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Nucleophilic [^{18}F]Fluorination and subsequent decarbonylation of methoxy-substituted nitro- and halogen-benzenes activated by one or two formyl groups

Bin Shen,[a] Dirk Löffler,[a] Gerald Reischl,[a] Hans-Jürgen Machulla,[a]* and Klaus-Peter Zeller[b]

As model reactions for the introduction of ^{18}F into protected aromatic amino acids, the replacement of NO_2, Cl, Br and F by [^{18}F]fluoride in 2-isophthalaldehyde and 2-terephthalaldehyde derivatives which model ^{18}F-DOPA and ^{18}F-tyrosine was investigated by comparing labelling yields and reaction rates with those of corresponding mono-aldehyde compounds. All isophthalaldehydes showed maximum radiochemical yields (79 to 86%) at 140°C and in comparison with the corresponding mono-aldehydes the reaction proceeded faster. At lower temperature the reaction already resulted in high yields, e.g. 2-nitroisophthalaldehyde was labelled with a yield of 78% at 25°C after 7 min, whereas 2-nitrobenzaldehyde only reached a yield of 1.7% under the same reaction conditions. The ^{18}F/NO_2 exchange in nitroterephthalaldehydes proceeded more slowly and with lower radiochemical yields when compared with corresponding isophthalaldehydes and monoaldehydes. The decarbonylation of ^{18}F-labelled aromatic dialdehydic compounds with 4 eq. of Wilkinson's catalyst at 150°C in benzonitrile resulted in high yields, e.g. 2-[^{18}F]fluoro-5-methoxyisophthalaldehyde and 4-[^{18}F]fluoro-2-methoxy-5-methylisophthalaldehyde were decarbonylated efficiently with yields of 67 ± 3% and 72 ± 2%, respectively.

Keywords: nucleophilic substitution; [^{18}F]Aromatic amino acid; [^{18}F]Fluoride ion; benzaldehyde; decarbonylation

Introduction

Fluorine-18-labelled compounds constitute one of the most important groups of radiopharmaceuticals for positron emission tomography. Nucleophilic aromatic substitution (S_NAr) with [^{18}F]fluoride has been considered to be a highly attractive method for the synthesis of ^{18}F-labelled aromatic radiopharmaceuticals, because [^{18}F]fluoride is readily available at medical cyclotrons and the specific radioactivity of radiopharmaceuticals are high. Usually, S_NAr reaction is carried out on arenes which are activated both by an electron-withdrawing group (EWG, e.g. –NO_2, –CN, –RCO, –COOR, –Cl, –Br, –I or –CHO) and an appropriate leaving group (LG, e.g. –NO_2, –F, –Cl, –Br, –I, or –$N^+(CH_3)_3$) in *ortho* or *para* position to each other.[1] Good radiochemical yields (RCY) are known to be obtained in case of isotopic exchange (^{18}F/^{19}F) and substitution of nitro and tetramethylammonium.[1–3] In general, rates of the S_NAr process and maxium radiochemical yields increase with the lowered electrophilicity of the LG-substituted aromatic carbon atom of the precursor.[4]

When aiming at ^{18}F-labelling of aromatic amino acids a nucleophilic substitution has to be realized in presence of hydroxylic groups increasing the electron density of the aromatic system and, thus, strongly decreasing the reactivity for a nucleophilic attack. Moreover, the EWG has to be removed fast and efficiently after radiolabelling. The aldehydic group offers that type of possibility as it can be removed by Wilkinson's catalyst. Up to now substituted benzaldehydes were applied in ^{18}F-labelled compounds with subsequent synthetic steps for adding the amino acid residue.[5–7] After we proved the decarbonylation of ^{18}F-labelled benzaldehydes to proceed fast and efficiently the particular concept appeared promising to be applied for aromatic dialdehydes in order to facilitate S_NAr at low temperature with short reaction times, yet with really high labelling yields.

In this study, a number of aromatic dialdehydic model compounds with different substitution patterns and LG were synthesized and labelled for demonstrating superior labelling properties. The decarbonylation step was tested and optimized with respect to the applicability for a synthesis of ^{18}F-labelled aromatic amino acids (Figure 1).

Experimental

General

For performing the labelling reactions, as solvent DMF (stored over molecular sieve) was purchased from Fluka (Germany).

Bin Shen and Dirk Löffler have contributed equally to this work.

[a]*Radiopharmacy, PET Centre, Eberhard Karls University Tübingen, Tübingen, Germany*

[b]*Institute of Organic Chemistry, Eberhard Karls University Tübingen, Tübingen, Germany*

**Correspondence to: Hans-Jürgen Machulla, Radiopharmacy, PET Centre and Eberhard Karls University Tübingen, Tübingen, Germany.*
E-mail: machulla@uni-tuebingen.de

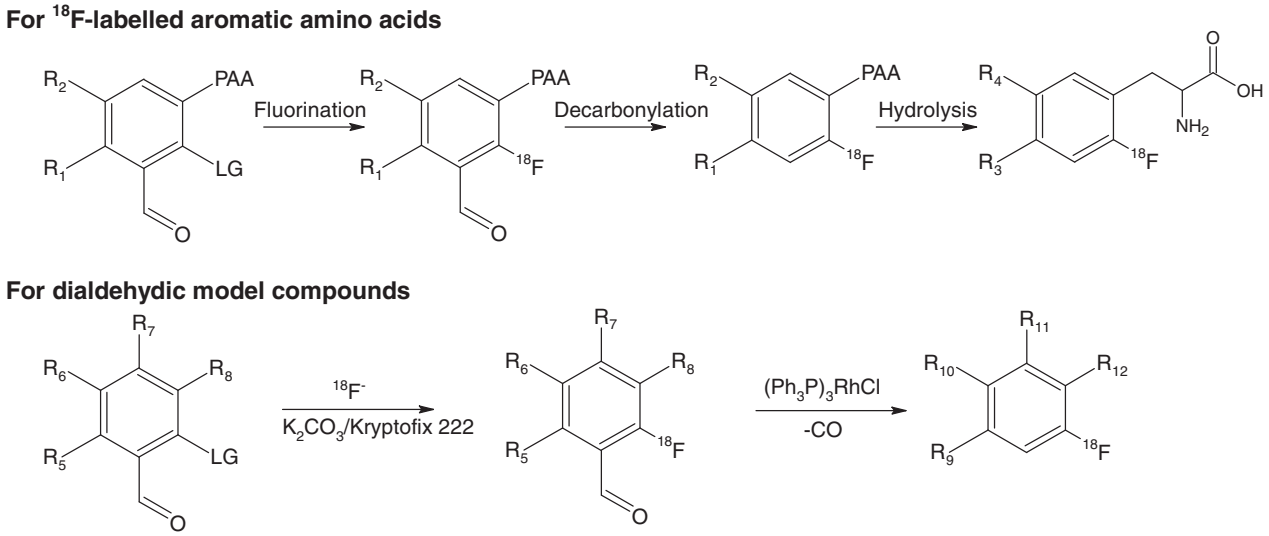


Figure 1. ^{18}F-labelling and decarbonylation of model compounds aiming at syntheses of ^{18}F-labelled aromatic amino acids (R_1, R_2 = H or OMe; R_3, R_4 = H or OH; R_5-R_{12} = H or OMe or CHO or Me).

Acetonitrile (for DNA synthesis) and Kryptofix 222 were obtained from Merck (Darmstadt, Germany). For the middle pressure liquid chromatography system (MPLC, Büchi, Switzerland) silica gel 60 (0.040–0.063 mm, Merck was used, eluents were mixtures of petroleum ether (60/90°C) and ethyl acetate. Precursors and reference standards were characterized by their melting points (Gallenkamp MPG 350, Germany, values are uncorrected), IR (Spectrum One FT-ATR-IR, Perkin-Elmer, Boston, USA), MS (Finnigan-MAT TSQ 70, Bremen, Germany) and NMR (Bruker Avance 400, Rheinstetten). For NMR measurements, as internal standards the deuterated solvents were used (DMSO-d_6: $\delta = 2.49$ 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; Acetone-d_6: $\delta = 2.04$ in ^{1}H and $\delta = 29.80$ and 206.70 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 unless stated differently.

Precursors and reference standards

As precursors and reference standards, the following compounds (**a, b, e, i** and the corresponding fluorinated reference compounds) were of the highest purity available from either Sigma-Aldrich, Fluka, ABCR, Alfa Aesar or Fluorochem and were used as received. For the preparation of **f, j, k** and the corresponding fluorinated standards the procedures were described elsewhere.[8] All the precursors presented in Table 1 were synthesized as described in the supporting document.

Production of [^{18}F]fluoride

No-carrier-added (n.c.a.) [^{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.

Labelling with [^{18}F]fluoride (n.c.a.)

The radioactivity was introduced into a 5.0 mL sealed vial (Supelco, graduated screw top V-Vials®, autoclavable borosilicate USP Type 1 glass) 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) at 140°C by azeotropic distillation with acetonitrile (2 × 1 mL). Then, precursor (10 mg) dissolved in DMF (1.0 mL) was added into the vial containing the [Kryptofix222] $K^{+18}F^-$ complex. The sealed vial was kept heating at 140°C. A sample (1–5 μL) was withdrawn for analysis at 1, 3, 7, 10, 20 and 30 min. For a number of experiments ($n = 20$), the amount of radioactivity that remained absorbed in the reaction vial after removing the reaction solution and washing with water (3 × 3.3 mL) was determined as 12 ± 8% (based on the activity after labelling).

Decarbonylation

The labelling was performed as described above, in the time at which the maximum RCY was obtained and the reaction vial was cooled down in an icebath. Water (3 × 3.3 mL) was used to wash the reaction solution out of the vial. This solution was passed through two cartridges connected in series (Alumina N and C18, Waters, USA), and the ^{18}F-labelled product was obtained after elution from the C18 cartridge with 4 mL dichloromethane and evaporation of the solvent. To the residue, 1 mL of benzonitrile was added and the solution was transferred into a sealed vial with $RhCl(PPh_3)_3$ (amounts of catalyst used were based on quantity of the precursor to be labelled). Then, the mixture was heated in an aluminium block. Aliquots of the solution were taken out at different times for analysis.

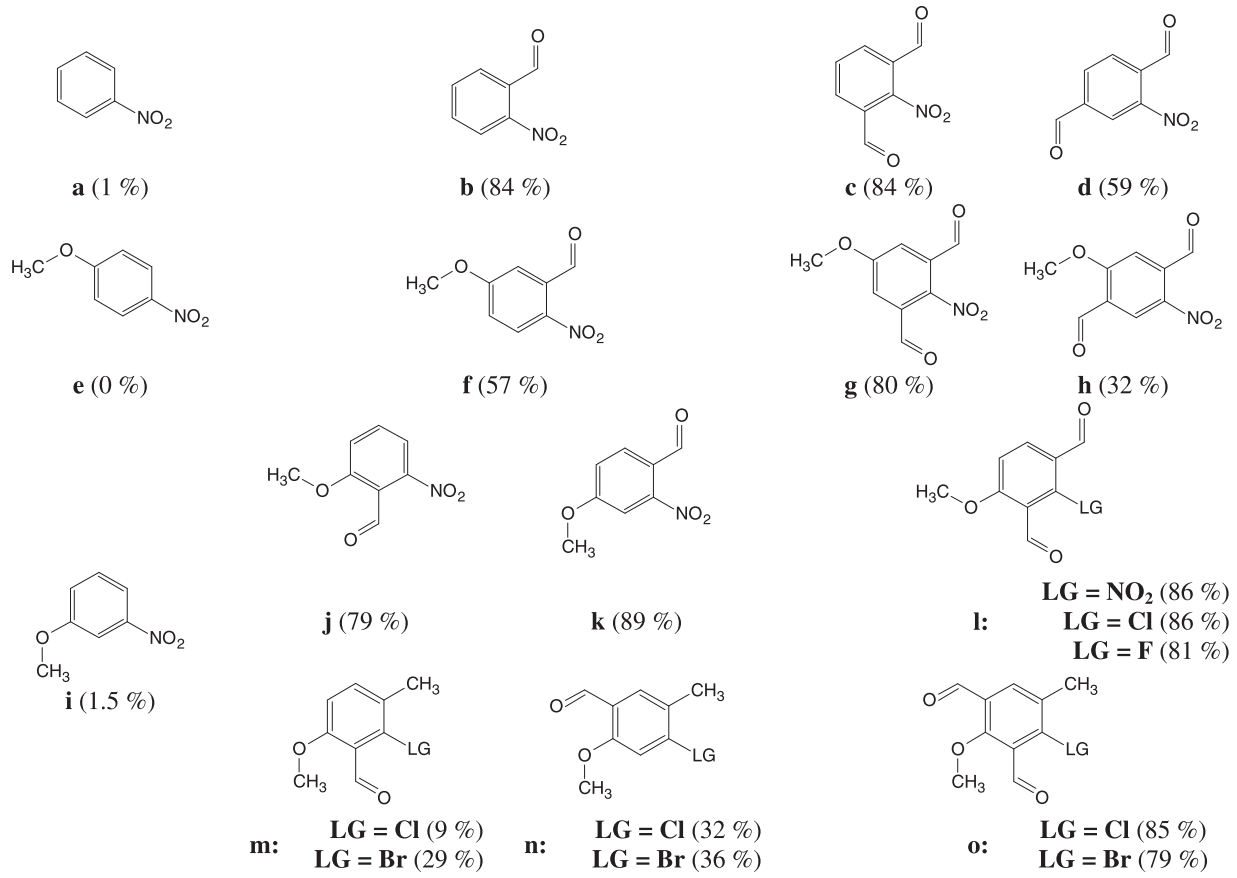
Analytical assay

General

The identity and purity of the product obtained in the radiochemical reaction was checked by two independent methods. The reason was that radiochemical impurities of unknown origin can either remain unseparated on TLC or accidentally co-elute with the product peak even if high resolution chromatography is applied. When the data obtained by TLC and HPLC were in agreement, purity and identity were considered as to be assured.

Table 1. Maximum radiochemical yields (RCY_{MAX}) for ^{18}F-labelling of aromatic mono/dialdehyde derivatives

None formyl group | One formyl group | Two formyl groups



Labelling conditons: **a–k** 140°C, **l–o** 120°C, $n \geqslant 3$.

TLC analysis

An aliquot of the reaction solution on a silica gel plate (Polygram® Silica G/UV_{254}, 8 × 4 cm, Macherey&Nagel, Germany) was developed with petroleum ether/ethyl acetate (3:1, v/v). The radioactive spots were quantitatively assessed by means of electronic autoradiography (Instant Imager, Canberra Packard, USA). The R_f-values are presented in Tables 2 and 3. The size of the TLC plate and the location of the reference standard were marked by radioactive spots on the plate, thus allowing a correlation between the radioactive-labelled product and non-radioactive standards.

HPLC analysis

HPLC was applied for identification of radiolabelled products. HPLC was carried out by means of a Hewlett–Packard Model 1050 equipped with an UV detector and a NaI(Tl)-scintillation detector in series. Retention times of product were in agreement with the UV peaks of the reference compounds, R_t and k'-values are presented in Table 2 and Table 3. KF was added to the eluent as carrier in order to assure that radioactive [^{18}F]fluoride ions are eluted as a sharp peak.

For product purity control, an aliquot of the reaction mixture was taken at time of maximum RCY, non-radioactive standard was added and the mixture 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 to the radioactivity of the reaction solution injected onto HPLC.

LC/MS analysis

LC/MS measurements were performed on a quadrupole LC/MS (Agilent Technologies, Model 6120) with an HPLC (Agilent Technologies, Model 1200). A Phenomenex Luna (100 × 2.0 mm, 5 μ) C18 (2) column was used. Eluent was a gradient from 100% water to 100% methanol (within 30 min) buffered with ammonium acetate (144 mg/L).

Results and discussion

Labelling

The goal of this work was to study the effect of up to two formyl groups on the reactivity of nitrobenzene and halobenzene derivatives in S_NAr-based fluorination. As previously observed,[8]

Table 2. R_f values and retention times (R_t) of the ^{18}F-labelled products as analysed by TLC and HPLC

Precursor	Rf (TLC) of ^{18}F-labelled product	R_t on HPLC		
		[^{19}F]fluoro standard (min)	^{18}F-labelled product (min)	k'
a	—	10.11	10.52[k]	5.74
b	0.69	7.49	8.02[a]	2.94
c	0.51	7.56	7.98[f]	2.97
d	0.49	8.93	9.18[g]	4.91
e	—	10.16[i]	—	5.77
f	0.68	8.82	9.36[b]	3.64
g	0.70*	7.70	9.11[h]	4.13
h	0.48	8.78	9.19[h]	
i	—	13.48	13.90[b]	6.09
j	0.44	6.44	7.00[b]	2.38
k	0.61	7.94	8.47[b]	3.17
l	0.20	***	5.29[j]	***
m	0.54	8.51	9.60	4.00
n	0.52	11.55	11.99	5.08
o	0.55**	7.55	8.16[j]	1.80

Conditions for TLC: Petroleum ether/ethyl acetate, 3:1. *Conditions for TLC: Petroleum ether/ethyl acetate, 1:1. **Conditions for TLC: Petroleum ether/ethyl acetate, 2:1. ***not determined.
[a]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (50/50) containing 0.1% acetic acid and 0.1% KF. Flowrate: 1 mL/min.
[b]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (50/50) containing 0.1% KF. Flowrate: 1 mL/min.
[f]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (40/60) containing 10 mM Na_2HPO_4 and 0.1% KF. Flowrate: 1 mL/min.
[g]Column: phenylhexyl, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (20/80) containing 10 mM Na_2HPO_4 and 0.1% KF. Flowrate: 2 mL/min.
[h]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (30/70) containing 10 mM Na_2HPO_4 and 0.1% KF. Flowrate: 2 mL/min.
[i]Column: phenylhexyl, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (20/80) containing 0.1% KF. Flowrate: 2 mL/min.
[j]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna aqua, Phenomenex, USA). Eluent: acetonitrile/water (50/50) containing 0.1% KF. Flowrate: 1 mL/min.
[k]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (40/60) containing 0.1% KF. Flowrate: 2 mL/min.

Table 3. R_f values and R_t for the products in decarbonylation

Standard	R_f (TLC) of ^{18}F-labelled product	R_t on HPLC		
		[^{19}F]fluoro standard (min)	^{18}F-labelled product (min)	k′
1-fluoro-4-methoxybenzene	0.59	15.40	15.60[a]	7.10
2-fluoro-4-methoxy-1-methylbenzene	0.77	8.97	9.20[b]	4.9

Conditions for TLC: Petroleum ether/EtOAc, 3:1.
[a]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: Gradient acetonitrile/water (97/3) containing 0.1% KF to acetonitrile/water (90/10) containing 0.1% KF within 15 min. Flowarte: 1 mL/min.
[b]Column: C18, 5 μm, 250 mm × 4.6 mm (Luna, Phenomenex, USA). Eluent: acetonitrile/water (50/50) containing 0.1% KF. Flowrate: 2 mL/min.

DMSO can oxidize benzaldehyde precursors to benzoic acid derivatives, therefore DMF was used throughout this work.

For evaluating the reactivity and RCY of different compounds, reaction conditions were applied as previously determined.[9] The labelling was carried out with 10 mg or 0.05 mmol precursor in DMF (1 mL) in presence of K_2CO_3 and Kryptofix 2.2.2 at 25–140°C and the course of the reaction was monitored over a period of 30 min.

The study on the relationship between RCY and the number of formyl groups on S_NAr was performed in series of

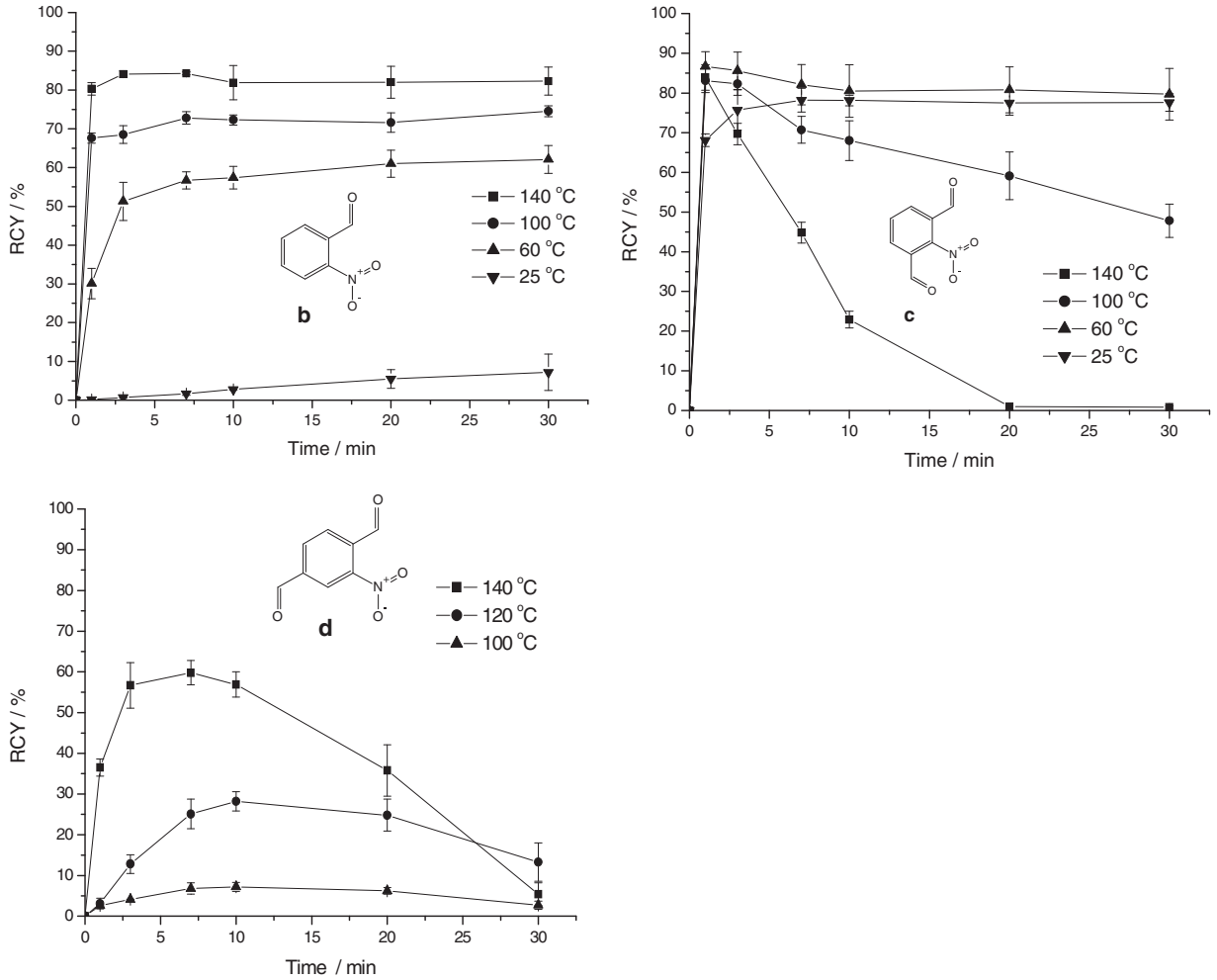


Figure 2. Radiochemical yields for ^{18}F-labelling of compounds (**b**), (**c**) and (**d**) in dependence on the reaction time at different temperatures.

compounds with none and one or two formyl groups (see Table 1). The labelling of nitrobenzene gave a RCY of 1 ± 0.1 % within 30 min. To our knowledge, the results for the labelling of this compound which is not activated by an EWG has not been reported in literature before. This might be due to the experimental difficulties originated by volatility of the labelled product. The detection of the product was achieved by cooling and, thus, carefully condensing within the sealed vial prior to the extraction of a sample for radio-HPLC.

The effect of aldehydic groups as EWG can be seen in case of the nitro-substituted compounds **(b)**, **(c)** and **(d)** (Figure 2). The labelling of 2-nitrobenzaldehyde (**b**) is in accordance with the values presented in literature,[3,10–12] a high RCY of 84 ± 0.4% was reached after 7 min at 140°C. In case of 2-nitroisophthalaldehyde (**c**), in which both formyl groups are in *ortho* position to the LG, the same maximum RCY of 84 ± 3% was obtained already after 1 min at 140°C, afterwards yield decreased probably due to thermal decomposition of the product. Most interestingly, the temperature dependence exhibited high yields of almost 80% after 10 min at 25°C. For compound (**d**) the second formyl group located *meta* to the LG has an adversary effect on RCY. The maximum RCY (59 ± 6%) was reached later (at 10 min) than for compounds (**b**) and (**c**) (both at 1 min). As already noted for the dialdehyde (**c**), higher labelling temperature obviously resulted in a rapid decomposition of the labelled product.

One $^{18}F^-$-consuming reaction might stem from the oxidation of the aldehydic group to a carboxylic group. In a blank experiment, the precursor (**d**) was reacted under labelling conditions but in the absence of fluorine. Monitoring the reaction by LC/MS (APCI$^-$), mass peaks at $[M-H]^-$ (*m/z* 194) and $[M-H\text{-}CO_2]^-$ (m/z 150) were detected. This is in accordance with the formation of mono-formyl-nitrobenzoic acid. In compound (**c**), no hints for oxidation to the benzoic acid were found. All reactions were carried out under strict exclusion of air. Therefore, we suspect a nitro group of a second precursor molecule as oxygen source for the transformation of an aldehydic to a carboxylic group.

All observations that were made for the compounds (**b**), (**c**) and (**d**) mirror a general tendency which was observed similarly in all other compounds with additional substituents shown in Table 1 and Table 4. In addition to structures in which both formyl groups are *ortho* to the LG, similar results were obtained for structure (**o-Cl**) and (**o-Br**), where one formyl group is *ortho* and the other *para* to the LG. Differences in reactivities can be recognized best when looking at the curves at low temperatures in Figure 3. The strongest increase of maximum RCY by introducing a second formyl group was

Table 4. Radiochemical yields (mean ± SD) of aromatic mono/dialdehydes within 30 min

Nr.	Temp.(°C)	*n*	RCY (%)					
			1 min	3 min	7 min	10 min	20 min	30 min
a	140		—	—	—	—	—	1 ± 0.1[a]
b	25	3	0.2 ± 0.1	0.7 ± 0.2	1.7 ± 0.4	2.8 ± 0.2	5.5 ± 2.4	7.2 ± 4.7
b	60	3	30.1 ± 3.9	51.3 ± 4.9	56.7 ± 2.2	57.4 ± 2.9	61.0 ± 3.5	62.1 ± 3.6
b	100	3	67.6 ± 1.3	68.5 ± 2.3	72.8 ± 1.6	72.3 ± 1.3	71.6 ± 2.5	74.5 ± 1.4
b	140	5	80.3 ± 1.6	84.1 ± 0.8	84.3 ± 0.4	81.9 ± 4.4	82.0 ± 4.1	82.3 ± 3.6
c	25	4	68.1 ± 1.6	75.7 ± 5.1	78.2 ± 3.0	78.1 ± 1.3	77.5 ± 3.1	77.6 ± 2.2
c	60	4	86.7 ± 3.7	85.6 ± 4.7	82.1 ± 5.1	80.5 ± 6.6	80.8 ± 5.8	79.7 ± 6.5
c	100	3	83.1 ± 3.0	82.3 ± 2.9	70.7 ± 3.4	68.0 ± 5.0	59.1 ± 6.0	47.8 ± 4.2
c	140	3	83.9 ± 3.2	69.7 ± 2.7	44.8 ± 2.6	22.9 ± 2.1	1.0 ± 0.0	0.8 ± 0.3
d	100	3	2.6 ± 0.1	4.1 ± 0.1	6.8 ± 1.4	7.2 ± 1.1	6.2 ± 0.8	2.7 ± 1.0
d	120	4	3.1 ± 1.3	12.8 ± 2.3	25.1 ± 3.6	28.2 ± 2.4	24.8 ± 3.9	13.3 ± 4.7
d	140	4	36.5 ± 2.1	56.7 ± 5.6	59.8 ± 3.0	56.9 ± 3.1	35.8 ± 6.3	5.4 ± 2.8
e	140	4	—	—	—	—	—	0 ± 0[a]
f	140	4	46.2 ± 1.2	53.3 ± 1.2	57.4 ± 1.0	53.1 ± 5.6	54.9 ± 4.6	53.6 ± 4.0
g	140	4	75.3 ± 0.5	79.3 ± 0.2	78.3 ± 2.5	79.7 ± 0.6	73.3 ± 1.5	66.3 ± 2.5
h	140	2	7.7 ± 0.4	16.5 ± 1.8	25.8 ± 4.4	31.9 ± 1.4	29.7 ± 2.4	13.2 ± 0.7
i	140	3	—	—	—	—	—	1.5 ± 0.8[a]
j	140	4	69.5 ± 0.4	72.3 ± 1.1	77.6 ± 1.4	78.5 ± 3.5	78.9 ± 4.0	78.7 ± 3.1
k	140	4	86.5 ± 0.6	88.3 ± 1.8	89.0 ± 2.4	86.3 ± 4.2	87.0 ± 3.7	86.6 ± 3.3
l-NO_2	120	3	85.7 ± 0.7	78.4 ± 2.8	68.3 ± 1.9	56.3 ± 9.1	23.7 ± 6.7	2.6 ± 0.5
l-Cl	120	3	85.9 ± 1.7	86.0 ± 1.5	80.3 ± 5.6	74.1 ± 3.4	63.4 ± 8.4	53.9 ± 5.7
l-F	120	3	81.3 ± 1.9	66.4 ± 3.1	61.7 ± 12.5	44.0 ± 10.7	29.3 ± 14.4	22.9 ± 14.9
m-Cl	120	5	0.6 ± 0.4	2.0 ± 0.6	4.7 ± 1.1	6.0 ± 1.5	7.4 ± 1.9	8.6 ± 1.9
m-Br	120	6	7.9 ± 2.2	15.6 ± 5.4	22.5 ± 4.8	25.4 ± 3.9	28.7 ± 2.1	27.5 ± 2.3
n-Cl	120	5	1.4 ± 1.3	8.3 ± 2.5	18.4 ± 3.8	22.0 ± 5.6	29.5 ± 4.1	31.8 ± 3.0
n-Br	120	5	6.0 ± 3.9	15.2 ± 3.7	27.1 ± 4.0	32.0 ± 4.6	33.0 ± 3.5	35.7 ± 4.9
o-Cl	25	3	2.6 ± 1.2	8.5 ± 0.9	18.9 ± 2.3	23.1 ± 2.1	28.4 ± 2.7	29.5 ± 3.2
o-Cl	60	3	57.0 ± 0.6	70.6 ± 3.6	75.7 ± 5.9	74.8 ± 6.2	70.9 ± 67.9	67.9 ± 5.3
o-Cl	120	5	84.0 ± 2.9	84.7 ± 3.4	80.3 ± 2.0	72.4 ± 2.6	55.9 ± 2.5	45.7 ± 3.2
o-Br	120	3	78.9 ± 5.9	79.2 ± 3.6	73.4 ± 4.9	65.9 ± 3.2	49.4 ± 6.7	35.3 ± 7.5

—, not determined.
[a]value determined by radio-HPLC.

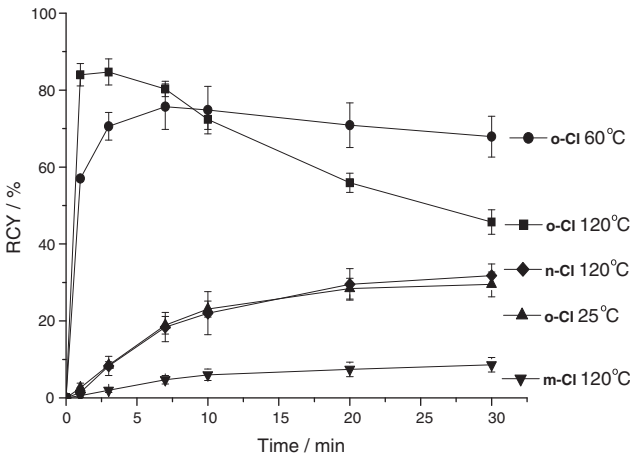


Figure 3. Time dependence curves for ^{18}F-labelling of compounds (**m-Cl**), (**n-Cl**) and (**o-Cl**) at different temperatures.

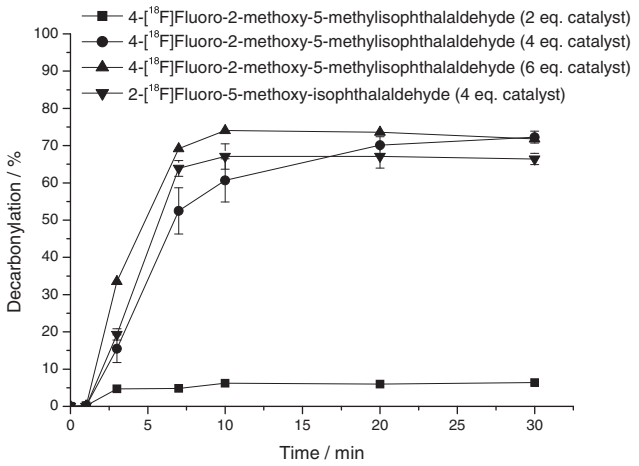


Figure 4. Decarbonylation yield of ^{18}F-labelled compounds (**g**) and (**o-Cl**) with 2, 4 or 6 molar eq. catalyst at 150°C.

measured for compounds in which the mono-aldehyde only gave low or medium RCY, e.g. 2-chloro-6-methoxy-3-methylbenzaldehyde (**m-Cl**). The introduction of a second aldehyde group increased the reactivity of compound (**o-Cl**) so much that RCYs of (**o-Cl**) obtained at 25°C were same as those of **n-Cl** at 120°C.

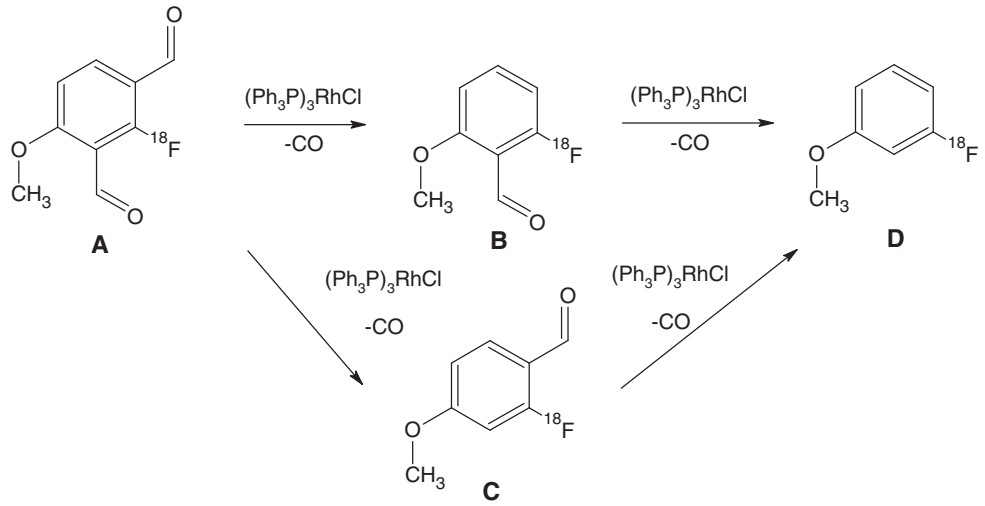


Figure 5. Two possible pathways of the decarbonylation reaction.

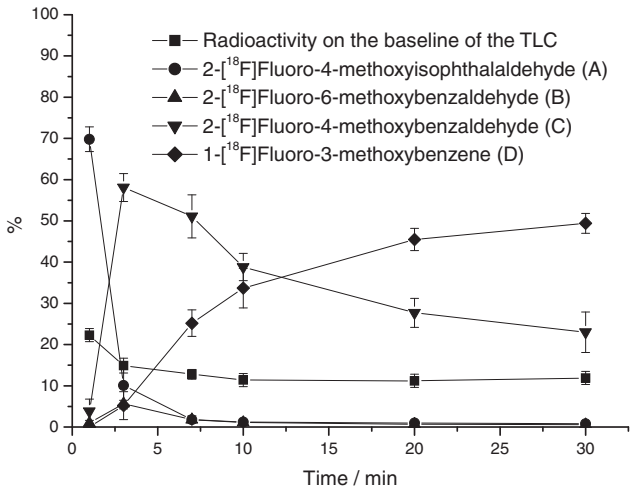


Figure 6. Conversion of 2-[^{18}F]fluoro-4-methoxyisophthalaldehyde in the decarbonylation (120°C, 3 eq. catalyst).

Decarbonylation

The application of two formyl groups is obviously an advantage for performing nucleophilic aromatic substitutions at low temperatures with short reaction times in high labelling yields. A prerequisite, however, is the fast and efficient removal of the two aldehydic groups from the ^{18}F-labelled product. As shown in Figure 4 decarbonylation was efficiently performed within 20 min both for 2-[^{18}F]fluoro-5-methoxyisophthalaldehyde and 4-[^{18}F]fluoro-2-methoxy-5-methylisophthalaldehyde, when at least four equivalent of Wilkinson's catalyst were applied. The fact of using Wilkinson's catalyst in stochiometric amounts was in accordance with the literature[13] and our previous report.[5]

The decarbonylation in dialdehydes can be expected to proceed by two different pathways as illustrated in Figure 5. In the case of 2-[^{18}F]fluoro-4-methoxyisophthalaldehyde (**I–F**) the intermediates and the product of the reaction were monitored by radio-TLC because the R_f-values differed so much to be clearly separated. In Figure 6 the data clearly show that the more sterically hindered formyl group is removed faster than the other one.

Conclusion

For the nucleophilic aromatic fluorination of *o,o*- and *o,p*-diformylated nitro- and halogenarenes by [^{18}F]fluoride good radiochemical yields were found between 79 and 86%. Compared with *o*- or *p*-formyl-substituted nitro- and halogenarenes, the reaction proceeded faster and often in better yields even at room temperature. The formyl groups can efficiently be removed by decarbonylation with Wilkinson's catalyst. Moreover, the results of compounds (**o**) indicate the applicability of S_NAr to be particularly promising for a synthesis of ^{18}F-tyrosine.

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