9 (26.6). Anal. calcd for $C_{10}H_{14}N_4O_3S_2$: C 39.72, H 4.66, N 18.53, S 21.20. Found: C 39.95, H 4.60, N 18.46, S 20.83.

***N*-[3-Ethylpropanedithioate]-*N*-methyl-2-(2-nitroimidazol-1-yl)acetamide (3b).** The same general coupling procedure was applied for **3b** which was purifed by flash chromatography on silica gel (EtOAc; R_f = 0.40) to give a yellow oil (0.04 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) two rotamers, δ = 1.29 et 1.34 (t, 3H, J = 7.3 Hz, –CS_2 CH_2CH_3), 3.00 and 3.13 (s, 3H, N–CH_3), 3.19 and 3.26 (q, 2H, J = 7.3 Hz, –$CS_2CH_2CH_3$), 3.22 and 3.34 (t, 2H, J = 7.0 Hz, –CH_2CS_2Et), 3.82 and 3.83 (t, 2H, J = 7.0 Hz, N–CH_2–CH_2–), 5.19 and 5.30 (s, 2H, –CH_2–CONH–), 7.08 and 7.04 (d, 1H, J = 1.2 Hz, imidazol-H), 7.19 and 7.18 (d, 1H, J = 1.2 Hz, imidazol-H); ^{13}C NMR (125 MHz, $CDCl_3$) two rotamers, δ = 11.8 and 11.8 (SCH_2CH_3), 30.9 and 31.2 (SCH_2CH_3), 35.6 and 33.6 (N-CH_3), 48.6 and 48.8 (–CH_2–CS_2Et), 49.9 and 49.2 (N-CH_2-), 50.9 and 51.0 (–CH_2–CO), 126.9 and 126.8 ($CH_{imidazol}$), 127.7 and 127.7 ($CH_{imidazol}$), 144.8 and 144.8 (C-NO_2), 164.6 and 164.5 (*C*ONMe), 232.8 and 234.4 (CS_2Et); IR (NaCl, film): δ = 3121, 2971, 2932, 1779, 1667 (C=O), 1493, 1371, 1206, 1160, 1053, 915, 842; MS (FAB, MNBA): m/z (%) = 315.0 ([M-H]$^-$, 21.5), 253.0 (9.6), 183.0 (100), 136.1 (9.0), 126.0 (13.5), 112.0 (85.4), 96.0 (23.3). Anal. calcd for $C_{10}H_{14}N_4O_3S_2$: C 39.72, H 4.66, N 18.53, S 21.20. Found: C 39.95, H 4.60, N 18.46, S 20.83.

Ethyl 3-phthalimidopropanedithioate (4). To a suspension of PyBOP (3.095 g, 5.94 mmol) in THF (5 mL) was added a solution of 2-(methoxycarbonyl)benzoic acid (1.622 g, 5.94 mmol) in THF (5 mL) and triethylamine (1.127 mL, 8.11 mmol). The mixture was stirred at 20 °C for 40 min; **2a** (1.422 g, 5.41 mmol) was introduced in one portion followed by a slow addition of triethylamine (1.127 mL, 8.11 mmol). After stirring at 20 °C for 3 h, a catalytic amount of *p*-TsOH was added before refluxing overnight. After cooling at 20 °C, the solution was poured on aq sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (3×40 mL). The organic phase was dried ($MgSO_4$) and concentrated before purification by flash chromatography on silica gel (EtOAc:hexane, 10:90, R_f = 0.27); **4** was then treated with trifluoroacetic anhydride (5 mL) in dichloromethane (5 mL) to remove any traces of water. Yield: 1.357 g (90%), yellow solid. mp: 82–83 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.26 (t, 3H, J = 7.5 Hz, –SCH_2CH_3), 3.18 (q, 2H, J = 7.5 Hz, –SCH_2 CH_3), 3.37 (t, 2H, J = 7.0 Hz, –CH_2CS_2Et), 4.14 (t, 2H, J = 7.0 Hz, N–CH_2–), 7.70–7.75 (m, 2Harom), 7.83–7.90 (m, 2H$_{arom}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 11.9 (–SCH_2CH_3), 30.7 (SCH_2CH_3), 38.2 (–CH_2CS_2Et), 49.1 (N–CH_2–), 123.3, 132.0, 134.0, 168.0 (Phth-*C*=O), 233.0 (CS_2Et); IR (NaCl, film): δ = 2972, 2930, 2861, 1772, 1713 (C=O, Ft), 1466, 1436, 1393, 1357, 1185, 916; MS (CI, CH_4-N_2O): m/z (%) = 279.2 (M$^-$, 4.9), 250.2 (24.1), 146.3 (100). Anal. Calc. for $C_{13}H_{13}NO_2S_2$: C 55.89, H 4.69, N 5.01. Found: C 56.02, H 4.62, N 4.84.

***N*-(3,3,3-trifluoropropyl)phthalimide (5).** To a suspension of potassium phthalimide (5.079 g, 27.42 mmol) in dry DMSO (50 mL), was added 1-bromo-3,3,3-trifluoropropane (1.46 mL, 13.71 mmol) and the resulting mixture was stirred for 6 h at 20 °C. The excess of potassium phthalimide was filtered off, the solution poured on brine (400 mL) and extracted with diethyl ether (3×200 mL). The combined organic phases were washed with brine (3×200 mL) and dried ($MgSO_4$) before concentration. The residue was purified by flash chromatography on silica gel (EtOAc:hexane, 10:90; R_f = 0.23) to afford **5**

(1.882 g, 56%) as a white solid. mp: 117–117.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.55 (tq, 2H, J = 7.2 Hz and 10.4 Hz, –CH_2–CF_3), 3.97 (t, 2H, J = 7.2 Hz, N–CH_2–), 7.70–7.80 (m, 2H$_{arom}$), 7.83–7.91 (m, 2H$_{arom}$); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ = −66.1 (t, J = 10.4 Hz);^{13}C NMR (50 MHz, $CDCl_3$) δ = 31.2 (q, $J_{C\text{-}F}$ = 3.8 Hz, N-CH_2-), 32.2 (q, J_{C-F} = 28.6 Hz, –CH_2–CF_3), 123.4, 125.6 (q, J_{C-F} = 273.5 Hz, –CF_3), 131.8, 134.2, 167.6 (Phth-C=O); IR (NaCl, film): ν = 3464, 1703 (C=O, Ft), 1464, 1386, 1335, 1251, 1185, 1141, 977; MS (CI, CH_4–N_2O): m/z (%) = 243.9 ([M + H]$^+$, 20.8), 223.9 (13.7), 159.9 (100). Anal. Calc. for $C_{11}H_8F_3NO_2$: C 54.33, H 3.31, N 5.76. Found: C 54.50, H 3.25, N 5.72.

3,3,3-Trifluoropropylamine hydrochloride (7). To a solution of **5** (0.8 g, 3.29 mmol) in isopropanol (32 mL)/water (4.8 mL), was added $NaBH_4$ (0.623 g, 16.48 mmol). The mixture was strirred for 24 h at 20 °C. The solution was ice-cooled before adding carefully AcOH (3.6 mL) and then heated to 80 °C for 2 h. NaOH 4 N (32 mL) was added to the cooled mixture and the amine was distilled under an argon flow into a flask containing HCl 5 N (10 mL, at 0 °C), until no more product could be recovered. Evaporation of the solution yielded the hydrochloride of **7** (0.396 g, 80%) as a white solid. ^{1}H NMR (200 MHz, D_2O) δ = 2.82 (tq, 2H, J = 10.4 Hz and 6.7 Hz, –CH_2–CH_2–CF_3), 3.50 (t, 2H, J = 6.7 Hz, –CH_2–CH_2–CF_3); ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$) δ = −66.9 (t J = 10.4 Hz); MS (FAB, GLYC): m/z (%) = 113.9 (M$^+$, 100), 97.0 (16.5), 77.0 (92.1), 68.9 (11.2), 51.0 (12.5), 30.0 (33.7).

2-(2-nitro-imidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)acetamide (EF3). The general coupling procedure was applied for EF3 which was purifed by flash chromatography on silica gel (EtOAc-hexane, 80:20; EtOAc-hexane, 80:20, R_f = 0.33) to give 94% of a pale yellow solid. ^{1}H NMR (300 MHz, CD_3CN) δ = 2.38 (tq, 2H, J = 6.9 Hz et J = 11.0 Hz, –CH_2–CF_3), 3.44 (dt, 2H, J = 6.5 Hz et 6.5 Hz, NH-CH_2-), 5.00 (s, 2H, –CH_2–CONH–), 6.92 (*brt*, 1H, J = 6.5 Hz; CONH), 7.12 (s, 1H, imidazol-H), 7.27 (s, 1H, imidazol-H); ^{19}F NMR (282 MHz, CD_3CN/$CFCl_3$) δ = −64.4 (t, J = 11.0 Hz); MS (CI, CH_4–N_2O): m/z (%) = 267.2 ([M + H]$^+$, 100), 221.1 (37.5), 154.1 (12.9), 126.0 (16.6).

[^{18}F]-*N*-(3,3,3-trifluoropropyl)phthalimide (5). Radiolabeling procedure. In a polyethylene vessel (dried under argon) containing DBH (0.061 g, 0.21 mmol) in suspension in CH_2Cl_2 (0.2 mL), [^{18}F]-(HF)$_n$.pyridinium (9.2 μL, 28 mCi, 6 equiv of fluoride) was added. A solution of **4** (0.015 g, 0.05 mmol) in CH_2Cl_2 (0.2 mL) was added. The mixture was stirred for 10 min at 20 °C. Then, 'cold' (HF)$_n$.pyridinium (71.8 μL) was introduced and stirring at 20 °C was continued for another 10 min. This process allowed to obtain labeled **5** with 5.6% of radiochemical yield (decay corrected) as determined by radio-TLC (EtOAc:hexane, 40:60; R_f = 0.66). The crude mixture was filtered on neutral alumina and eluted with CH_2Cl_2 to isolate [^{18}F]-**5** (1.58 mCi; 0.021 mmol; radiochemical purity: 99%).

[^{18}F]-2-(2-nitro-imidazol-1-yl)-*N*-(3,3,3-trifluoropropyl) acetamide (EF3). Radiolabeling procedure. [^{18}F]-**5** was dissolved in N_2H_4.×H_2O (1 mL) and heated at 75 °C under argon flow for 10 min. The free amine was distilled into a flask containing a solution of **1** (0.03 g, 0.09 mmol) in anhydrous acetonitrile (1 mL) cooled at 0 °C; 80% of the radioactivity has been distilled as the free amine (1.2 mCi, d.c.; 0.017 mmol). Stirring the mixture of **1** and labeled **5** at 20 °C for 30 min allowed to recover 65% of this radioactivity coupled to the 2-nitroimidazole acetic acid as [^{18}F]-EF3 (determined by radio-TLC; EtOAc, R_f = 0.30) (0.780 mCi; 0.011 mmol).

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