Tetrahedron 64 (2008) 11846–11851

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Radiochemical ^{18}F-fluoroarylation of unsaturated α-, β- and γ-amino acids, application to a radiolabelled analogue of baclofen

Sarah B. Höfling [a], Christina Hultsch [b], Hans-Jürgen Wester [b], Markus R. Heinrich [a,*]

[a] Organische Chemie 1, Technische Universität München, Lichtenbergstrasse 4, 85747 Garching, Germany
[b] Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, 81675 München, Germany

ARTICLE INFO

Article history:
Received 14 July 2008
Accepted 31 July 2008
Available online 20 September 2008

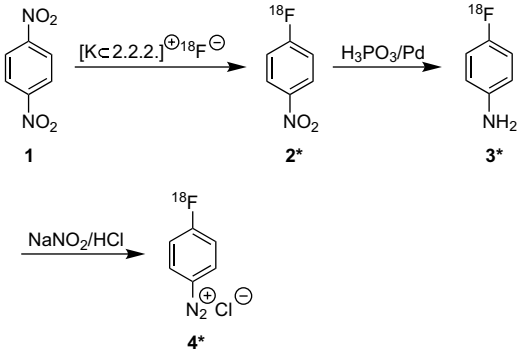
ABSTRACT

Unsaturated α-, β- and γ-amino acids have been investigated as substrates for the reductive Meerwein arylation. Radical reactions of this type have been shown to be a valuable tool for the fast and efficient introduction of the 4-[^{18}F]fluorophenyl group into precursor molecules allowing short-time syntheses of potential PET radiotracers, which would be more difficult to access by other methods.

1. Introduction

Positron emission tomography (PET) is a powerful non-invasive method for imaging and quantification of physiological and biochemical processes in vivo. The wide scope of physiological targets of interest suitable for diagnosis, planning and monitoring of therapeutic interventions by means of imaging has led to an increasing search for new radiopharmaceuticals. Due to its superior properties, i.e., its broad availability, its low positron energy (E_{max}=635 keV) and half-life ($t_{1/2}$=109.7 min),[1] no-carrier-added (n.c.a.) F-18 is the most commonly used PET isotope. Although favoured by these advantages, chemical synthesis and incorporation of fluorine-18 into the target molecule in reasonable overall reaction times (ideally less than 2 h) often remains the key obstacle for the development of new radiopharmaceuticals.[2]

Although well known for short reaction times, aryl radical chemistry[3] has so far only rarely been used for the synthesis of ^{18}F-labelled radiopharmaceuticals. Among the numerous radical reactions, which could advantageously be applied in radiochemical syntheses, ^{18}F-fluoroarylation reactions provide a new route to radiopharmaceuticals containing a deactivated, 4-[^{18}F]fluoro substituted phenyl group.[4,5] The radiosynthesis of 4-[^{18}F]fluorobenzenediazonium salts **4***, which represent the key precursors for this reaction type, is an established three-step procedure starting from 1,4-dinitrobenzene (**1**) (Scheme 1).[6,7] Nucleophilic substitution of **1** with activated [^{18}F]fluoride to give 4-[^{18}F]fluoronitrobenzene (**2***), followed by reduction to 4-[^{18}F]fluoroaniline (**3***) and diazotization leads to 4-[^{18}F]fluorobenzenediazonium salts **4***. Radiochemical yields of 50–65% are obtained within overall reaction times of about 60 min.[5]



Scheme 1. Radiosynthesis of 4-[^{18}F]fluorobenzenediazonium salts **4** from 1,4-dinitrobenzene (**1**).

Radiochemical syntheses proceeding via the aryl radical-based introduction of the 4-[^{18}F]fluorophenyl group have so far been studied for the compounds shown in Figure 1.[4–6]

Synthetic access to the halogenated 4-[^{18}F]fluorobenzene **5***[6,8] and the *S*-(4-[^{18}F]fluorophenyl)cysteines **6***[4] is possible by copper-mediated or photochemically induced Sandmeyer reactions. The 4-[^{18}F]fluorophenyl substituted piperidine and tropane derivatives **7*** and **8*** were obtained by employing the reaction conditions of the reductive Meerwein arylation.[5,9] The formation of the ^{18}F-labelled stilbene **9***, which represents a lead structure for the development of Alzheimer plaque imaging reagents,[10] occurs in a radical addition–fragmentation reaction starting from β-chloro- or β-bromostyrenes.[11]

* Corresponding author. Tel.: +49 89 289 13328; fax: +49 89 289 13329.
E-mail address: markus.heinrich@ch.tum.de (M.R. Heinrich).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.117

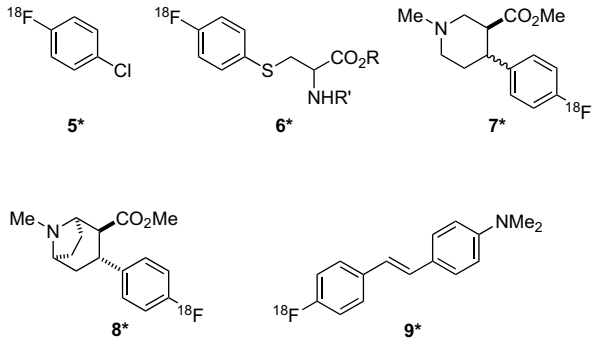


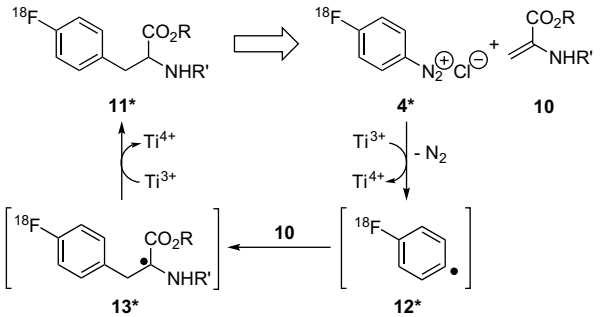
Figure 1. ^{18}F-radiolabelled compounds synthesized by radical reactions employing 4-[^{18}F]fluorobenzenediazonium salts **4**.

In this study, we report on the application of the radical ^{18}F-fluoroarylation methodology to provide a novel access to 4-[^{18}F]fluorophenyl substituted α-, β- and γ-amino acids.

2. Results and discussion

2.1. α-Amino acids

An application of the reductive Meerwein arylation to the synthesis of α-amino acids requires 2-aminoacrylates **10** as precursors (Scheme 2). In the reaction, the [^{18}F]fluorophenyl radical (**12***), which is formed from the diazonium chloride **4*** upon reduction and nitrogen loss, adds to the olefinic substrate **10**. The regioselectivity of the addition step is controlled by steric and electronic factors. In the case of the aminoacrylates **10**, both effects undoubtedly favour the aryl radical attack in β-position to give the adduct **13***. Although radical formation from **4*** as well as the addition step can be expected to be efficient, complications might occur due to the fact that **13*** must be classified as a captodative radical.[12] Captodative radicals usually show low reactivity and the anticipated reductive conversion of **13*** to the desired product **11*** might therefore not be fast enough to prevent side reactions.

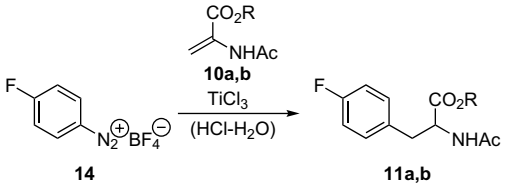


Scheme 2. Retrosynthetic cleavage of 4-[^{18}F]fluorophenylalanine **11*** and envisaged synthesis of **11*** by radical ^{18}F-fluoroarylation of 2-aminoacrylates **10**.

To find a suitable 2-aminoacrylate **10** with respect to the protecting groups R and R′ (Scheme 2), we carried out preliminary non-radioactive reactions. The results are summarized in Table 1.

Extensive telomerization, but no product formation was observed with methyl 2-acetamidoacrylate (**10a**) (Table 1, entry 1). The unprotected acid **10b**, however, gave the desired product **11b** without notable contamination by oligomers. Experiments with increasing amounts of olefin **10b** were carried out to get a first prediction on the radiochemical applicability of the reaction (Table 1, entries 2–4). Earlier investigations on the fluoroarylation

Table 1
Non-radioactive fluoroarylation of 2-aminoacrylates **10a** and **10b**



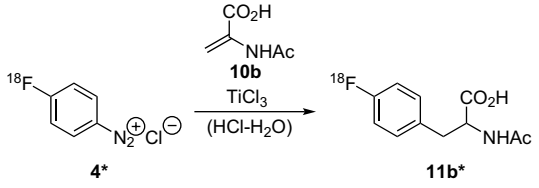
Entry	Aminoacrylate **10**[a]	Equivalents **10**/salt **14**	Yield **11** (%)[b]
1	**10a**: R=Me	2	**11a** (—)
2	**10b**: R=H	2	**11b** (25)
3	**10b**: R=H	4	**11b** (35)
4	**10b**: R=H	8	**11b** (45)

[a] Standard reaction conditions: 4-fluorobenzenediazonium tetrafluoroborate (0.5 mmol), 2-aminoacryate **10** (equivalents, see Table 1), $TiCl_3$ (1 M in 10% HCl, 4 mL, 4.0 mmol), 40 °C, 20 min.
[b] Yield determined by ^{1}H NMR.

revealed that an increase in olefin equivalents, which is accompanied by an advance in yield, indicates an applicability of this reaction for radiosynthesis. Otherwise the reaction is decisively troubled by a side process, and the large excess of olefin compared to the ^{18}F-labelled diazonium salt present in the radiochemical reaction might no longer turn out beneficial for product formation. After the promising observation, that increasing yields of 25%, 35% and 45% can be reached by raising the amount olefin **10b** from 2 to 4, and finally 8 equiv per diazonium salt **14**, we turned towards the radiochemical application.

Varying amounts of 2-acetamidoacrylate (**10b**) were reacted with [^{18}F]fluorobenzenediazonium chloride (**4***) and titanium(III) chloride. Further optimization of the reaction temperature led to the results summarized in Table 2.

Table 2
Radioactive ^{18}F-fluoroarylation of 2-acetamidoacrylate (**10b**)



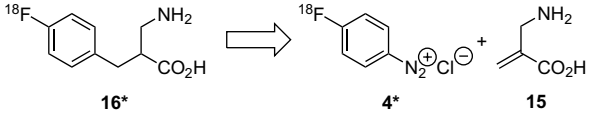
2-Acetamidoacrylate (**10b**) (mg)	Reaction temperature	Reaction time (min)	Radiochemical yield **11b*** (%)[a,b]
10	rt	1	7
10	rt	5	14
10	rt	10	20
10	rt	1	9
10	rt	5	19
10	rt	10	27
20	rt	1	14
20	rt	5	24
20	rt	10	27
20	40 °C	1	14
20	40 °C	5	29
20	40 °C	10	30
20	60 °C	1	26
20	60 °C	5	40
20	60 °C	10	38
20	**80 °C**	**1**	**43**
20	80 °C	5	41
20	80 °C	10	39

[a] Yields determined by radio-HPLC; preparative radiochemical yields (corrected by the recovery of total radioactivity).
[b] Standard reaction conditions: see Section 3.

The radiochemical yields reported in Table 2 are preparative yields; corrected by the recovery of total radioactivity. This adjustment is necessary since volatile [^{18}F]fluorobenzene is formed depending on the reaction conditions. In contrast to the experiments carried out at room temperature and 40 °C, in which the radioactivity is completely recovered, the reactions performed at 60 °C and 80 °C are accompanied by a radioactivity loss of up to 14% after 10 min reaction time. In almost all cases, longer reaction times were shown to be beneficial for product formation. Only at 80 °C, the maximum yield is already obtained after 1 min. This maximum of 43% represents also the best result in the whole series of experiments. Apart from the fluorinated phenylalanine derivative **11b***, only 4-[^{18}F]fluorobenzene, unreacted precursor **4*** and small amounts of a so far unidentified product (<10%) were detected by radio-HPLC.

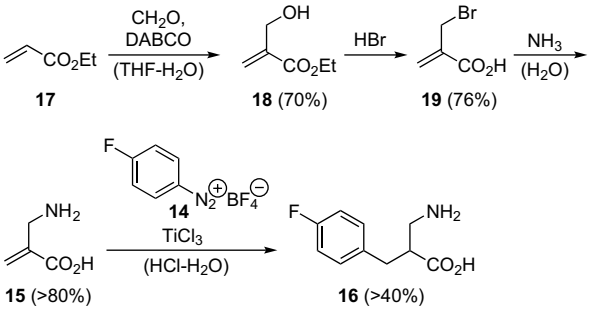
2.2. β-Amino acids

To evaluate the applicability of the ^{18}F-fluoroarylation methodology with regard to the synthesis of β-amino acids, we chose the retrosynthetic deconnection shown in Scheme 3.



Scheme 3. Retrosynthetic cleavage of the radiolabelled β-amino acid **16*** to its potential precursors **4*** and 2-(aminomethyl)acrylic acid **15**.

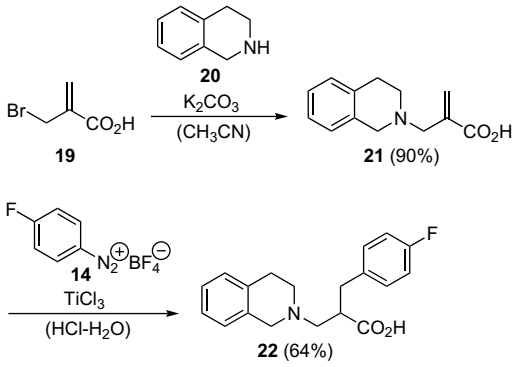
Synthetic access to the required olefinic substrate 2-(aminomethyl)acrylic acid (**15**) turned out to be difficult by following the literature procedures.[13] A selective combination and optimization of previously described single steps led to a practicable route to the desired acrylate **15** (Scheme 4).



Scheme 4. Preparation and fluoroarylation of 2-(aminomethyl)acrylic acid (**15**).

Baylis–Hillman hydroxymethylation[14] of ethyl acrylate **17** to **18** followed by simultaneous bromination and ester cleavage in hydrobromic acid gave 2-(bromomethyl)acrylic acid (**19**). Introduction of the amino group is finally achieved in concentrated aqueous ammonia. Although larger quantities of the unsaturated β-amino acid are accessible by this reaction sequence, we were unable to completely purify product **15** from its oligomers. Both recrystallization and chromatographic methods failed to afford **15** in more than 90% purity. Due to its poor purity, **15** is not applicable as precursor for ^{18}F-fluoroarylation. The non-radioactive fluoroarylation experiment, which was carried out with a sample of acid **15** containing about 10% of its oligomer, gave 40% of the β-amino acid **16** (Scheme 4).

Due to the difficulties encountered in the purification of the unsaturated precursor **15** and product **16**, we decided to evaluate the fluoroarylation of a second unsaturated β-amino acid derivative. 2-(Bromomethyl)acrylic acid **19** was, therefore, attached to the tetrahydroisoquinoline **20** to give the modified β-amino acid **21**.[15] In contrast to compound **15**, the tetrahydroisoquinoline **21** could easily be purified by column chromatography and proofed to be more stable towards oligomerization (Scheme 5).

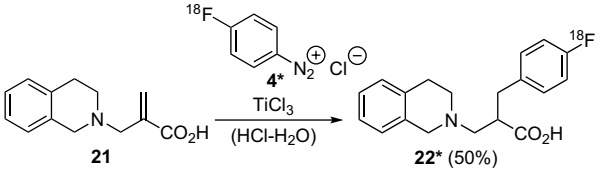


Scheme 5. Preparation and fluoroarylation of tetrahydroisoquinoline **21**.

The significantly higher yield of 64% obtained from the fluoroarylation of **21** (compared to 40% for compound **15**) must be ascribed to the remarkable instability of the unmodified amino acid **15** under the fluoroarylation conditions. Fortunately, the radical fluoroarylation of **21** is also not significantly hampered by the presence of abstractable hydrogen atoms in the benzylic position of the tetrahydroisoquinoline moiety.[3] The 2-methylacrylate unit should, therefore, allow efficient labelling of structurally even more demanding substrate molecules.

Radiochemical experiments on the ^{18}F-fluoroarylation of the tetrahydroisoquinoline **21** gave the radiolabelled product **22*** in a yield of 50% using reaction conditions similar to those developed for the synthesis of the fluorinated α-amino acids. However, intensified formation of 4-[^{18}F]fluorobenzene (up to 30%) was found. Table 3 indicates that relatively high radiochemical yields can be obtained for ^{18}F-fluoroarylation of the unsaturated β-amino acid

Table 3
Radioactive ^{18}F-fluoroarylation of tetrahydroisoquinoline (**21**)



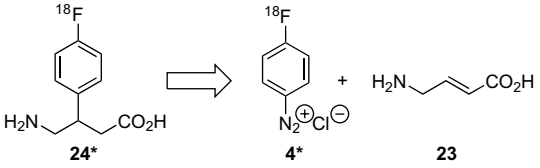
Tetrahydroisoquinoline (**21**) (mg)	Reaction temperature (°C)	Reaction time (min)	Radiochemical yield **22*** (%)[a,b]
10	60	1	30
10	60	5	33
10	60	10	30
5	80	1	32
5	80	5	35
5	80	10	33
10	80	1	51
10	80	5	50
10	80	10	49
20	80	1	52
20	80	5	51
20	80	10	51

[a] Yields determined by radio-HPLC; preparative radiochemical yields (corrected by the recovery of total radioactivity).
[b] Standard reaction conditions: see Section 3.

derivative **21**. Moreover, comparatively low amounts of olefin are required. In addition to the labelling product **22*** and 4-[^{18}F]fluorobenzene a so far unidentified side product (<30%) was detected by radio-HPLC.

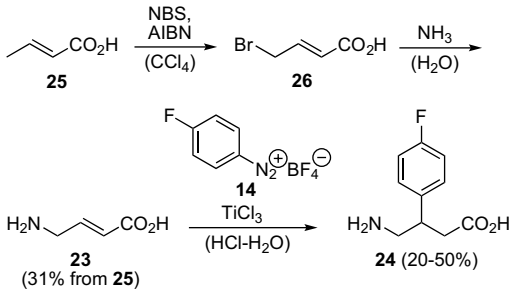
2.3. γ-Amino acids and fluorinated baclofen

The synthesis of γ-amino acids was envisaged using 4-aminocrotonic acid (**23**) as fluoroarylation precursor (Scheme 6).



Scheme 6. Retrosynthetic cleavage of γ-amino acid **24*** to its potential precursors **4*** and 4-aminocrotonic acid (**23**).

Preparation of 4-aminocrotonic acid (**23**) could only partially be accomplished by following literature-known procedures.[16] Radical bromination of crotonic acid **25** gave the desired brominated acid **26**, but subsequent amination by treating **26** with liquid ammonia at low temperature turned out to be troublesome. The reaction was difficult to conduct on a large scale and did moreover not give reproducible results. With respect to both drawbacks, we found it beneficial to convert bromide **26** to amine **23** by using 25% aqueous ammonia (Scheme 7).



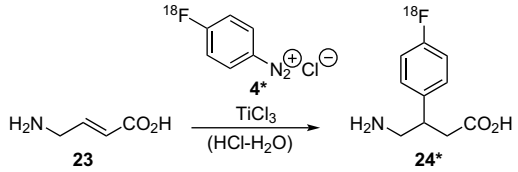
Scheme 7. Preparation and fluoroarylation of 4-aminocrotonic acid (**23**), NBS=*N*-bromosuccinimide, AIBN=azobisisobutyronitrile.

Fluoroarylation of **23** under standard conditions gave **24** in yields of 20% and 50% when 2 equiv and 4 equiv of olefin **23** per diazonium salt **14** were used, respectively. The significant increase in yield obtained by doubling the amount of olefin should allow a radiochemical application of this reaction. In contrast to the olefinic substrates employed in fluoroarylation reactions before (**10b**, **15** and **21**), aryl radical addition to 4-aminocrotonic acid (**23**) is not completely regioselective. Along with the desired isomer **24**, additional products are observed, which originate from the aryl radical attack on the α-position of **23**. In accord with earlier studies, a ratio of β/α-attack of 4:1 is usually determined for olefins comparable to 4-aminocrotonic acid (**23**).[17]

The results obtained from the optimization of the radiochemical reaction are summarized in Table 4. Only minor amounts of side products other than unreacted diazonium salt **4*** and 4-[^{18}F]fluorobenzene were detected by radio-HPLC. The radiochemical yields reported in Table 4 are preparative yields, corrected by the recovery of total radioactivity, which is necessary due to radioactivity loss caused by the volatility of the by-product 4-[^{18}F]fluorobenzene.

For the ^{18}F-fluoroarylation of 4-aminocrotonic acid (**23**) larger amounts of olefin, elevated reaction temperatures and longer reaction times appear to be beneficial. The maximum radiochemical yield of 28% was obtained after 5 min with 20 mg of olefin at 80 °C (Table 4).

Table 4
Radioactive ^{18}F-fluoroarylation of 4-aminocrotonic acid (**23**)



4-Aminocrotonic acid (**23**) (mg)	Reaction temperature	Reaction time (min)	Radiochemical yield **24*** (%)[a,b]
20	rt	1	14
20	rt	5	15
20	rt	10	17
20	40 °C	1	22
20	40 °C	5	25
20	40 °C	10	25
10	60 °C	1	16
10	60 °C	5	23
10	60 °C	10	23
20	60 °C	1	26
20	60 °C	5	26
20	60 °C	10	26
20	80 °C	1	24
20	**80 °C**	**5**	**28**
20	80 °C	10	26

[a] Yields determined by radio-HPLC; preparative radiochemical yields (corrected by the recovery of total radioactivity).
[b] Standard reaction conditions: see Section 3.

The β-amino acid **24** represents an analogue of the selective $GABA_B$ agonist baclofen (**27**) (Fig. 2). Baclofen is used for treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, multiple sclerosis, amyotrophic lateral sclerosis and trigeminal neuralgia. Its beneficial effects result from actions at spinal and supraspinal sites.[18]

Competitive binding studies with *R*-(−)-[H^3]-baclofen revealed that the fluorinated analogue **24** is by a factor of 2.5 less active than baclofen (**27**), but shows far better binding than the hydrogen- and hydroxyl-substituted derivatives **28** and **29**. (Table 5).[19]

In summary, we have shown that the radical fluoroarylation methodology, which is based on the reductive Meerwein arylation, can be applied for the radiochemical synthesis of ^{18}F-labelled α-, β- and γ-amino acids. The fluorinated γ-amino acid obtained represents a potential radiotracer for the imaging of $GABA_B$ receptors.

3. Experimental

3.1. Non-radioactive experiments

3.1.1. General procedure for non-radioactive fluoroarylation

To a solution of titanium(III)-chloride (4 mL, 1 M in 10% HCl, 4 mmol) at 40 °C the olefin (1.0 mmol) was added. Solid

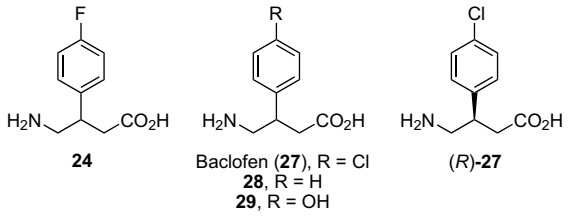


Figure 2. Baclofen (**27**) and analogues **24**, **28** and **29**.

Table 5
Binding data of baclofen analogues (IC_{50}, μM)[19]

Baclofen analogue	*R*-(−)-[H^3]-baclofen binding
(*rac*)-Baclofen (**27**), R=Cl	0.33
28, R=H	>100
29, R=OH	>100
24, R=F	0.80

4-fluorobenzenediazonium tetrafluoroborate (105 mg, 0.50 mmol) was added in small portions over 15 min and the resulting mixture was stirred at 40 °C for 20 more minutes. After cooling to room temperature, the reaction mixture was either extracted with EtOAc (non-protonable products) or directly concentrated in vacuo (protonable products). Purification was achieved by silica gel column chromatography or preparative HPLC.

*3.1.2. 2-Acetylamino-3-(4-fluorophenyl)propionic acid (**11b**)*[20]

Preparation according to the general procedure for non-radioactive fluoroarylation. Purification by preparative HPLC. R_f=0.8 (*n*BuOH−AcOH−EtOH−H_2O, 4:1:1:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.09 (dd, *J*=5.6, 14.2 Hz, 1H), 3.21 (dd, *J*=5.6, 14.2 Hz, 1H), 4.80–4.88 (m, 1H), 6.12 (d, *J*=7.3 Hz, 1H), 6.97 (dd, J_{HF}=8.7 Hz, *J*=8.7 Hz, 2H), 7.12 (dd, J_{HF}=5.4 Hz, *J*=8.7 Hz, 2H), 9.25 (br s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.9 (CH_3), 36.5 (CH_2), 53.3 (CH), 115.4 (d, J_{CF}=21.3 Hz, 2×CH), 130.9 (d, J_{CF}=7.9 Hz, 2×CH), 131.5 (d, J_{CF}=3.1 Hz, C_q), 170.7 (s, C_q), 174.1 (s, C_q), one C_q-signal missing; ^{19}F NMR (234 MHz, $CDCl_3$) δ −116.1; MS (ESI) *m*/*z*: 226 (M^++H). All analytical data is in agreement with those reported in Ref. 20

*3.1.3. 2-(Hydroxymethyl)acrylic acid ethyl ester (**18**)*[21]

A suspension of paraformaldehyde (3.30 g, 110 mmol) and phosphorous acid (1 N, 0.4 mL) in water (10 mL) was heated for 90 min to 90 °C under continuous stirring. The resulting clear solution was cooled to room temperature and is then treated with THF (10 mL), ethyl acrylate (10.9 mL, 100 mmol) and 1,4-diazabicyclo[2.2.2]octane (1.10 g, 10.0 mmol). After stirring for 36 h at room temperature, solid NaCl (3.50 g) and Et_2O were added, and the organic phase was separated. Together with the organic phases obtained from further extraction with Et_2O (3×30 mL), the combined solutions were washed with satd aqueous NaCl and dried over Na_2SO_4. Removal of the solvent in vacuo and distillation under reduced pressure gave **18** (9.10 g, 69.6 mmol, 70%) as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, *J*=7.1 Hz, 3H), 4.23 (q, *J*=7.1 Hz, 2H), 4.32 (d, *J*=0.7 Hz, 2H), 5.82 (m, 1H), 6.24 (d, *J*=0.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.9 14.1 (CH_3), 60.8 (CH_2), 62.5 (CH_2), 125.5 (CH_2), 139.5 (C_q), 166.3 (C_q). All analytical data is in agreement with those reported in Ref. 21

*3.1.4. 2-(Bromomethyl)acrylic acid (**19**)*[22]

A solution of hydroxyester **18** (5.20 g, 39.9 mmol) in 48% aqueous HBr (previously degassed with argon) under argon is heated to 125 °C for 10 min. The resulting mixture is cooled to −78 °C (acetone–dry ice) until precipitation of a colourless solid starts. The reactions vessel is then warmed to 0 °C by immersion in an ice-bath. The precipitated solid was collected by filtration and dissolved in a 1:1 mixture of CH_2Cl_2 and 1 N HCl (2×30 mL). The combined organic phases obtained also from further extraction of the acidic aqueous phase with CH_2Cl_2 (3×30 mL) were washed with satd aqueous NaCl and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave **19** (3.70 g, 22.4 mmol, 56%) as a colourless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.17 (d, *J*=0.8 Hz, 2H), 6.11 (dd, *J*=0.4, 0.8 Hz, 1H), 6.50 (d, *J*=0.4 Hz, 1H), 9.00 (br s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.4 (CH_2), 131.7 (CH_2), 136.8 (C_q), 170.5 (C_q); MS (EI) *m*/*z* (rel int.): 164 (100, M^+), 147 (68), 119 (37), 85 (70). All analytical data is in agreement with those reported in Ref. 22

*3.1.5. 2-(Aminomethyl)acrylic acid (**15**)*

A solution of acid **19** (245 mg, 1.48 mmol) in 25% aqueous NH_3 was stirred for 17 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 1 N HCl. After washing with EtOAc, the aqueous phase was evaporated to dryness to give **15** as a colourless solid along with oligomers resulting from partial degradation. ^{1}H NMR (250 MHz, D_2O) δ 3.82 (s, 2H), 6.11 (s, 1H), 6.51 (s, 1H); ^{13}C NMR (63 MHz, D_2O−CD_3OD) δ 41.4 (CH_2), 131.7 (CH_2), 134.6 (C_q), 168.0 (C_q).

*3.1.6. 2-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)acrylic acid (**21**)*[15]

To a mixture of acid **19** (900 mg, 5.50 mmol) and K_2CO_3 (912 mg, 6.60 mmol) in dry CH_3CN (12 mL) under argon was added tetrahydroisoquinoline **20** (1.03 mL, 8.20 mmol). While stirring at 40 °C, the reaction course is monitored by TLC. Complete consumption of acid **19** was usually observed after 2 h, and the resulting mixture was then filtered. Concentration of the filtrate in vacuo and purification by column chromatography gave **21** (1.07 g, 4.90 mmol, 90%) as a light yellow oil. R_f=0.5 (CH_2Cl_2−MeOH−AcOH, 66:33:1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10 (t, *J*=6.0 Hz, 2H), 3.44 (t, *J*=6.0 Hz, 2H), 3.86 (s, 2H), 4.28 (s, 2H), 5.72 (s, 1H), 6.43 (s, 1H), 7.22 (m, 4H); ^{13}C NMR δ 29.8 (CH_2), 51.8 (CH_2), 57.0 (CH_2), 61.0 (CH_2), 121.4 (CH_2), 126.7 (CH), 127.3 (CH), 127.5 (CH), 129.6 (CH), 135.4 (C_q), 136.0 (C_q), 166.6 (C_q), one C_q-signal missing. All analytical data is in agreement with those reported in Ref. 15

*3.1.7. 2-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-3-(4-fluorophenyl)propionic acid (**22**)*

Preparation according to the general procedure for non-radioactive fluoroarylation. Purification by column chromatography. R_f=0.85 (CH_2Cl_2−MeOH−AcOH, 8:2:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.77–3.29 (m, 3H), 3.76 (t, *J*=5.9 Hz, 2H), 3.63 (t, *J*=5.9 Hz, 2H), 3.58 (s, 2H), 4.09 (m, 2H), 6.87–7.14 (m, 8H), 11.48 (s, 1H); ^{13}C NMR (360 MHz, $CDCl_3$) δ 25.8 (CH_2), 35.2 (CH_2), 43.4 (CH), 49.2 (CH_2), 53.5 (CH_2), 56.7 (CH_2), 115.3 (d, J_{CF}=21.2 Hz, 2×CH), 125.6 (CH), 126.5 (CH), 126.7 (CH), 127.3 (CH), 130.3 (d, J_{CF}=7.9 Hz, 2×CH), 131.8 (C_q), 133.9 (C_q), 134.3 (d, J_{CF}=3.2 Hz, C_q), 162.8 (d, J_{CF}=244.4 Hz, C_q), 174.8 (C_q); ^{19}F NMR (234 MHz, $CDCl_3$+$CFCl_3$) δ −117.2; MS (ESI) *m*/*z*: 314 (M^++H); HRMS (ESI) calcd for $C_{19}H_{21}FNO_2$ [M^++H] 314.1556, found 314.1555.

*3.1.8. (E)-4-Bromobut-2-enoic acid (**26**)*[23]

A suspension of crotonic acid (8.60 g, 100 mmol), *N*-bromosuccinimide (21.4 g, 120 mmol) and AIBN (500 mg, 3.05 mmol) in CCl_4 (200 mL) was heated to 95–100 °C. Heating was stopped when all undissolved material had moved from bottom to the top of the solution (ca. 6 h). The resulting mixture was cooled in an ice-bath, filtered and evaporated to dryness to give crude **26**, which was used for the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.03 (dd, *J*=1.3, 7.3 Hz, 2H), 6.04 (td, *J*=1.3, 15.3 Hz, 1H), 7.11 (td, *J*=7.3, 15.3 Hz, 1H); ^{13}C NMR (63 MHz, CD_3OD) δ 30.4 (CH_2), 124.5 (CH), 145.3 (CH), 170.5 (C_q). All analytical data is in agreement with those reported in Ref. 23

*3.1.9. (E)-4-Aminobut-2-enoic acid (**23**)*[24]

A solution of crude bromide **26** (7.80 g, 47.3 mmol) in 25% aqueous NH_3 was stirred for 20 h at room temperature. The solvent was removed in vacuo and the residue was dissolved in MeOH. After stirring for 1 h, the mixture was kept at 5 °C for 15 h. Filtration and drying in vacuo gave **23** (1.47 g, 14.5 mmol, 31%) as an ochre-coloured solid. ^{1}H NMR (250 MHz, D_2O) δ 3.55 (dd, *J*=1.1, 6.0 Hz, 2H), 5.90 (td, *J*=1.1, 15.8 Hz, 1H), 6.34 (td, *J*=6.0, 15.8 Hz, 1H); ^{13}C NMR (63 MHz, D_2O+CD_3OD) δ 40.8 (CH_2), 132.3 (CH), 133.9 (CH), 174.7 (C_q). All analytical data is in agreement with those reported in Ref. 24

*3.1.10. 4-Amino-3-(4-fluorophenyl)butyric acid (**24**)*

Preparation according to the general procedure for non-radioactive fluoroarylation. Purification by preparative HPLC. ^{1}H NMR (250 MHz, D_2O) δ 2.55 (dd, J=8.8, 16.0 Hz, 1H), 2.66 (dd, J=5.5, 16.0 Hz, 1H), 3.05 (m, 1H), 3.15–3.29 (m, 2H), 6.97 (dd, J_{HF}=8.8 Hz, J=8.8 Hz, 2H), 7.17 (dd, J_{HF}=5.5 Hz, J=8.8 Hz, 2H); ^{13}C NMR (90 MHz, D_2O+CD_3OD) δ 39.3 (CH_2), 40.3 (CH), 44.8 (CH_2), 117.0 (d, J_{CF}=21.6 Hz, 2×CH), 130.7 (d, J_{CF}=8.4 Hz, 2×CH), 135.1 (d, J_{CF}=3.2 Hz, C_q), 163.3 (d, J_{CF}=244.1 Hz, C_q), one C_q-signal missing; ^{19}F NMR (234 MHz, CD_3OD+$CFCl_3$) δ −114.8; MS (ESI) m/z: 198 (M^++H); HRMS (ESI) calcd for $C_{10}H_{13}FNO_2$ [M^++H] 198.0930, found 198.0927.

3.2. Radioactive experiments

3.2.1. Synthesis of 4-[^{18}F]fluorobenzenediazonium salt

Preparation of 4-[^{18}F]fluoroaniline was performed according to Olma et al.[7] Diazotization was performed according to Patt et al.[4] The 4-[^{18}F]fluorobenzenediazonium salt was used without further purification.

*3.2.2. ^{18}F-fluoroarylation of **10b**, **21** and **23***

For ^{18}F-fluoroarylation the precursors **10b**, **11** and **23** were dissolved in aqueous titanium(III) chloride (500 μL). 4-[^{18}F]fluorobenzenediazonium ion (10 MBq) was added in 100 μL HCl/HNO_2 (90 μL, 1 M HCl; 10 μL, 1 M HNO_2). Reaction was performed using varying reaction conditions (Tables 2 and 3). The radiochemical yields were determined by RP-HPLC (column: Nucleosil 100 C18, 5 μm, 125×4.6 mm; CS GmbH) using gradient elution at a flow rate of 1 mL/min and UV detection at 214 nm. Solvent A: 0.05% of TFA in water; solvent B: 0.04% of TFA in CH_3CN. The following gradient was used for **11b***: 0 min 20% B, 10 min 90% B, 15 min 90% B (t_R=5.9 min). For **22*** as the gradient was used: 0 min 20% B, 15 min 90% B (t_R=8.9 min). For **24*** as the gradient was used: 0 min 5% B, 10 min 35% B, 12 min 100% B (t_R=6.4 min). Compound identification was performed by the comparison of retention times with those obtained with the synthesized reference compound.

Acknowledgements

This work was financed by the Fonds der Chemischen Industrie (Liebig fellowship) and the Leonhard-Lorenz-Stiftung. The support of Prof. Dr. Thorsten Bach (TU München) and his group is gratefully acknowledged.

References and notes

1. (a) Phelps, M. E. *J. Nucl. Med.* **2000**, *41*, 661–681; (b) Le Bars, D. *J. Fluorine Chem.* **2006**, *127*, 1488–1493.
2. For a recent review, see: Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, 2853–2873.
3. For a review on aryl radical chemistry, see: Galli, C. *Chem. Rev.* **1988**, *88*, 765–792.
4. Patt, J. T.; Patt, M. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 1229–1238.
5. Hultsch, C.; Blank, O.; Wester, H.-J.; Heinrich, M. R. *Tetrahedron Lett.* **2008**, *49*, 1881–1883.
6. Feliu, A. J. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1245–1253.
7. Olma, S.; Ermert, J.; Coenen, H. H. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 1037–1050.
8. (a) For a recent synthesis of [^{18}F]fluorobenzenes from iodonium salts, see: Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. *J. Am. Chem. Soc.* **2007**, *129*, 8018–8025; (b) For a reviews on Sandmeyer reactions, see: Merkushev, E. B. *Synthesis* **1988**, 923–937.
9. For first reports on the reductive Meerwein arylation, see: (a) Citterio, A.; Vismara, E. *Synthesis* **1980**, 291–292; (b) Citterio, A.; Cominelli, A.; Bonavoglia, F. *Synthesis* **1986**, 308–309.
10. Kung, H. F.; Lee, C. W.; Zhuang, Z. P.; Kung, M. P.; Hou, C.; Plossl, K. *J. Am. Chem. Soc.* **2001**, *123*, 12740–12741.
11. For a first synthesis of stilbenes from arenediazonium salts, see: Obushak, N. D.; Lyakhovich, M. B.; Ganushchak, N. I.; Bilaya, E. E. *J. Org. Chem. USSR* **1983**, *19*, 1391–1392.
12. For captodative radicals, see: (a) Birkhofer, H.; Hädrich, J.; Beckhaus, H. D.; Ruechardt, C. *Angew. Chem.* **1987**, *99*, 592–594; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 573–575; (b) Stella, L.; Harvey, J. N. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: 2001; Vol. 1, pp 360–378.
13. (a) Whitesides, G. M.; Singh, R. *J. Am. Chem. Soc.* **1990**, *112*, 1190–1197; (b) Rambaud, M.; Villieras, J. or *Org. Synth.* **1993**, *Collect. Vol. VIII*, 265–267; *Org. Synth.* **1988**, *66*, 220–221.
14. Bittman, R.; Byun, H.-S.; Reddy, K. C. *Tetrahedron Lett.* **1994**, *35*, 1371–1374.
15. Grigg, R.; Myers, P.; Somasunderam, A.; Sridharan, V. *Tetrahedron* **1992**, *48*, 9735–9744.
16. Allan, R. D.; Twitchin, B. *Aust. J. Chem.* **1978**, *31*, 2283–2289.
17. Citterio, A.; Minisci, F.; Vismara, E. *J. Org. Chem.* **1982**, *47*, 81–88.
18. (a) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1302–1306; (b) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213–1221; (c) Allan, R. D.; Bates, M. C.; Drew, C. A.; Duke, R. K.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511–2524; (d) Langlois, N.; Dahuron, N.; Wang, H.-S. *Tetrahedron* **1996**, *52*, 15117–15126.
19. (a) Berthelot, P.; Vaccher, C.; Flouquet, N.; Debaert, M.; Luyckx, M.; Brunet, C. *J. Med. Chem.* **1991**, *34*, 2557–2560; (b) Costantino, G.; Macchiarulo, A.; Guadix, A. E.; Pellicciari, R. *J. Med. Chem.* **2001**, *44*, 1827–1832.
20. Tyagi, O. D.; Boll, P. M.; Parmar, V. S.; Taneja, P.; Singh, S. K. *Indian J. Chem., Sect. B* **1992**, *31*, 851–854.
21. Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924–926.
22. (a) Dürrmann, H.; Weyerstahl, P. *Chem. Ber.* **1979**, *112*, 3480–3485; (b) See also Ref. 13a.
23. Tulla-Pucha, J.; Barany, G. *Tetrahedron* **2005**, *61*, 2195–2201.
24. Liu, S.; Hanzlik, R. P. *J. Med. Chem.* **1992**, *35*, 1067–1075.