Research Article

Syntheses of novel N-([18F]fluoroalkyl)-N-nitroso-4-methyl-benzenesulfonamides and decomposition studies of corresponding 19F- and bromo-analogues: potential new compounds for the 18F-labelling of radiopharmaceuticals

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Summary

N-([18F]fluoroalkyl)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl = (−CH$_2$)[18,19F]F, $n = 2$–4)] were synthesized in radiochemical yields ranging from 75–90% to provide new secondary labelling precursors for the syntheses of ^{18}F-labelled compounds. Preliminary decomposition studies utilizing the corresponding non-radioactive ^{19}F-compounds as well as the bromo containing analogous compounds were performed to evaluate their stability regarding temperature and basicity of the labelling medium. Furthermore, initial difficulties in labelling these compounds led to the development of a modified labelling procedure applying nearly solvent-free conditions. Extensive decomposition experiments of the new fluoro- as well as the bromo-compounds were conducted under various conditions in order to get experimental data about their stability and reactivity. As a result, different trends for the stability of the bromo as well as

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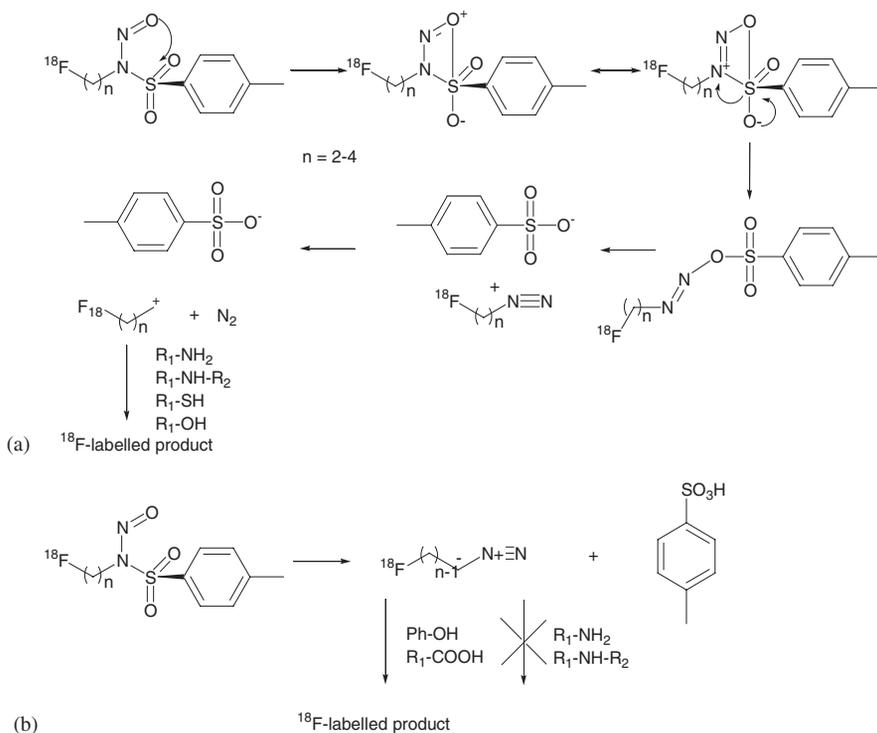
the fluoro compounds could be observed. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: ^{18}F-nitroso-sulfonamides; secondary labelling precursor; decomposition studies; ^{18}F-fluoroalkylation

Introduction

[18]F-Fluoroalkylation is a useful alternative method for introducing the ^{18}F-label into polyfunctional molecules like radiopharmaceuticals for positron emission tomography (PET).[1] Especially for H-acidic compounds, which do not lend themselves to direct nucleophilic fluorination, fluoroalkylation makes it possible to introduce [^{18}F]fluoralkyl groups, such as C_2H_4[^{18}F]F, into NH, OH, and SH functionalities applying 2-[^{18}F]fluoroethyltosylate.[2] Bifunctional alkanes like 1-bromo-2-[^{18}F]fluoroethane and analogues can also be applied as precursors for ^{18}F-fluoroalkylations, which are easily prepared via anion activated nucleophilic ^{18}F-substitution of the corresponding di-bromoalkanes.[3] ^{18}F-Fluorobenzylation applying 4-[^{18}F]fluorobenzylbromide has been used for the syntheses of fluorinated radiopharmaceuticals.[4] A general drawback of these labelling precursors is their lack of selectivity with regard to polyfunctional molecules containing HO- or NH-groups. A selective base-supported ^{18}F-fluoroalkylation of the H-acidic groups like phenolic HO- or COOH-moieties can be accompanied by the undesired alkylation of the nucleophilic NH-group, making the use of suitable NH-protecting groups necessary. To circumvent these difficulties, the development and search for new potential labelling precursors with different labelling properties are of great interest in radiopharmaceutical chemistry. The synthesis of a 4-[^{18}F]fluorobenzenediazonium cation for example has recently been described for the labelling of aromatic compounds via azo-coupling.[5] *N*-Alkyl-*N*-nitrosoamides are compounds of diminished stability and are of great interest in medicine[6], biochemistry[7] and industrial chemistry.[8] Especially in organic chemistry *N*-nitrosamides have been widely used[9] and opened a route to highly reactive carbocations. *N*-4-R-Benzyl-*N*-nitrosopivalamide for example decomposes via a unimolecular pathway[10] to generate short-lived nitrogenous entity-separated ion-pairs, comprising highly reactive 4-R-benzyl cations and the pivalate ion.[8] When the solvent is non-nucleophilic to the carbocation, then the only

product of significance is the ester. Since the benzyl cation is unable to rearrange, to build fragments, and to lose protons, S_N1-type reactions with the counter ion and any sufficiently nucleophilic partner is its only fate. Extensive studies of the electronic effects on the kinetics of thermal deamination were reported by Darbeau et al.[11] In radiopharmaceutical chemistry the concentration of the ^{18}F-labelling precursor is generally in the nanomolar range and the compound which is to be labelled is present in high molar excess. Taking this fact into consideration, radiolabelled carbocations could become useful tools in radiochemistry as new secondary labelling precursors (Scheme 1). Furthermore, the syntheses of [^{18}F]fluorodiazoalkanes for the selective alkylation of H-acidic compounds in the presence of amines could possibly be achieved via basic decomposition of these compounds (Scheme 1). The present study aimed at synthesising these new N-[^{18}F]fluoroalkyl-N-nitroso-4-

Scheme 1. (a) possible thermolytic decomposition of new N-[^{18}F]fluoroalkyl-N-nitroso-4-methyl-benzenesulfonamides.[11b] (b) possible base induced formation of [^{18}F]fluorodiazo-alkanes
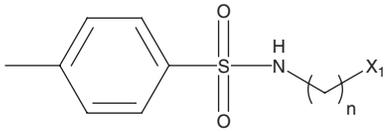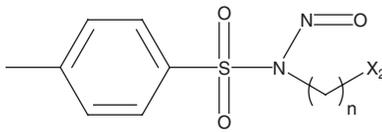
methyl-benzenesulfonamides as a prerequisite for further studies concerning the labelling of organic compounds and radiopharmaceuticals.
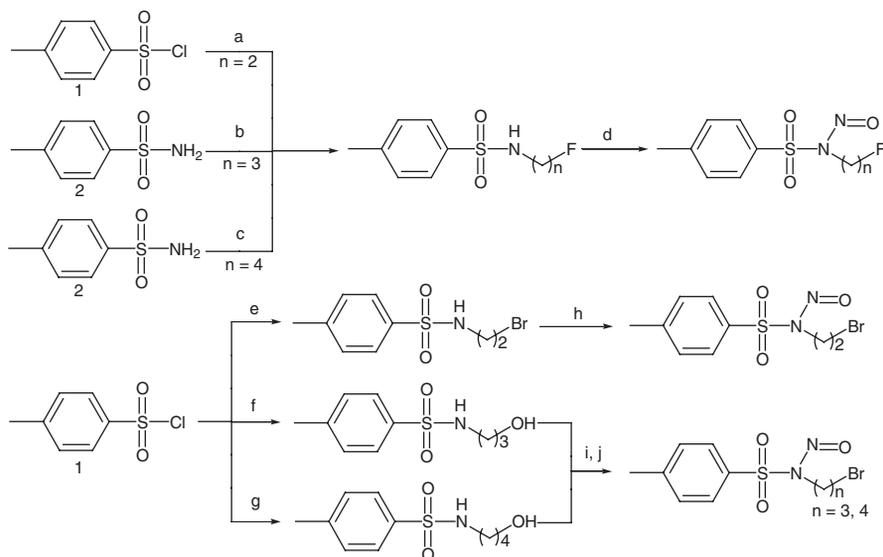
Results and discussion

Syntheses of ^{19}F-standard compounds and labelling precursors (cf. Table 1)

The syntheses of the non-radioactive standard compounds for analytical purposes such as high performance liquid chromatography (HPLC)- and thin layer chromatography (TLC)-conditions as well as for decomposition studies to prove their eligibility for the labelling was achieved according to Scheme 2. In the case of 3, 2-fluoroethylamine and 4-methylbenzenesulfonylchloride (**1**) were used for the synthesis, whereas compounds **4** and **5** were obtained *via* fluoroalkylation of the deprotonated 4-methylbenzenesulfonamide (**2**). The di-fluoroalkylated by-product which was formed during the alkylation step could be separated via column chromatography. The final nitrosation of all fluoroalkyl-nitrosamides was performed with sodium nitrite in acetic acid according to Hyde *et al.*[12] to yield fluoroalkyl-nitrosamides (**11–13**). The labelling precursors for the syntheses of ^{18}F-labelled compounds were all synthesized starting from 4-methylbenzenesulfo-

Table 1. Synthesized compounds

n	X$_1$ (F)	X$_1$ (Br)	X$_1$ (OH)	X$_2$ (F)	X$_2$ (Br)
2	3	6		11	14
3	4	7	9	12	15
4	5	8	10	13	16

Scheme 2. Syntheses of N-(fluoroalkyl)-N-nitroso-4-methyl-benzenesulfona-mides (11–13) and N-(bromoalkyl)-n-nitroso-4-methyl-benzenesulfonamides (14–16) (cf. Table 1): (a) 2-fluoroethylamine hydrochloride, K$_2$CO$_3$, THF; (b) NaH, Cu(I)Cl, 1-bromo-3-fluoropropane, DMF; (c) NaH, Cu(I)Cl, 1-bromo-4-fluorobutane; (d) acetic acid, NaNO$_2$; (e) 2-bromoethylamine hydrochloride, NaHCO$_3$, THF/water; (f) according to Augstein et al.[13]; (g) according to Augstein et al.[13]; (h) acetic acid, NaNO$_2$; (i) according to Augstein et al.[13]; (j) acetic acid, NaNO$_2$

nylchloride (**1**). Compound **6** was obtained by using 2-bromoethylamine and **1** and subsequently nitrosated to yield **14**. The homologous compounds **15** and **16** were synthesized starting from the reaction of the corresponding 3-hydroxypropylamine and 4-hydroxybutylamine with **1** to yield **9**[13] and **10**. The nitrosation of these intermediates was not successful and lead only to the formation of by-products due to the H-acidic conditions. Therefore, previous to the final nitrosation step, the OH-moieties of **9** and **10** were converted into the corresponding bromides.[13] Nitrosation yielded **15** and **16** in good yields.

Radioactive labelling of N-([^{18}F]fluoroalkyl)-N-nitroso-4-methyl benze-nesulfonamides [n-alkyl = (−CH$_2$)$_n$[^{18}F]F, n = 2–4)]

Initial labelling experiments were performed applying standard conditions which involved the azeotropic drying of the aqueous [^{18}F]fluoride-solution in the presence of Kryptofix®2.2.2. and potassium carbonate

with acetonitrile.[2] After drying, a ^{18}F-stock solution in acetonitrile was prepared and the labelling precursors, (*N*-bromoalky)-*N*-nitroso-4-methyl-benzensulfonamides [*n*-alkyl = (–CH₂)Br *n* = 2–4)]) (**14–16**), dissolved in acetonitrile were added at 75°C. Aliquots were taken at several time points and the radiochemical yields (RCYs) were determined with HPLC and TLC. The RCYs of all labelled products (*N*-([^{18}F]fluoroalkyl)-*N*-nitroso-4-methyl-benzensulfonamide [*n*-alkyl = (–CH₂)ₙ[18]F]F *n* = 2–4)] were in the unsatisfactory range of <5% after 2 min reaction time at 75°C. Neither longer reaction times nor changes in the reaction temperature led to increased RCYs. The only way to achieve slightly better RCYs (+2–3%) was to increase the concentration of the labelling precursors (**14–16**) because even after the observed decomposition there was still enough labelling precursor left. But a higher precursor concentration would possibly result in a more difficult purification from the labelled product and is therefore not advisable. To our understanding, these difficulties in labelling are in accordance with the experimental data of the decomposition experiments we conducted afterwards. To obtain experimental data about the behaviour of the *N*-([^{18}F]fluoroalkyl)-*N*-nitroso-4-methyl-benzenesulfonamides as well as the corresponding bromo-labelling precursors under typical labelling conditions and various temperatures we performed decomposition studies to get information about how to modify the labelling set-up in general to maximise RCYs.

Thermal decomposition studies of N-([¹⁹F]fluoroalkyl)-N-nitroso-4-methyl-benzenesulfonamides (¹⁹F-standard compounds) in acetonitrile at 75°C (Figure 1(A))

To get information about the general thermal stability of the ^{19}F-compounds **11–13** we conducted decomposition experiments without adding nucleophiles or bases.

The decomposition studies of compounds **11–13** were performed applying the dynamic ^{1}H NMR (400 MHz) technique. All ^{19}F-standard compounds underwent thermal decomposition in [D₃]acetonitrile at 75°C. This solvent was used because it is usually applied in nucleophilic ^{18}F-labelling reactions at temperatures between 70 and 80°C. The product distribution was determined with ^{1}H NMR as well as FD-mass spectrometry (at the end of experiment) focusing especially on the protons of the aryl-groups. Plots (Figure 1) of the decomposition data gave first order decomposition kinetics (Figure 1(A)).[10] Additionally the
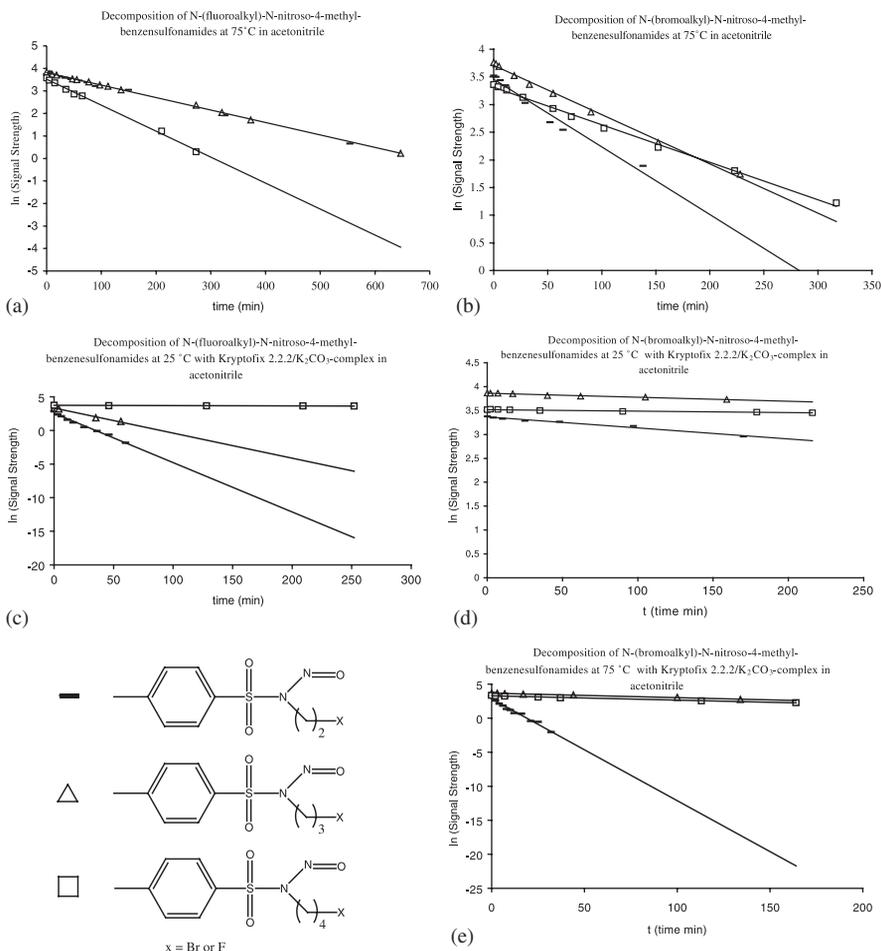
Figure 1. Decomposition studies of *N*-(halogenoalkyl)-*N*-nitroso-4-methyl benzenesulfonamides (fluoro-derivatives **11–13** and bromo-derivatives **14–16**): (a) **11–13**, acetonitrile, 75°C (b) **14–16**, acetonitrile, 75°C, (c) **11–13**, acetonitrile, 25°C, Kryptofix® 2.2.2./K$_2$CO$_3$ (d) **14–16**, acetonitrile, 25°C, Kryptofix® 2.2.2./K$_2$CO$_3$ (e) **14–16**, acetonitrile, 75°C, Kryptofix® 2.2.2./K$_2$CO$_3$

rate constants for each decomposition were determined (Table 2). Half-lives ($t_{1/2}$) for the decomposition were calculated to be 124 min (**11**, [-*N*-(CH$_2$)$_2$F]), 122 min (**12**, [-*N*-(CH$_2$)$_3$F]) and 60 min (**13**, [-*N*-(CH$_2$)$_4$F]). These results indicate that the electron withdrawing effect of the fluorine atom is decreasing with a longer alkyl chain and the compound becomes less stable. This effect is not quantitatively noticeable for the fluoroethyl and fluoropropyl compounds, as these two are of comparable stability but it becomes more pronounced for the

Table 2. (A) HPLC-retention times of the radio-labelled *N*-([¹⁸F]fluoroalkyl)-*N*-nitroso-4-methyl-benzenesulfonamides and of the labelling precursors *N*-(bromo-alkyl)-*N*-nitroso-4-methyl-benzenesulfonamides, (B) half-lifes and rate constants

A Compound no.	HPLC-retention time (min)	RCYs (%)[a]	Overall RCYs (%)[b]
11	16	75 ± 5	50 ± 7
12	17.2	85 ± 4	59 ± 4
13	18.4	90 ± 5	65 ± 5
14	17.8	—	—
15	19.7	—	—
16	20.4	—	—

B Compound no.	Decomp. 75°C		Kryptofix 2.2.2.®/K₂CO₃ 25°C		Kryptofix 2.2.2.®/K₂CO₃ 75°C	
	Half-life (min)	Rate constant (min^{-1})	Half-life (min)	Rate constant (min^{-1})	Half-life (min)	Rate constant (min^{-1})
11	124	0.0056	9.5	0.0734	—	—
12	122	0.0055	19.3	0.036	—	—
13	60	0.0115	1733	0.0004	—	—
14	57	0.0122	347	0.002	4.6	0.1497
15	78	0.0089	740	0.0009	97	0.0071
16	102	0.0068	2310	0.0003	107	0.0065

[a] determined via HPLC (decay corrected).
[b] product radioactivity after HPLC-purification referring to starting activity of used [¹⁸F]Fluoride (not decay corrected).

fluorobutyl compound, resulting in a diminished stability. Darbeau *et al.* suggested that this observation could be related to intramolecular electronic effects, namely that electron repulsing groups accelerate the thermolysis of nitrosamides whereas electron withdrawing groups have stabilising effects.[11b] Nevertheless, all these ¹⁹F-compounds are relatively stable under thermal conditions at 75°C.

Thermal decomposition studies of N-(bromoalkyl)-N-nitroso-4-methyl-benzenesulfonamides (labelling precursors) in acetonitrile at 75°C (Figure 1 (B))

It is also of great interest whether the labelling precursors **14–16** are stable under thermal conditions compared to the corresponding

[19]F-fluoro compounds. The thermal decomposition studies of compounds **14–16** applying the ^{1}H NMR technique were performed as described for the corresponding fluoro-compounds. The thermal stability of the bromo compounds showed a different trend in stability, compound **16** being the most stable. The half-lives were found to be 57 min (**14**, [-N-(CH$_2$)$_2$Br]), 78 min (**15**, [-N-(CH$_2$)$_3$Br]) and 102 min (**16**, [-N-(CH$_2$)$_4$Br]) (Figure 1(B); rate constants cf. Table 2). It is well known that as the alkyl fragment of the nitrosoamide becomes bulkier, the stability of the compound decreases.[14] The influence of the electron-withdrawing bromine in these compounds is obviously not the dominating factor governing stability. In general the bromo compounds are less stable than the fluoro analogues.

Thermal decomposition studies of N-([^{19}F]fluoroalkyl)-N-nitroso-4-methyl-benzenesulfonamides (^{19}F-standard compounds) in acetonitrile at 25 and 75°C with Kryptofix®2.2.2./K$_2$CO$_3$-complex (Figure 1(C))

To obtain data about the time-dependent decomposition of the ^{19}F-standard compounds **11–13** under typical labelling conditions (acetonitrile as solvent, elevated temperatures, Kryptofix®2.2.2./K$_2$CO$_3$-complex to avoid liberation of HF and radioactivity adsorption on the vessel surface and to enhance the nucleophilicity of the [^{18}F]fluoride), ^{1}H NMR experiments were performed at 75°C as well as 25°C. At a temperature of 75°C decomposition of **11–13** was complete within 1–2 min. The fast liberation of gas (presumably nitrogen) was obvious and spoiled the ^{1}H NMR experiment so that no additional data could be obtained. Even at 25°C the decomposition of compounds **11** ($t_{\frac{1}{2}}$ = 9.4 min) and **12** ($t_{\frac{1}{2}}$ = 19.3 min) was rather fast in comparison to compound **13** ($t_{\frac{1}{2}}$ = 1733 min) (Figure 1(C); rate constants cf. Table 2). These results demonstrate the higher stability of **13** and may provide higher RCYs during the labelling procedure.

These experimental results supported our previous assumption that the usually applied method of ^{18}F-fluorination (see experimental part) is unsuitable for the labelling of the bromo precursors to obtain N-([^{18}F]fluoroalkyl)-N-nitroso-4-methyl-benzenesulfonamides. Their stability under the typical labelling conditions is not high enough to guarantee the necessary RCYs which are required for an efficient ^{18}F-labelling of radiopharmaceuticals. These results demand a modification of the labelling procedure. The reaction has to progress fast and the

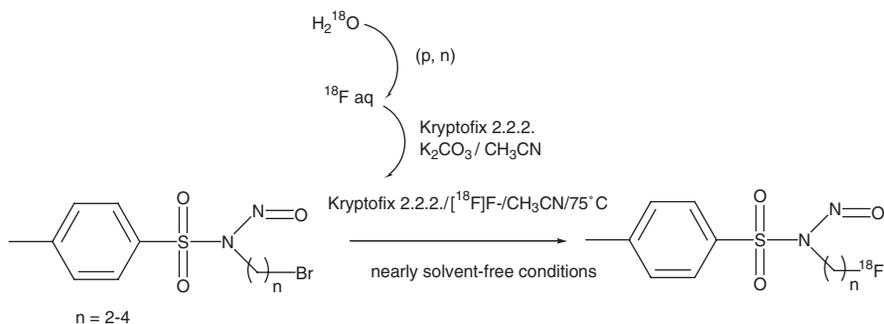solvent volume must be minimized since the decomposition is solvent-mediated.

Thermal decomposition studies of N-(bromoalkyl)-N-nitroso-4-methyl-benzenesulfonamides (labelling precursors) in acetonitrile at 25 and 75°C with Kryptofix®2.2.2./K$_2$CO$_3$-complex (Figure 1(D) and 1(E))

In addition to the decomposition studies of the fluoro compounds at typical labelling conditions and at 25°C, the stability of the bromo bearing precursors, which are also of general interest for the planned labelling reaction, was determined. Therefore, decomposition studies at 25°C in acetonitrile with Kryptofix® 2.2.2./K$_2$CO$_3$ were monitored with ^{1}H NMR. The focus was on the aromatic protons. Plots (Figure 1(D); rate constants cf. Table 2) of the decomposition data gave first order kinetics. When compared with the stability of the corresponding fluoro compounds, it became quite obvious that the half-lives of 347 min **14** [-N-(CH$_2$)$_2$Br], 740 min **15** [-N-(CH$_2$)$_3$Br] and 2310 min **16** [-N-(CH$_2$)$_4$Br] (Figure 1(D); rate constants cf. Table 2) reflect a diminished base lability. It is again noticeable that compound **16** is the most stable because of the longer bromo-alkyl chain.

When the reaction temperature is increased to 75°C, compound **14** decomposes with a relatively short half-life of 4.6 min whereas **15** [-N-(CH$_2$)$_3$Br] and **16** [-N-(CH$_2$)$_4$Br] remain comparably stable with half-lives of 97 and 107 min (Figure 1(E); rate constants cf. Table 2). Concerning a radioactive labelling, the ^{18}F-fluorination of **14** might be more difficult compared to its homologues because the reason for the above mentioned low radiochemical yields in this case is not only the decreased stability of the fluoro compound **11** but also that of the precursor (**14**). From this point of view it is even more necessary to establish an alternative labelling procedure.

Modified labelling procedure of N-([^{18}F]fluoroalkyl)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl = (–CH$_2$)[^{18,19}F]F,n = 2–4)] applying nearly solvent-free conditions

Decomposition of both the labelling precursors and the ^{18}F-labelled products in acetonitrile under basic conditions was observed. Decomposition of the fluoro-compounds **11–13** at typical labelling conditions was too fast to get high radiochemical yields which are a prerequisite for successful application in radiopharmaceutical chemistry. Therefore, we

Scheme 3. Radioactive labelling of bromo precursors 14–16 applying nearly solvent-free conditions to obtain N-([^{18}F]fluoroalkyl)-N-nitroso-4-methyl-benzenesulfonamides (11–13)

established a modified labelling procedure under nearly solvent-free conditions applying high concentrations of precursors and subsequent fast cooling.

This method included the normal azeotropic drying procedure as described above but no ^{18}F-stock solution in acetonitrile was prepared (Scheme 3). On the contrary, the [^{18}F]fluoride/Kryptofix®2.2.2-complex remained adsorbed on the reaction vessels' surface at a temperature of 75–80°C and the precursors **14–16**, dissolved in 0.2 ml acetonitrile at RT were added quickly. After 3 min reaction time (within this time, most of the acetonitrile evaporated into the vapour phase), ice-cold water was added for terminating the reaction and the mixture was passed through a solid phase cartridge (LiChrolute EN, Merck, Germany) to trap the radio-labelled compounds via fixation. After rinsing with water and drying with nitrogen, the cartridge was eluted with acetonitrile (40°C). The eluate was subsequently analysed via radio-HPLC and radio-TLC. The RCYs of the N-([^{18}F]fluoroalky)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl = (–CH$_2$)[$^{18, 19}$F]F, n=2–4)] were between 75 and 90% (Table 2).

Experimental

Syntheses of ^{19}F-compounds and labelling precursors

N-(2-Fluoroethyl)-4-methyl-benzenesulfonamide **(3)**. 2-Fluoroethylamine hydrochloride (2 g, 0.02 mol) and 4-methyl-benzenesulfonylchloride (**1**) (2 g, 0.01 mol) were suspended in THF (20 ml), aqueous potassium

carbonate solution (3 M, 52 ml) was added and stirred under reflux for 2 h. The progress of the reaction was monitored via TLC. After the reaction was complete, the mixture was concentrated to a small volume and the precipitating product was isolated via filtration. The crude precipitate was washed with ice-water and dried under vacuum (1×10^{-3} bar). Yield: 2.01 g (88%) of a white powder. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.8 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 4.7 (t, 2 H, CH$_2$–F), 3.2 (t, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 143.5, 136.5, 129.0, 126.8, 82.0, 79.6, 43.3, 21.3 ppm. ^{19}F NMR (400 MHz, CDCl$_3$): δ = −222 ppm. MS (FD): *m/z* (%) = 217 (100) [M$^+$]. Analysis: calculated. C, 49.75; H, 5.57; N, 6.45; found. C, 49.74; H, 5.42; N, 6.59.

N-(2-Fluoroethyl)-N-nitroso-4-methyl-benzenesulfonamide (**11**). (**3**) (2 g, 9.2 mmol) was dissolved in warm acetic acid (14 ml) and 1 ml of water. The solution was cooled to 5°C and NaNO$_2$ (2.3 g, 33 mmol) was added in small portions. After 20 min the reaction mixture was poured into ice water (50 ml) and extracted with dichloromethane (20 ml). The organic phase was washed with KOH 0.5 *N* (3 × 20 ml), dried over Na$_2$SO$_4$ and evaporated under vacuum. Yield: 1.97 g (86%) of a yellow powder. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.9 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 4.4 (dt, 2 H, CH$_2$–F, ^{2}J$_{HF}$ 47 Hz), 4.1 (dt, 2 H, CH$_2$–N, ^{3}J$_{HF}$ 24 Hz), 2.3 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 146.0, 134.4, 130.0, 128.1, 79.9 (^{1}J$_{CF}$ 170 Hz), 42.2 (^{2}J$_{CF}$ 29 Hz), 21.5. ^{19}F NMR (400 MHz, CDCl$_3$): δ = −222 ppm. MS (FD): *m/z* (%) = 246 (100) [M$^+$]. Analysis: calculated. C; 43.90; H, 4.50; N, 11.38; found. C, 44.20; H, 4.62; N, 11.49.

N-(3-Fluoropropyl)-4-methyl-benzenesulfonamide (**4**). 4-Methyl-benzenesulfonamide (**2**) (6 g, 35 mmol) was dissolved in DMF (100 ml) under argon, NaH (0.42 g, 10.5 mmol) was added and the mixture was stirred at 80°C for 1 h. To the solution, Cu(I)Cl (30 mg) and 1-bromo-3-fluoropropane were added and the mixture was heated at 80°C for 12 h. The solution was poured into water (150 ml) and extracted with ether (3 × 100 ml). The organic layer was dried over Na$_2$SO$_4$ and the solvent was removed under vacuum. The crude product was purified via column chromatography (*n*-hexane/ethylacetate 4:1) on silica gel. Yield: 2.2 g (27%) of a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 4.5 (m, 3 H, CH$_2$–F), 3.1 (q, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$), 1.8 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): 143.3,

136.5, 129.4, 126.8, 82.2, 80.6, 39.6, 21.2, 20.8, 13.9. ^{19}F NMR (400 MHz, CDCl$_3$) δ = −222 ppm. MS (FD): m/z (%) = 231 (100) [M$^+$]. Analysis: calculated. C, 51.93; H, 6.10; N, 6.06; found. C, 51.82; H, 5.92; N, 6.29.

N-(3-Fluoropropyl)-N-nitroso-4-methyl-benzenesulfonamide **(12)**. The nitrosation of (**4**) was performed as described for compound **11**. The crude product was purified via column chromatography (*n*-hexane/ ethylacetate 4/1) on silica gel. Yield: 51% of a yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.9 (d, 2 H, Ar–H), 7.4 (d, 2 H, Ar–H), 4.3 (m, 2 H, CH$_2$–F, ^{2}J$_{HF}$ 47 Hz), 3.8 (q, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$), 1.8 (m, 2 H, CH$_2$, ^{3}J$_{HF}$ 26 Hz) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 146.0, 134.4, 130.1, 127.8, 81.5, 79.9, 39.4, 28.7, 21.5 ppm. ^{19}F NMR (400 MHz, CDCl$_3$): δ = −222 ppm. MS (FD): m/z (%) = 260 (100) [M$^+$]. Analysis: calculated. C, 46.14; H, 5.03; N, 10.76; found. C, 46.28; H, 5.14; N, 10.94

N-(4-Fluorobutyl)-4-methyl-benzenesulfonamide **(5)**. The fluorobutyla- tion of 4-methyl-benzenesulfonamide (**2**) was performed as described for compound **4**. The crude product was purified via column chromato- graphy (n-hexane/ethylacetate 7/3). Yield: 60% of a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 4.3–4.8 (m, 2 H, CH$_2$–F), 3.0 (q, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$), 1.7 (m, 4 H, 2 × CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 143.2, 136.7, 129.5, 126.8, 84.0, 82.4, 60.1, 42.5, 27.2, 25.5, 21.2, 20.8, 13.9 ppm. ^{19}F NMR (400 MHz, CDCl$_3$): δ = −219 ppm. MS (FD): m/z (%) = 245 (100) [M$^+$]. Analysis: calculated C, 53.86; H, 6.57; N, 5.71; found. C, 53.69; H, 6.40; N, 5.93.

N-(4-Fluorobutyl)-N-nitroso-4-methyl-benzenesulfonamide **(13)**. The ni- trosation of **5** was performed as described for compound 11. No purification via column chromatography was necessary. Yield: 78% of a yellow oil (compound solidifies at 4°C). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.9 (d, 2 H, Ar–H), 7.4 (d, 2 H, Ar–H), 4.2–4.5 (m, 2 H, CH$_2$–F), 3.7 (t, 2 H, CH$_2$–N), 2.5 (s, 3 H, CH$_3$), 1.6 (m, 4 H, 2 × CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 145.9, 134.8, 130.0, 127.0, 83.7, 42.3, 27.5, 27.3, 23.7, 21.5 ppm. ^{19}F NMR (400 MHz, CDCl$_3$): δ = −219 ppm. MS (FD): m/z (%) = 274 (100) [M$^+$], 246 (65). Analysis: calculated. C, 48.16; H, 5.51; N, 10.21; found. C, 48.02; H, 5.36; N, 10.43.

N-(2-Bromoethyl)-N-methyl-benzenesulfonamide (**6**). 2-Bromoethylamine hydrobromide (10.7 g, 0.052 mol) and 4-methylbenzenensul-fonylchloride (**1**) (9.9 g, 0.052 mol) were dissolved in THF (60 ml). To the mixture, $NaHCO_3$ (11 g) in water (80 ml) was added and the mixture was heated for 6 h at 60°C. The reaction mixture was extracted with ether (3×70 ml), the organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. Yield: 7.4 g (51%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 3.4 (m, 4 H, $2 \times CH_2$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 143.6, 136.6, 129.7, 126.8, 44.3, 31.3, 21.3 ppm. MS (FD): *m/z* (%) = 279 (100) [M$^+$]. Analysis: calculated. C, 38.86; H, 3.61; N, 9.12; found. C, 39.02; H, 3.74; N, 9.30.

N-(2-Bromoethyl)-N-nitroso-4-methyl-benzenesulfonamide (**14**). The nitrosation of **6** was performed as described for compound **11**. No purification via column chromatography was necessary. Yield: 46% of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.9 (d, 2 H, Ar–H), 7.4 (d, 2 H, Ar–H), 4.1 (t, 2 H, CH_2–Br), 3.4 (t, 2 H, CH_2–N), 2.4 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 146.2, 134.1, 130.2, 127.9, 44.3, 25.2, 21.1 ppm. MS (FD): *m/z* (%) = 308 (100) [M$^+$], 278 (25), 156 (25). Analysis: calculated. C, 35.19; H, 3.61; N, 9.12; found. C, 34.98; H, 3.32; N, 9.31.

N-(3-Hydroxypropyl)-4-methyl-benzenesulfonamide (**9**). This compound was synthesized according to Augstein *et al.*[13] In the original literature no NMR-, MS- or elemental analyses data were presented. Yield: 78% (63% lit.) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 3.7 (t, 1 H, CH_2–O), 2.4 (s, 3 H, CH_3), 2.1 (m, 2 H, CH_2–N), 1.7 (m, 2 H, CH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 143, 136, 129.5, 126.8, 65.6, 40.6, 31.2, 21.3 ppm. MS (FD): *m/z* (%) = 229 (100) [M$^+$], 230 (**14**). Analysis: calculated. C, 52.38; H, 6.59; N, 6.11; found. C, 52.22; H, 6.53; N, 6.30.

N-(3-Bromopropyl)-4-methyl-benzenesulfonamide (**7**). This compound was synthesized according to Augstein *et al.*[13] In the original literature no NMR-, MS- or elemental analyses data were presented either and the crude product was not purified and used without purification. We performed column chromatography (*n*-hexane/ethylacetate 1:1) and obtained **7** as a pure compound. Yield: 29% of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 3.4 (t,

2 H, CH$_2$-Br), 3.1 (t, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$), 2.0 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 143.4, 136.4, 129,6, 126,8, 41.2, 32.1, 30.0, 21.3 ppm. MS (FD): m/z (%) = 292 (100) [M$^+$]. Analysis: calculated. C, 41.11; H, 4.83; N, 4.79; found. C, 40.02; H, 4.99; N, 4.82.

N-(3-Bromopropyl)-N-nitroso-4-methyl-benzenesulfonamide (**15**). The nitrosation of **7** was performed as described for compound **11**. No purification via column chromatography was necessary. Yield: 75% of a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.9 (d, 2 H, Ar–H), 7.4 (d, 2 H, Ar–H), 3.8 (t, 2 H, CH$_2$–N), 3.3 (t, 2 H, CH$_2$–Br), 2.4 (m, 4 H, 2 × CH$_2$), 2.0 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 146.0, 134.3, 130.1, 127.9, 41.5, 30.4, 29.3, 21.5 ppm. MS (FD) m/z (%) = 321 (52) [M$^+$], 293 (100). Analysis: calculated. C, 37.39; H, 4.08; N, 5.76; found. C, 37.25; H, 4.13; N, 5.82.

N-(4-Hydroxybutyl)-4-methyl-benzenesulfonamide (**10**). This compound was synthesized as described for compound 9. 4-Aminobutan-1-ol was used. Yield: 96% of a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 3.6 (t, 2 H, CH$_2$–OH), 3.0 (m, 2 H, CH$_2$–N), 2.4 (s, 3 H, CH$_3$), 1.5 (m, 4 H, 2 × CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 143.1, 136.7, 129.5, 126.8, 61.9, 42.8, 29.3, 25.9, 21.3 ppm. MS (FD): m/z (%) = 243 (100) [M$^+$]. Analysis: calculated. C, 54.30; H, 7.04; N, 5.76; found. C, 54.32; H, 6.97; N, 5.84.

N-(4-Bromobutyl)-4-methyl-benzenesulfonamide (**8**). This compound was synthesized as described for compound **7**. Column chromatography on silica gel (*n*-hexane/ethylacetate 1:1) was performed to purify the compound. Yield: 30% of a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.7 (d, 2 H, Ar–H), 7.3 (d, 2 H, Ar–H), 3.7 (m, 2 H, CH$_2$–N), 3.2 (t, 2 H, CH$_2$–Br), 2.4 (s, 3 H, CH$_3$), 1.7 (m, 4 H, 2 × CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 143.2, 133.7, 129.5, 127.3, 47.7, 32.7, 27.9, 24.9, 21.3 ppm. MS (FD): m/z (%) = 307 (15) [(M + 1)$^+$], 226 (100). Analysis: calculated. C, 43.14; H, 5.27; N, 4.57; found. C, 43.23; H, 5.20; N, 4.64.

N-(4-Bromobutyl)-N-nitroso-4-methyl-benzenesulfonamide (**16**). The nitrosation was performed as described for compound **11**. Column chromatography on silica gel (*n*-hexan/ethylacetate 7:4) was performed to purify the compound. Yield: 25% of a yellow oil. ^{1}H NMR

(400 MHz, CDCl$_3$): δ = 7.9 (d, 2 H, Ar–H), 7.4 (d, 2 H, Ar–H), 3.7 (t, 2 H, CH$_2$–Br), 3.3 (t, 2 H, CH2–N), 2.4 (s, 3 H, CH$_3$), 1.7 (m, 4 H, 2 × CH$_2$) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ = 145.9, 134.5, 130.1, 127.8, 42.0, 32.1, 29.2, 26.2, 21.5 ppm. MS (FD): m/z (%) = 336 (100) [(M + 1)$^+$], 308 (63). Analysis: calculated. C, 39.41; H, 4.51; N, 8.38; found. C, 39.27; H, 4.53; N, 8.46.

Radiosyntheses

N-([^{18}F]Fluoroalkyl)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl= (−CH$_2$)[^{18}F]F, n=2–4)] (general procedure)

No-carrier-added (nca) aqueous [^{18}F]fluoride (100–200 MBq, purchased from several institutions) prepared by the ^{18}O(p,n)^{18}F nuclear reaction on an enriched ^{18}O-water (95%) target was added to a solution of K$_2$CO$_3$ (15 μl (1 N)) and Kryptofix®2.2.2. (10–15 mg) in acetonitrile (800 μl). The water was removed using a stream of nitrogen at 80°C and evaporated to dryness with acetonitrile (2 × 1 ml). To the dried [^{18}F]F-Kryptofix®2.2.2./K$_2$CO$_3$-complex acetonitrile (0.5 ml) was added and precursor compounds 14–16 (10-15 mg, 32.2–48.8 mmol (**14**), 31.1–46.7 mmol (15), 29.8–44.7 mmol (16)) were added and heated in a sealed vial. At several time points aliquots were taken and the RCYs of the radio-labelled products were determined via HPLC (Sykam Pump Model S1121, Gilching, Germany; UV-detection: UV detector Linear, UVIS 200 (254 nm), Linear Instruments, San Jose, USA; radioactivity detection: scintillation detector, MED Isomed 110, Nuklear-Medizin-technik Dresden GmbH, Germany) and radio-TLC (Instant Imager, Packard Canberra, Dreieich, Germany). After only 2 min reaction time max. RCYs of up to 5% could be detected. These low yields led to the development of a modified labelling procedure.

N-([^{18}F]Fluoroalkyl)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl = (−CH$_2$)[^{18}F]F n=2–4)] (modified procedure)

No-carrier-added (nca) aqueous [^{18}F]fluoride (100–200 MBq) prepared by the ^{18}O(p,n)^{18}F nuclear reaction on an enriched ^{18}O-water (95%) target was added to a solution of K$_2$CO$_3$ (15 μl (1 N)) and Krypto-fix®2.2.2. (10–15 mg) in acetonitrile (800 μl). The water was removed using a stream of nitrogen at 80°C and evaporated to dryness with acetonitrile (2 × 1 ml). To the dried Kryptofix® 2.2.2./[^{18}F]fluoride

(70–180 MBq) complex at 75–80°C adsorbed on the sealed vessels' surface, the labelling precursor (**14–16**) (10–15 mg: 32.2–48.8 mmol (**14**); 31.1–46.7 mmol (**15**); 29.8–44.7 mmol (**16**)) dissolved in 0.2 ml acetonitrile (25°C) was added quickly and heated for 3 min at 75–80°C. During this time almost all of the acetonitrile evaporated into the vapour phase. The sealed vial was cooled in an ice bed (NaCl/ice) to stop the reaction, diluted with water (10 ml) and passed through a 18C-Sep-Pack cartridge to fix the radio-labelled compound. The cartridge was dried with nitrogen, eluted with acetonitrile (1 ml) and the volume was reduced to 0.5 ml. Water was added (0.5 ml) and the mixture was injected into an HPLC system (column: Lichrospher 100RP 18EC-5, flow 1 ml/min) to collect the radio-labelled compounds **11–13** (Table 1). After collecting the product, the HPLC solvent was diluted with water (10 × volume of collected HPLC solvent) loaded onto a 18C-Sep-Pack column, dried with nitrogen and eluted with acetonitrile (1–2 ml) to yield **11–13** (70–180 MBq, not decay corrected). The total preparation time was approximately 45 min.

^1H NMR spectra, kinetic measurements

The ^{1}H NMR spectra were recorded on a DRX 400 (Bruker Biospin) spectrometer. In order to obtain the spectrum of the compound directly after the solution process, the time consuming processes of temperature equilibration, locking and shimming were done with a sample tube containing pure deuterated acetonitrile. When the solid compound (40 mmol) was added, the sample tube was shaken to achieve homogeneity and the data acquisition for 16 scans (59 s) was initiated. Two minutes as minimum time intervals are normally sufficient at the beginning of decomposition. The evaluation of the time dependent spectra (thermal decomposition at 25°C and 75°C in acetonitrile, thermal decomposition in acetonitrile by addition of Kryptofix®2.2.2./ K_2CO_3) shows a linear correlation with the logarithm of the normalized integrated signal intensity within the graphs ($\delta = 7.85$ ppm/δ aromatic region).

Determination of product distribution via ^1H NMR and mass spectroscopy

Field desorption mass spectra and NMR spectra of the decomposed species revealed a mixture of compounds. The major ones are: $C_7H_7SO_2$ ($m/z = 155$), $C_7H_7SO_3H$ ($m/z = 172$) and the halogeno-alkyltosylate

M-28 (M molecular weight) indicating the liberation of N_2. The samples examined after longer decomposition times show species such as M-29 (loss of NO and capture of H) resulting in tosylsulfonamides. Detailed analysis of the aliphatic region in the proton NMR spectra of those samples exhibit two principal species: one explained by the loss of N_2 (*vide supra*) the other originating from the tosylsulfonamides as confirmed by spectra comparison.

Conclusion

N-([^{18}F]fluoroalkyl)-N-nitroso-4-methyl-benzensulfonamides [n-alkyl = $(-CH_2)$[^{18}F]F, $n = 2$–4)] might become a versatile new class of secondary labelling precursors for the syntheses of PET-radiopharmaceuticals via *in situ* generation of highly reactive carbocations such as [^{18}F]fluoro-ethyl-, [^{18}F]fluoropropyl- and [^{18}F]fluorobutyl-cations. The syntheses of highly selective [^{18}F]fluorodiazoalkanes for the ^{18}F-fluoroalkylation of H-acidic compounds may also be possible via base catalyzed decomposition of the ^{18}F-nitrosamides. The radioactive ^{18}F-fluorination of the corresponding bromo-precursors could be achieved in high yields of 75–90% (decay corrected) applying a modified labelling technique under nearly solvent-free conditions to circumvent solvent- and base mediated fast decomposition at elevated temperatures, which are prerequisites for nucleophilic ^{18}F-fluorinations in general. Isolation of the ^{18}F-compounds for further uses such as the proposed labelling of proteins and other biomolecules, was conducted via HPLC and solid phase fixation. Extensive decomposition experiments of the analogous non-radioactive ^{19}F- and the corresponding bromo-compounds under varying conditions provided deamination chemistry with the possibility to rationally and efficiently exploit the decomposition of nitrosamides as a possible route to reactive carbocations. Steric as well as electronic effects have a high impact on the stability and the handling of these new radio-labelled nitrosamides. The general value of these new ^{18}F-compounds as labelling precursors in radiochemistry is currently under investigation.

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