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Effect of aldehyde and methoxy substituents on nucleophilic aromatic substitution by [^{18}F]fluoride

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Abstract

For a series of benzaldehydes only with a leaving group or with both a leaving group and a single methoxy substituent ^{18}F-fluorination via nucleophilic aromatic substitution (S_NAr) was studied in DMF and Me_2SO. In general, the radiochemical yields were clearly higher in DMF than in Me_2SO. In the fluorodehalogenation reaction (leaving group: halogen = Br, Cl), extremely low radiochemical yields were observed in Me_2SO (<1%). By monitoring labeling reactions using HPLC, oxidation of the aldehyde function of the precursor was detected. Especially, 2-bromobenzaldehyde was oxidized fastest in Me_2SO (within 3 min reaction time, 90% of the precursor was consumed; radiochemical yield = 1.0 ± 0.5%); however, in DMF oxidation was always kept at a low level during the entire reaction (<5% of the precursor was oxidized; radiochemical yield = 73.0 ± 0.2%). In DMF, nitrobenzaldehydes with a methoxy substituent (methoxy group in *meta*-position to the nitro group) were labeled with good radiochemical yields (4-methoxy-2-nitrobenzaldehyde: 87 ± 3%; 2-methoxy-4-nitrobenzaldehyde: 83 ± 3%; 2-methoxy-6-nitrobenzaldehyde: 79 ± 4%) comparable to the non-substituted nitrobenzaldehydes (2-nitrobenzaldehyde: 84 ± 3%; 4-nitrobenzaldehyde: 81 ± 5%). Moreover, for structurally similar compounds, radiochemical yields showed a good correlation with ^{13}C-NMR ppm values of the aromatic carbon atom bearing the leaving group.

Keywords: Nucleophilic aromatic substitution; Benzaldehydes; Aldehyde oxidation; ^{18}F-labeled aromatic amino acids

1. Introduction

In PET and recent PET/MRI studies, new interest in ^{18}F-labeled aromatic amino acids is apparent [1,2]. With regard to the preparation of amino acids as no-carrier-added (nca) ^{18}F-tracers with high specific activities, nucleophilic aromatic substitution (S_NAr) is to be considered the most attractive type of reaction since fluorine-18 can be applied as [^{18}F]fluoride, which is easily and efficiently produced at a medical cyclotron.

As an example of [^{18}F]amino acid, [^{18}F]FDOPA can be prepared in a multi-step synthesis with the radionuclide being introduced in the first reaction step via S_NAr and the amino acid function is added afterwards [3–5]. Thus, high yields in the labeling reaction are necessary for a good overall radiochemical yield. By the strategy of S_NAr, a direct reaction with [^{18}F]fluoride can be realized easily, if a substituent is present that reduces the electron density of the benzene ring. The aldehyde group appears to be particularly well suited as an auxiliary substituent because it can either be removed catalytically or transferred into a different functional group for further synthetic steps. In the case of tyrosines, the hydroxy group has to be protected when performing nucleophilic substitutions with [^{18}F]fluoride in order to avoid solvation effects resulting in loss of the nucleoplilic properties of [^{18}F]fluoride, a common problem when performing reactions in the typically low radiochemical concentrations. Therefore, S_NAr might be realized in presence of a methoxy group in syntheses of tyrosines. However, it needs to be proven since the methoxy group increases the electron density on the benzene ring and generally decreases the radiochemical yield. Pursuing earlier research on the ^{18}F-labeling of benzaldehyde derivatives [6–14], we evaluated the contrary influence of the aldehyde

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and the methoxy groups on the labeling yield in case of S_NAr reactions.

2. Results and discussion

2.1. General

In this study, all compounds were labeled in DMF and Me_2SO at 140 °C with 10 mg of precursor. In previously reported results from our group [15,16], in general, the radiochemical yield showed a strong dependence on the type of solvent. This observation was consistent with findings of this study (Tables 1 and 2). Radiochemical yields were higher in DMF than in Me_2SO which had usually been used by other groups as solvent for S_NAr reactions.

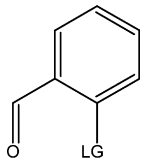
2.2. Benzaldehyde derivatives containing a leaving group

With respect to DMF as labeling solvent, in Me_2SO the extent of decrease of radiochemical yield was strongly dependent on the leaving group. With the fluoro or nitro group as substituent (compounds **1a**, **2a**, **1b**, **2b**), the radiochemical yield was reduced from 75–82% in DMF to 40–68% in Me_2SO. In case of the chloro- or bromo-substituent (compounds **1c**, **2c**, **1d**, **2d**), in Me_2SO the radiochemical yield decreased to less than 2% whereas yields of 65–75% were obtained in DMF (Table 1).

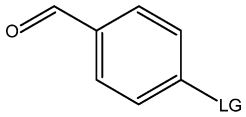
For a better understanding, we examined the labeling reaction in DMF and Me_2SO in the case of *ortho*-bromobenzaldehyde (**1d**) versus a possible effect of oxidation. HPLC analyses showed the formation of the correspondingly

Table 1
Maximum radiochemical yields for ^{18}F-labeling of benzaldehydes only with a leaving group

Leaving group



1

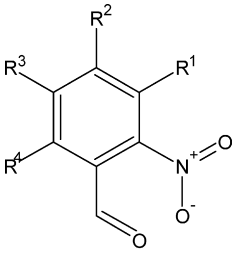


2

	Radiochemical yield[a] (%)			Radiochemical yield[a] (%)		
	DMF	Me_2SO		DMF	Me_2SO	
		This study	Literature		This study	Literature
F (a)	75 ± 1	64 ± 4	–	78.0 ± 0.5	56 ± 4	–
NO_2 (b)	84 ± 3	68.0 ± 0.4	53–78 [6–12]	81 ± 5	40 ± 3	53–75 [6,8–13]
Cl (c)	65 ± 1	0.6 ± 0.3	–	67 ± 3	1.0 ± 0.8	1–6 [12,13]
Br (d)	73.0 ± 0.2	1.0 ± 0.5	–	75.0 ± 0.5	0.8 ± 0.6	3–7 [12,13]

[a] Maximum radiochemical yield at 20 min.

Table 2
Maximum radiochemical yields for ^{18}F-labeling of single methoxy-substituted nitrobenzaldehydes



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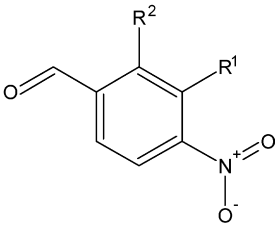

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	Radiochemical yield (%)		
	DMF	Me_2SO	
		This study	Literature
3a (R^1 = OMe)[a]	67 ± 3	6.0 ± 0.6	17–23 [7]
3b (R^2 = OMe)[a]	87 ± 3	74 ± 4	75–87 [7,9]
3c (R^3 = OMe)[b]	55 ± 5	4.0 ± 0.7	5 [7]
3d (R^4 = OMe)[b]	79 ± 4	41.0 ± 0.6	–
4a (R^1 = OMe)[a]	75 ± 1	23 ± 1	29–55 [7,9,10]
4b (R^2 = OMe)[a]	83 ± 3	75 ± 8	74 [10]

[a] Maximum radiochemical yield at 10 min.
[b] Maximum radiochemical yield at 20 min.

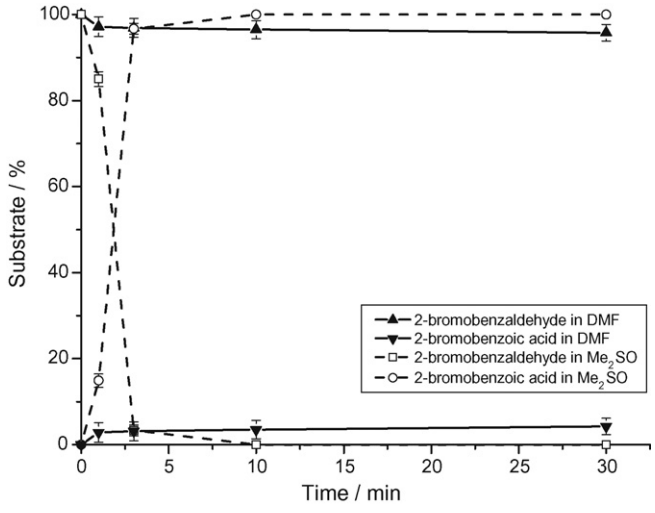

Fig. 1. Oxidation of *ortho*-bromobenzaldehyde (**1d**) to *ortho*-bromobenzoic acid during labeling reactions in DMF or Me_2SO.

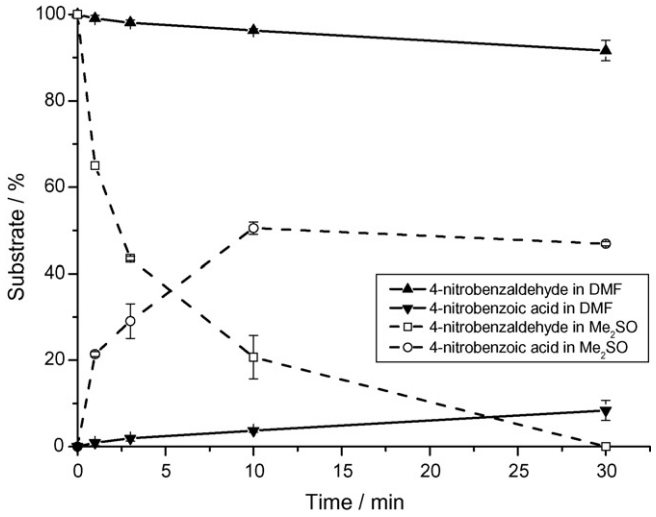

Fig. 3. Conversion of *para*-nitrobenzaldehyde (**2b**) during labeling reactions in DMF or Me_2SO.

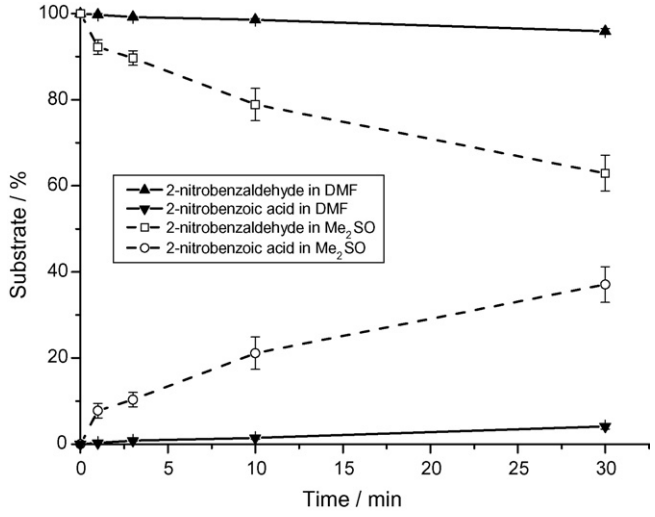

Fig. 2. Formation of *ortho*-nitrobenzoic acid by oxidation of *ortho*-nitrobenzaldehyde (**1b**) in labeling reactions in DMF or Me_2SO.

substituted benzoic acid as result of the oxidation of the carbonyl group (Fig. 1). In Me_2SO more than 90% of **1d** was oxidized within 3 min. In DMF less than 5% of benzoic acid was formed and after 1 min the amount of benzoic acid did not change. These results show oxidation proceeds rapidly in Me_2SO resulting in low labeling yields. Interestingly, no labeled benzoic acid derivatives were observed.

The effect of the carbonyl group *para* or *ortho* to the leaving group should be similar, when substituent effects are considered on the basis of mesomeric interactions. In DMF *ortho*- and *para*-isomers were similarly substituted by [^{18}F]fluoride independent of the leaving group (Table 1). In Me_2SO, no differences between *ortho*- and *para*-isomers were noted except in the case of the nitro group as leaving group. The *ortho*-isomer (**1b**) showed a radiochemical yield of 68 ± 0.4%, the *para*-isomer (**2b**) only 40 ± 3%. For **1b** and **2b**, the labeling reactions in both solvents were also analyzed by HPLC.

In DMF, the formation of oxidation products was always much slower and the concentration of benzoic acid remained below 5% (Figs. 2 and 3) and good labeling yields i.e. 84 ± 3% and 81 ± 5% for *ortho*- and *para*-nitrobenzaldehyde were observed.

In Me_2SO, almost 30% of **1b** was oxidized to benzoic acid within 30 min, the oxidation proceeded faster than in DMF, without giving rise to any other byproducts (Fig. 2). Therefore, radiochemical yield (68 ± 0.4%) was lower than in DMF (84 ± 3%). Labeling of **2b** in Me_2SO was accompanied by a high degree of oxidation. After 30 min there was almost no precursor left due to the conversion to benzoic acid (ca. 50% of

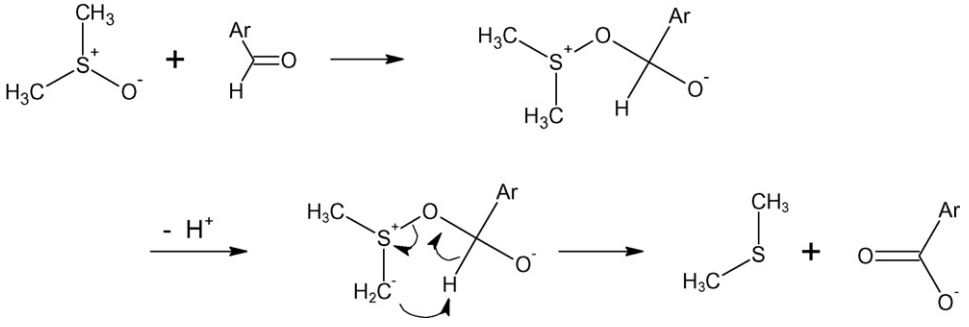

Fig. 4. Suggested mechanism for the oxidation of substituted benzaldehydes in Me_2SO.

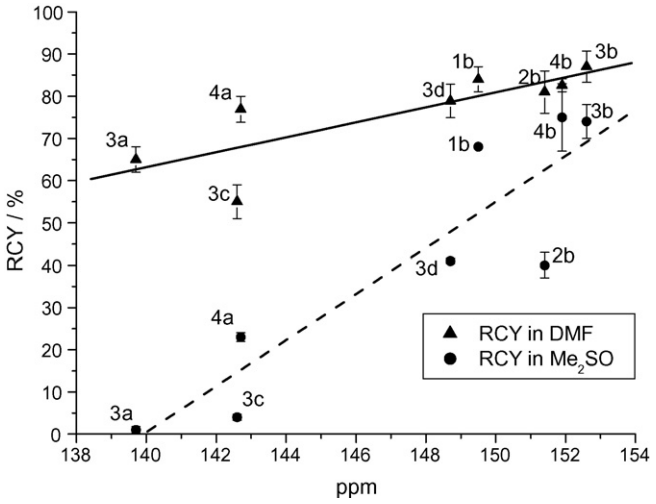

Fig. 5. Correlation of radiochemical yields (RCY) in DMF and Me_2SO with ^{13}C NMR chemical shifts of the aromatic carbon atom bearing the leaving group.

the precursor) and an unidentified byproduct (Fig. 3), but radiochemical yield (40 ± 3%) did not decrease significantly. Neither benzoic acid nor byproduct were detected as radioactively labeled products.

The small amount of oxidation of bromo- and nitrobenzaldehyde (Figs. 1–3) in DMF observed at the beginning of the reaction may be due to dissolved oxygen. The high oxidation rates observed in Me_2SO, however, seem to be the result of an oxidation process mediated by this solvent. Me_2SO is known to be a superior reagent for oxidation of alcohols to carbonyl compounds when it is activated by an electrophile [17–19]. The oxidation of benzaldehydes substituted with electron-withdrawing groups by Me_2SO in the presence of K_2CO_3 can be rationalized as an electrophilic addition of the aldehyde to the nucleophilic oxygen in Me_2SO, followed by deprotonation of the resulting sulfonium intermediate. The sulfur ylide, thus formed, may finally decompose under internal hydrogen abstraction into the anion of the benzoic acid and dimethylsulfide, a mechanism as found similarly in the Swern oxidation [18] (Fig. 4). In this study, benzoic acid was detected by HPLC and dimethylsulfide by GC–MS analysis.

In the case of the isomers **1** and **2** the substitution by [^{18}F]fluoride is reduced because the Cl- and Br-group are poorer leaving groups (Table 1). In these cases, the competing oxidation prevails. As already pointed out, the radiolabeled benzaldehydes formed by nucleophilic displacement by [^{18}F]fluoride do not suffer from subsequent oxidation by Me_2SO. In all cases the fluorine is introduced either *ortho* or *para* to the aldehyde group. Despite its strong electron-withdrawing character, fluorine is also a strong +M-donor. This mesomeric effect lowers the electrophilic character of the aldehydic carbon and may therefore protect the aldehyde from oxidation.

2.3. Benzaldehyde derivatives with a leaving group and an additional methoxy substituent

The methoxy group is an electron donating substituent (strong +M effect) and thus will not favor S_NAr. It is to be expected to decrease nucleophilic substitution at the benzene ring. However, methoxy-substituted benzaldehydes are important intermediates in the radiochemical synthesis of amino acids. Therefore, different nitrobenzaldehydes with a single methoxy group in different positions were studied (Table 2). In spite of the strong electron donating effect of the methoxy group, all radiochemical yields observed in DMF were higher than 55 ± 5%. With the methoxy group *para* to the nitro substituent and *meta* to the aldehyde (**3c**), the lowest substitution yield (55 ± 5%) was obtained. When the methoxy group was *meta* to the nitro group and *ortho* or *para* to the carbonyl group (**3b**, **4b**, **3d**), even better yields (**3b** = 87 ± 3%, **4b** = 83 ± 3% and **3d** = 79 ± 4%) were found compared to 2- or 4-nitrobenzaldehyde (**1b** = 84 ± 3% and **2b** = 81 ± 5%).

In the methoxy-substituted substrates **3** and **4** (Table 2) the yield decrease in Me_2SO was highest for compounds **3a**, **3c** and **4a** (methoxy group *meta* to the aldehyde) and less expressed in compounds **3b**, **3d** and **4b** (methoxy *ortho*- or *para*-oriented to the aldehyde). As discussed above for fluorobenzaldehyde, in the latter compounds direct mesomeric resonance between the methoxy and the carbonyl substituent reduces the electrophilicity of the aldehyde carbon and decreases oxidation of the benzaldehydes by Me_2SO (Fig. 4).

2.4. Correlation of radiochemical yields with ^{13}C NMR chemical shift values

Following earlier findings [7,10] establishing the correlation between radiochemical yield and the ^{13}C NMR chemical shift of the aromatic carbon atom bearing the leaving group, we studied this in both solvents. Good correlations were found for all nitro compounds (Fig. 5, regression line $y = 1.78x - 185$; $r^2 = 0.67$ for DMF; regression line $y = 5.45x - 763$; $r^2 = 0.82$ for Me_2SO). The precursors with higher ppm values for the aromatic carbon bearing the leaving group carry a lower electron density on this reaction center and are more active for nucleophilic substitution.

3. Conclusion

DMF is superior to Me_2SO as solvent in the labeling reaction for benzaldehydes by S_NAr. Benzaldehydes with bromo- or chloro-substituents as leaving group give very low radiochemical yields in Me_2SO due to fast oxidation. With one methoxy substituent at the nitrobenzaldehyde highest radiochemical yields are obtained in DMF when the methoxy group is *meta* to the nitro group and in *ortho*-, *para*-position to the aldehyde group.

4. Experimental

4.1. General

For performing the labeling reactions, Me_2SO and DMF as solvents (stored over molecular sieve) were purchased from Fluka, Germany. Acetonitrile (for DNA synthesis) and Kryptofix 222 were obtained from Merck (Darmstadt,

Germany). For the MPLC system (Büchi, Switzerland) silica gel 60 (0.040–0.063 mm; Merck) was used, eluents were mixtures of petrolether (60/90) and ethylacetate. Precursors and reference standards were characterized by their melting point (Gallenkamp MPG 350, Germany), IR (Spectrum One FT-ATR-IR, Perkin–Elmer, Boston, USA), MS (Finnigan MAT TSQ 70, Bremen, Germany) and NMR (Bruker Avance 400, Rheinstetten, Germany). For NMR measurements, as internal standards the deuterated solvents were used (DMSO-d6: $\delta = 2.49$ in ^{1}H and $\delta = 39.5$ in ^{13}C; $CDCl_3$: $\delta = 7.25$ in ^{1}H and $\delta = 77.0$ in ^{13}C). The chemical shift δ in ppm was referred to the internal standard. All radiochemical yields given in this work represent an average of three to five experiments.

4.2. Precursors and reference standards

As precursors and reference standards, the following compounds of the highest purity available were from either Sigma–Aldrich, Fluka, ABCR, Alfa Aesar, AVOCADO or Fluorochem and were used as received (authenticity of the fluoro compounds used as standards was confirmed by NMR and MS): 2-fluorobenzaldehyde (**1a**; purity 97%), 4-fluorobenzaldehyde (**2a**; >98%), 2-nitrobenzaldehyde (**1b**; 98%), 4-nitrobenzaldehyde (**2b**; 98%), 2-chlorobenzaldehyde (**1c**; 99%), 4-chlorobenzaldehyde (**2c**; 97%), 2-bromobenzaldehyde (**1d**; >98%), 4-bromobenzaldehyde (**2d**; >97%), 3-methoxy-2-nitrobenzaldehyde (**3a**; >97%), 4-nitro-2-methoxybenzaldehyde (**4b**; 97%), 2-fluoro-3-methoxybenzaldehyde (97%), 2-fluoro-4-methoxybenzaldehyde (98%), 2-fluoro-5-methoxybenzaldehyde (98%), 2-fluoro-6-methoxybenzaldehyde (98%), 4-fluoro-3-methoxybenzaldehyde (98%), 4-fluoro-2-methoxybenzaldehyde (98%), 2-bromobenzoic acid (98%), 2-nitrobenzoic acid (98%) and 4-nitrobenzoic acid (>98%).

All other precursors in Table 2 were synthesized as follows.

4.2.1. 4-Methoxy-2-nitrobenzaldehyde (*3b*)

4-Bromo-3-nitroanisole (1.75 g, 7.5 mmol) was dissolved in anhydrous THF (80 mL) under argon. The solution was cooled to −78 °C, and phenyl lithium (4 mL, 7.5 mmol) was added dropwise. The temperature was kept between −70 and −90 °C for 2 h. Then, DMF (1.5 mL, 20 mmol) was added dropwise and the reaction solution was stirred between −70 and −90 °C for an additional hour. After warming to 0 °C within 1 h the solution was quenched by adding acetic acid (100%; 5 mL). The resulting mixture was partitioned between 100 mL of diethylether and 50 mL of water. The organic layer was washed with 50 mL of saturated $NaHCO_3$ solution, 50 mL of water and 50 mL of brine, dried over Na_2SO_4 and concentrated to afford a crude product, which was purified by MPLC (petrolether:ethylacetate, 9:1) to yield 0.9 g **3b** as yellow crystals (65%).

mp: 95–96 °C (96–97 °C [20]).

^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 10.28$ (s, 1H, –C*H*O), 7.96 (d, 1H, $J = 8.5$ Hz, H_{arom}), 7.50 (d, 1H, $J = 2.6$ Hz, H_{arom}), 7.22 (d, 1H, $J = 8.8$ Hz, H_{arom}), 3.95 (s, 3H, –OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 56.3$, 109.6, 119.1, 123.4, 131.5, 151.6, 163.7, 187.0.

IR ($\bar{\nu}$, cm^{-1}): 3104 (85%), 3066 (82%), 2945 (84%), 2841 (85%), 1679 (56%), 1600 (59%), 1564 (77%), 1524 (41%), 1500 (56%), 1458 (74%), 1435 (70%), 1403 (79%), 1353 (52%), 1320 (60%), 1282 (54%), 1241 (38%), 1200 (65%), 1184 (52%), 1140 (59%), 1067 (48%), 1025 (44%), 963 (78%), 910 (56%), 897 (47%), 825 (29%), 775 (57%), 758 (54%), 698 (76%), 675 (73%), 655 (62%).

MS-EI (70 eV): *m/z:* 181 ($[M]^{\bullet+}$, $C_8H_7NO_4$, 4%); 151 ($[M - NO]^+$, $C_8H_7O_3$, 100%); 134 ($[M - NO - OH]^+$, $C_8H_6O_2$, 21%); 119 (4%); 108 (18%); 106 (26%); 95 (22%); 92 (12%); 77 ($[C_6H_5]^+$, 8%); 63 ($[C_5H_3]^+$, 23%); 50 (3%).

HRMS (EI): *m/z* measured: 181.03411 ($[M]^{\bullet+}$, $C_8H_7NO_4$); *m/z* calculated: 181.037486.

4.2.2. 5-Methoxy-2-nitrobenzaldehyde (*3c*)

To a stirred suspension of *5-hydroxy-2-nitrobenzaldehyde* (3.99 g, 24 mmol) and K_2CO_3 (3.18 g, 24 mmol) in DMF (40 mL), methyliodide (1.49 mL, 24 mmol) was added dropwise at 0 °C. After the addition, the suspension was stirred at room temperature. The reaction was monitored by TLC. After 3 h, the starting material was completely reacted. The reaction mixture was poured into water and extracted with 3× 50 mL of diethylether. The combined organic layers were washed with 100 mL of water and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by MPLC using petrolether:ethylacetate (1:1) to yield 3.77 g **3c** as yellow crystals (87%).

mp: 81–82 °C (83 °C [21]).

^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 10.46$ (s, 1H, –C*H*O), 8.13 (d, 1H, $J = 9.1$ Hz, H_{arom}), 7.30 (s, 1H, H_{arom}), 7.13 (d, 1H, $J = 9.1$ Hz, H_{arom}), 3.94 (s, 3H, –OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 60 MHz): $\delta = 55.7$, 113.5, 118.9, 127.6, 134.6, 142.6, 164.3, 188.8.

IR ($\bar{\nu}$, cm^{-1}): 3102 (81%), 2982 (82%), 2946 (79%), 2845 (82%), 2666 (83%), 2166 (87%), 1922 (87%), 1689 (37%), 1609 (77%), 1580 (29%), 1499 (31%), 1479 (47%), 1459 (61%), 1442 (47%), 1419 (51%), 1390 (45%), 1326 (24%), 1286 (25%), 1233 (29%), 1187 (41%), 1159 (33%), 1079 (39%), 1024 (38%), 1001 (48%), 963 (66%), 929 (27%), 892 (28%), 847 (31%), 834 (22%), 771 (52%), 741 (23%), 688 (42%), 667 (45%).

MS-EI (70 eV): *m/z*: 181 ($[M]^{\bullet+}$, $C_8H_7NO_4$, 10%); 180 ($[M - H]^+$, $C_8H_6NO_4$, 29%); 163 ($[M - H_2O]^{\bullet+}$, $C_8H_5NO_3$, 5%); 151 ($[M - NO]^+$, $C_8H_7O_3$, 41%); 133 ($[M - H_2O - NO]^{\bullet+}$, $C_8H_5O_2$, 21%); 123 (32%); 108 (65%); 95 (54%); 77 ($[C_6H_5]^+$, 24%); 64 (37%); 63 ($[C_5H_3]^+$, 100%); 52 ($[C_4H_4]^{\bullet+}$, 21%); 49 (14%).

HRMS (EI): *m/z* measured: 181.03488 ($[M]^{\bullet+}$, $C_8H_7NO_4$); *m/z* calculated: 181.037486.

4.2.3. 2-Methoxy-6-nitrobenzaldehyde (*3d*)

To a stirred solution of hexamethylenetetramine (3.63 g, 25.92 mmol) in trifluoro acetic acid (35 mL) *3-nitrophenol* (3 g, 21.6 mmol) was added. The solution was refluxed at 130 °C under Ar. After 27 h, TLC showed complete conversion of the starting material. The reaction solution was cooled down and quenched by adding 6N HCl (120 mL). After 20 min of

stirring, the resulting solution was extracted with 2× 100 mL of dichloromethane. The combined organic layers were washed with 2× 50 mL of saturated $NaHCO_3$ solution, 50 mL of saturated NaCl and 50 mL of water and dried over Na_2SO_4. After evaporation of the solvent, 1.5 g of crude *2-hydroxy-6-nitrobenzaldehyde* were obtained. This product was used directly in the following synthetic step.

2-hydroxy-6-nitrobenzaldehyde was methylated to **3d** by the same method as used for the synthesis of **3c**: *2-hydroxy-6-nitrobenzaldehyde* (1.45 g, 9.0 mmol), K_2CO_3 (1.38 g, 10 mmol) and methyliodide (0.62 mL, 10 mmol) in DMF (17 mL) were stirred at room temperature for 3 h, two products were obtained after purification on MPLC (petrolether:ethylacetate, 1:1): 0.33 g of *2-methoxy-4-nitrobenzaldehyde* (8.6%, based on *3-nitrophenol*) and 0.59 g of **3d** (15.8%, based on *3-nitrophenol*).

3d:

mp: 108–109 °C (110–111 °C [22]).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.36 (s, 1H, –C*H*O), 7.59 (t, 1H, J = 8.3 Hz, H_{arom}), 7.42 (d, 1H, J = 8.1 Hz, H_{arom}), 7.22 (d, 1H, J = 8.3 Hz, H_{arom}), 3.94 (s, 3H, –OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.7, 115.5, 116.0 120.5, 133.6, 148.7, 159.7, 187.6.

IR ($\bar{\nu}$, cm^{-1}): 3092 (86%), 3034 (87%), 2954 (86%), 2879 (82%), 1959 (88%), 1706 (42%), 1609 (67%), 1527 (34%), 1468 (50%), 1437 (59%), 1388 (73%), 1353 (42%), 1309 (62%), 1269 (37%), 1208 (57%), 1190 (58%), 1162 (51%), 1048 (38%), 971 (62%), 900 (58%), 833 (50%), 804 (41%), 792 (33%), 733 (30%).

MS-EI (70 eV): *m/z:* 181 ([*M*]$^{\bullet+}$, $C_8H_7NO_4$, 10%); 163 ([M − H_2O]$^{\bullet+}$, $C_8H_5NO_3$, 10%); 151 ([*M* − NO]$^+$, $C_8H_7O_3$, 100%); 136 ([*M* − COOH]$^+$, $C_7H_6NO_2$, 66%); 133 ([*M* − H_2O − NO]$^+$, $C_8H_5O_2$, 17%); 119 (11%); 108 (41%); 92 (18%); 77 ([C_6H_5]$^+$, 27%); 76 (38%); 63 ([C_5H_3]$^+$, 19%); 50 (6%); 43 (5%).

HRMS (EI): *m/z* measured: 181.03436 ([*M*]$^{\bullet+}$, $C_8H_7NO_4$); *m/z* calculated: 181.037486.

4.2.4. 3-Methoxy-4-nitrobenzaldehyde (*4a*)

To the stirred suspension of *3-methoxy-4-nitrobenzylalcohol* (1.13 g, 6.2 mmol) and sodium acetate (1.1 g) in dichloromethane (30 mL) at 0 °C, pyridinium dichromate (2.32 g, 17.1 mmol) was introduced slowly over 15 min. After 2 h at room temperature the mixture was filtered and dichloromethane evaporated. To the residue 100 mL of diethylether were added and the mixture was treated in an ultrasonic bath. The suspension was filtered and the filtrate washed with 50 mL of 1N HCl to remove the pyridinium salt. The diethylether solution was dried over Na_2SO_4, evaporated, and the residue was purified by MPLC (petrolether:ethylacetate, 2:1), yielding 0.55 g of **4a** (49%) as yellow crystals.

mp: 105–107 °C (104–105 °C [23]).

^{1}H NMR (Me_2SO-d6, 400 MHz): δ = 10.07 (s, 1H, –C*H*O), 8.05 (d, 1H, J = 8.1 Hz, H_{arom}), 7.81 (s, 1H, H_{arom}), 7.64 (d, 1H, J = 8.3 Hz, H_{arom}), 3.59 (s, 3H, –OC*H*$_3$). ^{13}C NMR (Me_2SO-d6, 100 MHz): δ = 57.0, 114.2, 121.8, 125.4, 139.6, 142.7, 151.9, 192.1.

IR ($\bar{\nu}$, cm^{-1}): 3108 (87%), 3047 (87%), 2868 (85%), 2756 (87%), 1699 (65%), 1607 (59%), 1520 (48%), 1488 (63%), 1467 (67%), 1422 (79%), 1389 (60%), 1361 (58%), 1316 (61%), 1272 (51%), 1189 (78%), 1162 (61%), 1145 (62%), 1096 (71%), 1028 (56%), 1006 (72%), 962 (65%), 869 (64%), 841 (49%), 826 (45%), 760 (60%), 737 (47%), 703 (70%), 679 (74%).

MS-EI (70 eV): *m/z:* 181 ([*M*]$^{\bullet+}$, $C_8H_7NO_4$, 100%); 163 ([*M* − H_2O]$^{\bullet+}$, $C_8H_5NO_3$, 2%); 151 ([*M* − NO]$^+$, $C_8H_7O_3$, 68%); 134 ([*M* − NO − OH]$^+$, $C_8H_6O_2$, 64%); 119 (54%); 104 (10%); 95 (23%); 91 (12%); 77 ([C_6H_5]$^+$, 34%); 63 ([C_5H_3]$^+$, 29%); 51 ([C_4H_3]$^+$, 22%); 50 (15%); 39 ([C_3H_3]$^+$, 11%).

HRMS (EI): *m/z* measured: 181.03632 ([*M*]$^{\bullet+}$, $C_8H_7NO_4$); *m/z* calculated: 181.037486.

4.3. Production of [^{18}F]fluoride

No-carrier-added (nca) [^{18}F]fluoride was produced at the PETtrace cyclotron (General Electric Healthcare, Uppsala, Sweden) via the ^{18}O(p,n)^{18}F nuclear reaction by irradiating 1.5 mL of >95% enriched [^{18}O]water (Rotem, Israel) with 16.5 MeV protons.

4.4. Labeling

The radioactivity was introduced into a 5.0 mL sealed vial containing 100 μL of 3.5% aqueous K_2CO_3 and 15.0 mg Kryptofix 222. The [^{18}F]fluoride solution was dried for 20 min under a mild stream of argon (ca. 2 mL min^{-1}) at 140 °C by azeotropic distillation with acetonitrile (2× 1 mL). Then, 10 mg of precursor in 1.0 mL of solvent were added into the vial containing the [Kryptofix 222] K^{18}F complex. The sealed vial was heated to 140 °C. TLC samples were withdrawn (1–5 μL) for determination of the radiochemical yield at 1, 3, 7, 10, 20 and 30 min.

4.5. Analytical assay

4.5.1. TLC analysis

An aliquot of the reaction solution on a silica gel plate (Polygram® Silica G/UV$_{254}$, 8 cm × 4 cm, Macherey&-Nagel, Germany) was developed with petrolether/ethylacetate (3/1, v/v). The radioactive spots were quantitatively assessed by means of electronic autoradiography (InstantImager, Canberra Packard, USA). The size of the TLC plate and the location of the reference standard (from UV detection; R_f values are presented in Table 3) were marked by radioactive spots on the plate, thus a correlation between radioactive labeled product and non-radioactive standards was assured.

4.5.2. HPLC analysis

HPLC was applied for identification of labeled products and for monitoring of side reactions during the labeling reaction. HPLC was carried out by means of a Hewlett-Packard Model 1050 equipped with a NaI(Tl)-scintillation detector and an UV detector (280 or 254 nm) in series. Two columns with different selectivities were used to assure identity of products. Analysis

Table 3
R_f, R_t and k' for precursors and standards, determined by two different HPLC methods

Compound	R_f	HPLC method A		HPLC method B	
		R_t (min)	k'	R_t (min)	k'
1a	0.69	7.49[a]	2.94	7.62[b]	4.04
2a	0.63	7.21[a]	2.79	7.56[b]	4.00
1b	0.51	6.68[a]	2.52	–	–
2b	0.51	6.65[a]	2.5	–	–
1c	0.71	10.88[a]	4.73	–	–
2c	0.66	10.38[a]	4.47	–	–
1d	0.72	11.43[a]	5.02	–	–
2d	0.65	11.58[a]	5.1	–	–
3a	0.24	7.25[b]	2.82	–	–
3b	0.42	8.53[b]	3.49	–	–
3c	0.51	8.71[b]	3.58	–	–
3d	0.21	7.42[b]	2.91	–	–
4a	0.55	8.77[b]	3.62	–	–
4b	0.39	7.56[b]	2.98	–	–
4-Fluoro-3-methoxybenzaldehyde	0.61	8.22[b]	3.33	9.97[b]	5.60
4-Fluoro-2-methoxybenzaldehyde	0.56	7.69[b]	3.05	10.22[b]	5.76
2-Fluoro-6-methoxybenzaldehyde	0.44	6.44[b]	2.39	7.15[b]	3.73
2-Fluoro-5-methoxybenzaldehyde	0.68	8.82[b]	3.64	11.15[b]	6.38
2-Fluoro-4-methoxybenzaldehyde	0.61	7.94[b]	3.18	9.62[b]	5.37
2-Fluoro-3-methoxybenzaldehyde	0.59	7.75[b]	3.08	9.69[b]	5.41
2-Nitrobenzoic acid	–	4.24[a]	1.23	–	–
4-Nitrobenzoic acid	–	4.85[a]	1.55	–	–
2-Bromobenzoic acid	–	5.13[a]	1.7	–	-

Method A: C18 column (Luna, 5 μm, 250 mm × 4.6 mm, Phenomenex); flow: 1 mL min^{-1}; eluent: acetonitrile/water (50/50, v/v). Method B: Phenyl-hexyl column (Luna, 5 μm, 250 mm × 4.6 mm, Phenomenex); flow: 2 mL min^{-1}; eluent: acetonitrile/water (30/70, v/v).
[a] UV at 280 nm.
[b] UV at 254 nm.

was performed in two runs. First, the reaction mixture was analyzed and in a second run the identity of the product was verified by co-injection of the standard with the reaction mixture. Retention times of product and byproduct (i.e. benzoic acid) were in agreement with the UV peaks of the reference compounds, R_t and k' values are presented in Table 3.

Method A

A C18 column (Luna, 5 μm, 250 mm × 4.6 mm, Phenomenex, USA) was used with a flow rate of 1 mL min^{-1}. Eluent was acetonitrile/water (50/50, v/v).

Method B

A phenyl-hexyl column (Luna, 5 μm, 250 mm × 4.6 mm, Phenomenex, USA) was used with a flow rate of 2 mL min^{-1}. Eluent was acetonitrile/water (30/70, v/v).

For product purity control, an aliquot of the reaction mixture (at 10 or 20 min) was injected onto HPLC. After separation, the product fraction was collected and measured by means of a gamma-counter (1480 Wallac WIZARD 3″, Perkin–Elmer, USA). The radiochemical product yield was calculated by relating the radioactivity of the product peak with the amount of radioactivity injected onto the column.

For determination of the benzoic acid arising from oxidation, an aliquot of the reaction mixture (at 1, 3, 10 and 30 min) was injected onto HPLC. The eluent included 0.1% trifluoro acetic acid. UV peaks of benzoic acids and precursors were detected. Concentration curves of benzoic acids and the precursors were used to calibrate the integration area of the UV peak for normalization.

4.5.3. GC–MS analysis

The dimethylsulfide formed by oxidation was analyzed by means of GC–MS (Hewlett-Packard 5890 Series II Plus) by taking samples from the gas phase above the reaction solution at 30 min reaction time. Column: Chrompack Poraplot Q (27.5 m × 0.32 mm); He-flow: 9.6 mL min^{-1}; temperature program: 10 °C min^{-1} from 85 to 200 °C. R_t (dimethylsulfide): 8.29 min.

References

[1] F.W. Floeth, D. Pauleit, H.J. Wittsack, K.J. Langen, G. Reifenberger, K. Hamacher, M. Messing-Junger, K. Zilles, F. Weber, W. Stummer, H.J. Steiger, G. Woebker, H.W. Muller, H. Coenen, M. Sabel, J. Neurosurg. 102 (2005) 318–327.
[2] D. Pauleit, F. Floeth, K. Hamacher, M.J. Riemenschneider, G. Reifenberger, H.W. Muller, K. Zilles, H. Coenen, K.J. Langen, Brain 128 (2005) 678–687.
[3] C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts, A. Luxen, Eur. J. Org. Chem. (2004) 2899–2904.
[4] P.N. Krasikova, V.V. Zaitsev, S.M. Ametamey, O.F. Kuznetsova, O.S. Fedorova, I.K. Mosevich, Y.N. Belokon, Š. Vyskočil, S.V. Shatik, M. Nader, P.A. Schubiger, Nucl. Med. Biol. 31 (2004) 597–603.
[5] G.N. Reddy, M. Haeberli, H.F. Beer, A.P. Schubiger, Appl. Radiat. Isot. 44 (1993) 645–649.
[6] A. Plenevaux, C. Lemaire, A.J. Palmer, P. Damhaut, D. Comar, Appl. Radiat. Isot. 43 (1992) 1035–1040.

[7] Y.-S. Ding, C.-Y. Shiue, J.S. Fowler, A.P. Wolf, A. Plenevaux, J. Fluorine Chem. 48 (1990) 189–205.
[8] I. Ekaeva, L. Barre, M.C. Lasne, F. Gourand, Appl. Radiat. Isot. 46 (1995) 777–782.
[9] C. Lemaire, P. Damhaut, A. Plenevaux, R. Cantineau, L. Christiaens, M. Guillaume, Appl. Radiat. Isot. 43 (1992) 485–494.
[10] R. Rengan, P.K. Chakraborty, M.R. Kilbourn, J. Label. Compd. Radiopharm. 33 (1993) 563–572.
[11] D.-R. Hwang, C.S. Dence, J. Gong, M.J. Welch, Appl. Radiat. Isot. 42 (1991) 1043–1047.
[12] S. Stone-Elander, N. Elander, Appl. Radiat. Isot. 44 (1993) 889–893.
[13] C. Lemaire, M. Guillaume, L. Christiaens, R. Cantineau, Appl. Radiat. Isot. 38 (1987) 1033–1038.
[14] T. Tierling, Berichte des Forschungzentrums Jülich (2002) 3952.
[15] A. Al-Labadi, K.P. Zeller, H.-J. Machulla, Radiochim. Acta 94 (2006) 143–146.
[16] A. Al-Labadi, K.P. Zeller, H.-J. Machulla, J. Radioanal. Nucl. Chem. 270 (2006) 313–318.
[17] F.W. Sweat, W.W. Epstein, J. Org. Chem. 32 (1967) 835–838.
[18] A.J. Mancuso, D. Swern, Synthesis (1981) 165–185.
[19] T.T. Tidwell, Synthesis (1990) 857–870.
[20] M.A. Gal'bershtam, Z.N. Budarina, Zhurnal Organicheskoi Khimii 5 (5) (1969) 953–956.
[21] M. Smith, E. Elisberg, M.L. Sherrill, J. Am. Chem. Soc. 68 (1946) 1301.
[22] S.M. Kupchan, H.C. Wormser, J. Org. Chem. 30 (1965) 3792–3800.
[23] F. Rieche, Chem. Ber. 22 (1889) 2347–2364.