Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **43**, 721-737 (2000)

DIRECT N.C.A. ELECTROPHILIC RADIOIODINATION OF DEACTIVATED ARENES WITH N-CHLOROSUCCINIMIDE

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Summary

An efficient method for the direct electrophilic no-carrier-added (n.c.a.) radioiodination of deactivated arenes has been developed using N-chlorosuccinimide (NCS)/radioiodide in trifluoromethanesulfonic acid (triflic acid). Optimization of the one pot labelling procedure using chlorobenzene as a model substrate resulted in a radiochemical yield of 75% within 15 min at room temperature. Drying of the aqueous radioiodide solution prior to radiolabelling was not required. Radioiodination of weakly activated and deactivated monosubstituted benzene derivatives gave rise to radiochemical yields of about 80% with an electrophilic substitution pattern. Strongly deactivated aromatic compounds were radioiodinated with high radiochemical yields of about 70% exclusively in their *meta*-position using a reaction temperature of 75°C and a reaction time of 1 h. With regard to the reaction mechanism, *in situ* formed radioiodo(I) trifluoromethanesulfonate (triflyl [^{131}I]hypoiodite) is discussed as electrophilic reagent.

Key words: direct radioiodination, n.c.a. labelling, electrophilic substitution, deactivated arenes, N-chlorosuccinimide, triflyl hypoiodite

 Accepted 2000

Introduction

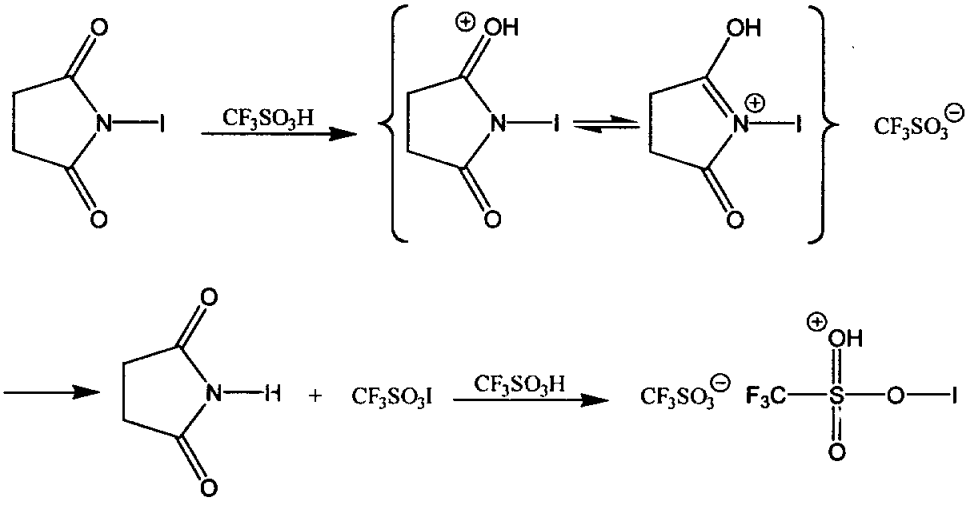
Radioiodinated tracers are widely used in life sciences for *in vitro* and *in vivo* applications [1, 2]. Isotopes such as iodine-120, -123, -124, and perhaps even -131 are suitable radionuclides for the preparation of diagnostic imaging agents for positron- or single-photon-emission-tomography (PET or SPECT). Radioiodination of target molecules should be rapid and result in a high radiochemical yield (RCY) and high specific activity. Due to the relatively higher stability of the aromatic carbon-iodine bond radioiodine should be, whenever possible, introduced into an aromatic moiety of the tracer. While a variety of n.c.a. radioiodination methods have been described [3, 4], electrophilic aromatic substitution, which is easily possible via *in situ* oxidation of n.c.a. radioiodide, is still the most commonly used method. However, with all organic oxidants like chloramine-T, Iodogen™ (1,3,4,6-tetrachloro-3α,6α-diphenylglycoluril), etc. satisfactory yields are only obtained with strongly activated arenes [5 – 14].

Among a number of oxidizing agents N-halosuccinimides such as N-bromosuccinimide (NBS), N-chlorotetrafluorosuccinimide (NCTFS) and N-chlorosuccinimide (NCS) can be employed for electrophilic radioiodination and radiobromination [10 - 14]. NCS in combination with trifluoroacetic acid anhydride (TFAA) has been well documented for the radioiodination of strongly and weakly activated arenes such as anisole, toluene and benzene resulting in radiochemical yields of 72 %, 30 % and 1 %, respectively [13]. In this case possibly N-radioiodosuccinimide (N*IS) is the source of electrophilic iodine, since N*IS can be generated *in situ* by reacting radioiodide with NCS [15, 16].

Recently it has been reported that N-iodosuccinimide (NIS) can be used in combination with trifluoromethanesulfonic acid (triflic acid) for the direct equimolar iodination of deactivated arenes [17]. The authors postulate the intermediate formation of iodine(I)-trifluoromethanesulfonate (triflyl hypoiodite) (**1**) in its protosolvated activated form as the de facto "superelectrophilic" iodinating species (Scheme 1). Previously, the formation and existence of triflyl hypoiodite has been documented spectrometrically [18, 19].

Here, this approach is applied for the radioiodination of deactivated aromatic compounds and the results of a systematic investigation using NCS/Na$^{[131]}$I in triflic acid

as a powerful system for the electrophilic aromatic iodination with n.c.a. $^{131}I^-$ are described. Chlorobenzene was chosen as a model compound of moderately deactivated arenes for optimizing the reaction parameters. Other simple monosubstituted arenes were employed to explore the selectivity and reactivity effects of the developed radioiodination system.



Scheme 1: Postulated mechanism for the formation of triflyl hypoiodite (**1**) [from 17]

Experimental

Materials and methods

Monosubstituted arenes, N-chlorosuccinimide and the *ortho-*, *meta-* and *para*-iodinated arenes were obtained from Aldrich (Steinheim, Germany). Trifluoromethanesulfonic acid and sodium bisulfite were purchased form Fluka (Buchs, Switzerland). $Na^{131}I$, Product Code IBS 30, was obtained from Amersham Buchler (Braunschweig, Germany). All solvents and reagents were purchased from commercial sources in the highest purity available and were used without further purification.

Analyses of the total radiochemical yields of all radioiodinated arenes were performed by radio-HPLC using a Knauer pump (Typ 64) and a Knauer UV/vis photometer with a detector wavelength of 254 nm. Sample injection was accomplished by a Rheodyne-Injector block (7125). For continuous measurement of radioactivity the outlet of the UV

detector was connected to a NaI(Tl) well type scintillation detector and the recorded data were processed by a software system (Nuclear Interface, Münster, Germany). The radiochemical yield was calculated in terms of percentage of total radioactivity in the injected sample. For the determination of the total radiochemical yield (sum of isomers) a Multosorb RP-18 (250 x 4mm) column was used obtained form CS-Chromatographie Service GmbH (Langerwehe, Germany). On this column also the isomeric distribution of the radioiodinated derivatives of phenol, benzene, chlorobenzene and nitrobenzene was determined using a mobile phase consisting of various concentrations of methanol in water at a flow rate of 1.0 mL/min. Separation of the radioiodinated isomers of benzamide and benzoic acid was performed using a Cyclobond III/ α-Cyclodextrin (250 x 4mm) column (Alltech, Unterhaching, Germany) with a mobile phase of various concentrations of acetonitrile in water at a flow rate of 1.0 mL/min.

The radioiodinated isomers of toluene and anisole were analyzed by radio-gas chromatography (radio-GC) using a Hewlett Packard research chromatograph HP 6890 Series. The individual peaks were discontinuously trapped on charcoal. The iodinated anisole isomers were separated on a glass column (4 m length, 4 mm i.d.) filled with 6% Bentone-38 and 20% silicone oil on 60-80 mesh Chromosorb W-AW-DMCS [20]. The separation of the iodinated toluene isomers was performed using a glass column (8 m length, 4 mm i.d.) filled with 20% azoxydianisole on Chromosorb W-AW-DMCS (60-80 mesh) [21]. The collected peak fractions were measured in a well-type Auto-Gamma Scintillation Spectrometer (Packard, Model 5375).

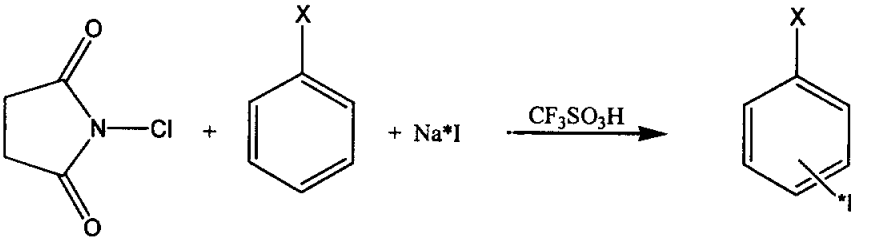
Radiolabelling, general procedure

A defined amount of N-chlorosuccinimide was placed in a conical 2 mL reaction vessel equipped with a magnetic stirring bar and a Teflon-rubber septum. Then 0.5 mL of triflic acid containing the desired amount of the aromatic substrate was added. Finally about 2 μL of a n.c.a. $Na^{131}I$ solution (typically containing 1MBq [≅ 27 μCi]) was introduced via a microlitre syringe. After stirring for the desired reaction time at a given temperature, a 20 μL aliquot of the reaction mixture was transferred into a vial containing 150 μL tetrahydrofuran and was subsequently quenched with 50 mM sodium bisulfite in 2N NaOH (150 μL). After neutralizing with acetic acid the resulting mixture

was analyzed by radio-HPLC or radio-GC. All radioiodination experiments were repeated 2 to 4 times for calculation of radiochemical yields and standard deviations.

Results and Discussion

Radioiodination of weakly activated arenes via NCS could be achieved by He Youfeng et al. [13] using TFAA as solvent. Since labelling of deactivated arenes with this method was not possible, the solvent was changed in this study from TFAA to triflic acid (cf. Scheme 2). It is already known, that NIS in triflic acid provides a suitable way for iodination of several deactivated aromatic compounds and a possible reaction pathway has been described by Olah et al. (cf. Scheme 1) [17]. Since NIS can be formed *in situ* from NCS and sodium iodide [15], the radioiodination probably follows the same reaction pathway with *in situ* formed protosolvated triflyl [^{131}I]hypoiodite as the actual iodinating species. Using monosubstituted benzenes as aromatic model compounds the scope of this labelling system was investigated on the n.c.a. level.



X = -OH, -OCH_3, -CH_3, -H, -Cl, -$CONH_2$, -COOH, -NO_2

Scheme 2: N.c.a. radioiodination of monosubstituted arenes using NCS in triflic acid

Optimization of reaction parameters

The dependence of the radioiodination yield on the reaction time is shown in Figure 1. In order to explore the difference between activated and deactivated arenes the formation time of radioiodochlorobenzene (sum of isomers) was compared with that of radioiodotoluene and radioiodobenzoic acid at room temperature in one molar educt solutions.

The radiochemical yields achieved and the speed with which the electrophilic aromatic substitution reached completion were influenced by the presence of electron donating or withdrawing groups on the aromatic ring. The reaction kinetics were slower with lower electronic activation of the aromatic substrate. N.c.a. radioiodination of the weakly activated toluene resulted in a radiochemical yield of about 85% within 5 minutes.

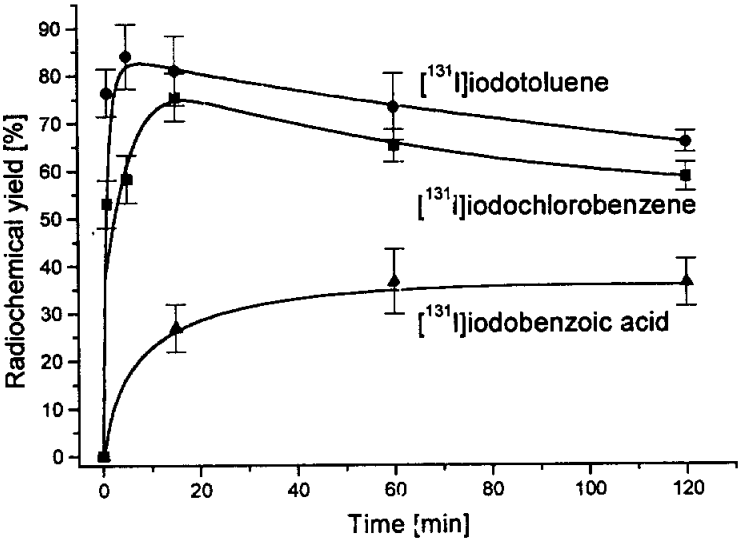


Figure 1: Radiochemical yield of [^{131}I]iodotoluene, [^{131}I]iodochlorobenzene and [^{131}I]iodobenzoic acid as a function of time
reaction conditions: 15 µmol NCS, 0.5 mmol arene, n.c.a. Na^{131}I, 0.5 mL triflic acid, RT

Labelling of the weakly deactivated chlorobenzene also gave a high yield of 75%, however, with a slightly longer reaction time of about 15 minutes. More extended reaction times lead to a decrease in the yield of both the aromatic compounds, probably due to decomposition of the radioiodinated products. Radioiodination of the strongly deactivated aromatic ring of benzoic acid was not completed even after two hours. In this case a radiochemical yield of about 45% could be obtained after 7 hours. However, the reaction time for benzoic acid could be shortened by heating the reaction mixture for 1 hour at 75°C, obtaining a considerably higher radiochemical yield of about 65%.

The dependence of the radiochemical yield on the amount of chlorobenzene is shown in Figure 2 and was measured not only for maximizing the radiolabelling yield but also for minimizing educt concentration in order to facilitate product separation and purification.

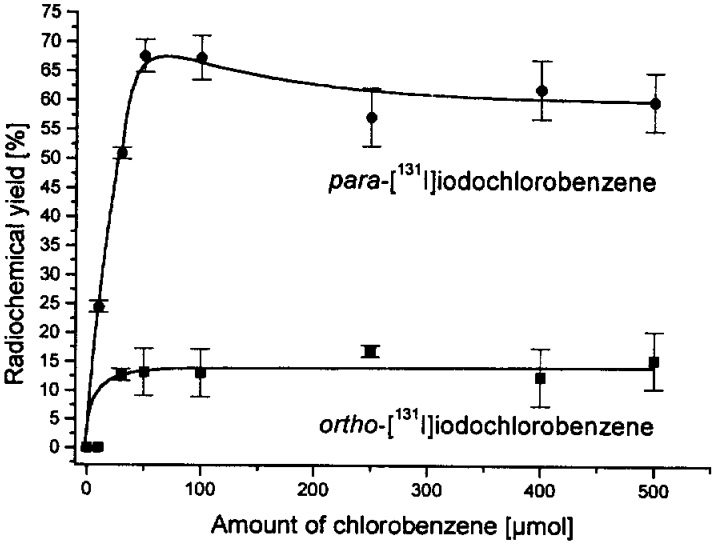


Figure 2: Dependence of the radiochemical yield of *ortho*- and *para*-[^{131}I]iodochlorobenzene on the amount of chlorobenzene
reaction conditions: 15 µmol NCS, n.c.a. Na^{131}I, 0.5 mL triflic acid, 15 min at RT

Moreover, the precursor concentrations for n.c.a. radioiodination and radiobromination via N-halosuccinimides described in the literature vary in a wide range, thus making a more detailed investigation reasonable [10 - 12].
Use of 50 µmol of chlorobenzene in 500 µL triflic acid gave a total radiochemical yield of about 80%. In addition, further minimization of the educt amount could be performed simply by decreasing the reaction volume to 100 µL. In this case only 10 µmol of the precursor was required to maintain the same total radiochemical yield.

The relationship between the amount of NCS and the radiochemical yield of radioiodochlorobenzene is illustrated in Figure 3. These experiments were performed in order to determine the optimum amount of NCS for the *in situ* formation of the iodinating

species. High radioiodination yields were obtained with amounts of NCS in the range of 7.5 μmol per 500 μL. Higher amounts of NCS had practically no influence either on the total radiochemical yield or on the isomeric distribution of the radioiodinated *ortho*- and *para*-products.

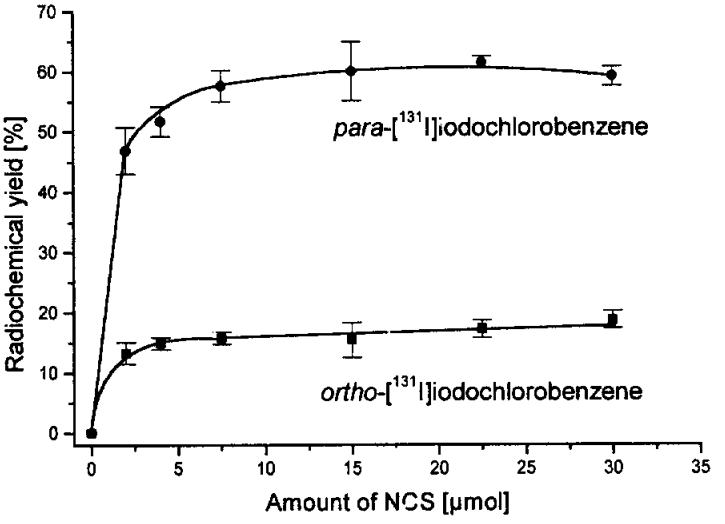


Figure 3: Dependence of the radiochemical yield of *ortho*- and *para*-[^{131}I]iodochlorobenzene on the amount of NCS
reaction conditions: 0.5 mmol chlorobenzene, n.c.a. Na^{131}I, 0.5 mL triflic acid, 15 min at RT

It is well known that radioiodination via N-chloro oxidizing agents often leads to chlorination side-reactions. The chlorination yield depends on the reactivity of the aromatic substrate and the concentration of the oxidant. Here, however, chlorinated side-products could not be detected during the radioiodination of chlorobenzene and all the other investigated aromatic compounds in the studied concentration range of NCS as proven by HPLC.

The effect of water on the radioiodination system is shown in Figure 4. Working in the presence of water is especially advantageous for radioiodination, since drying of the radioiodide can be avoided and the risk of evaporating radioactivity is minimized. This is even more important when working with short-lived iodine-120 ($t_{½}$ = 81 min) and

iodine-123 ($t_{½}$ = 13.2 h). Figure 4 shows, that the NCS/triflic acid system tolerates about 10 vol% water (50 µl) with no decrease of the radiochemical yield. However, due to the dilution of triflic acid the radiochemical yield decreases at higher amounts of water. Higher water concentrations lead to the formation of hydronium trifluoromethanesulfonate since water can act as a base in a strong acid like triflic acid [22]. Also, addition of water makes alternative reaction pathways possible, e.g. oxidation of water by the electrophilic radioiodine species.

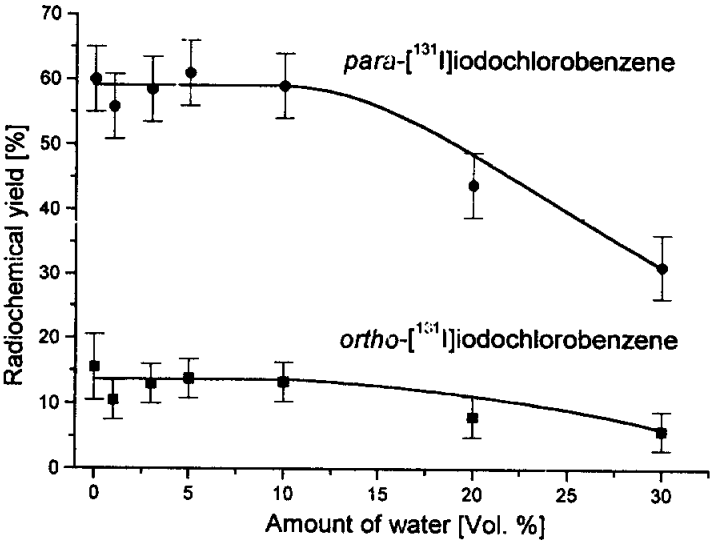


Figure 4: Dependence of the radiochemical yield of *ortho-* and *para*-[^{131}I]iodochlorobenzene as a function of added water
reaction conditions: 15 µmol NCS, 0.5 mmol chlorobenzene, n.c.a. $Na^{131}I$, 0.5 mL triflic acid + H_2O, 15 min, RT

Figure 5 shows the influence of the reaction temperature on the radiochemical yield. Increasing the temperature above 40°C led to a significant decrease in the radiochemical yield of *ortho-* and *para*-[^{131}I]iodochlorobenzene (almost 0% at 150°C). At the same temperature the formation of *meta*-[^{131}I]iodochlorobenzene could be observed with an increasing radiochemical yield up to about 40% at 75°C.

At room temperature the formation of the *ortho-* and *para*-isomer is kinetically controlled, since the *ortho/para*-directing resonance effect between the deactivating

chlorine and the ring is more important than the electron withdrawing one by the field effect. At higher temperatures the free energy is obviously high enough to exceed the activation for isomerisation and the thermodynamically controlled *meta*-[^{131}I]iodochlorobenzene is formed. The total radiochemical yield for all isomers of about 75% remained constant up to a temperature of 80°C. Higher temperatures led to decomposition of the products.

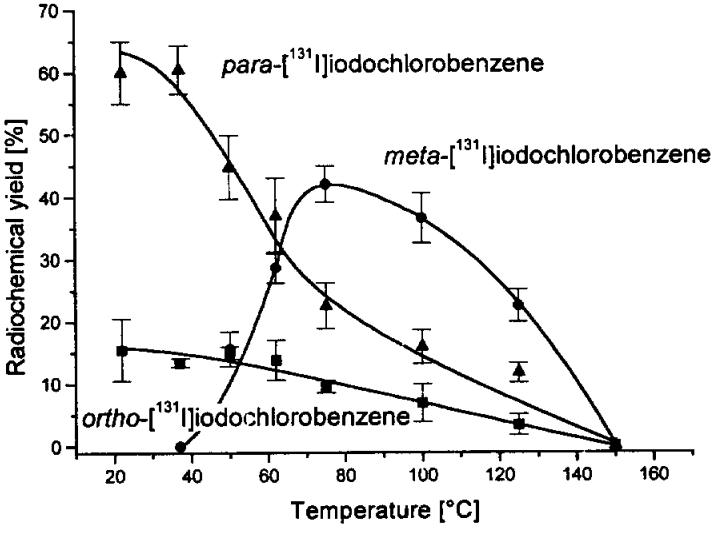


Figure 5: Effect of the reaction temperature on the n.c.a. radioiodination of chlorobenzene
reaction conditions: 15 µmol NCS, 0.5 mmol chlorobenzene, n.c.a. Na^{131}I, 0.5 mL triflic acid, reaction time 15 minutes

The effect of added NaI as isotopic carrier on the radiochemical yield is graphically depicted in Figure 6. The radiochemical yield remained constant when the amount of carrier iodide was varied by three orders of magnitude up to a NaI / NCS ratio of 0.01. For simple statistical reasons the radiochemical yield should only decrease at higher ratios than 1, however, more than a hundred fold excess of NCS is necessary to maintain optimum yields.

The radiochemical yields and the *ortho/para*-isomer distribution of iodochlorobenzenes formed are not affected by the addition of small amounts of carrier iodide. Obviously, the carrier iodide does not cause a change of the reaction mechanism. The postulated

electrophilic in situ radioiodination via an intermediately formed superelectrophilic triflyl hypoiodite as iodinating species is at least not disproved by the dependence on carrier iodide, because the oxidative reaction pathway with the formation of the iodinating species should not be influenced by small amounts of carrier iodide. In some experiments directly added NIS as carrier also did not influence the radiochemical yield of both isomers, an observation in agreement with an unchanged reaction mechanism. As discussed, this points to an intermediate formation of $N^{+}IS$, from which proto-solvated triflyl hypoiodite is formed according to Scheme 1.

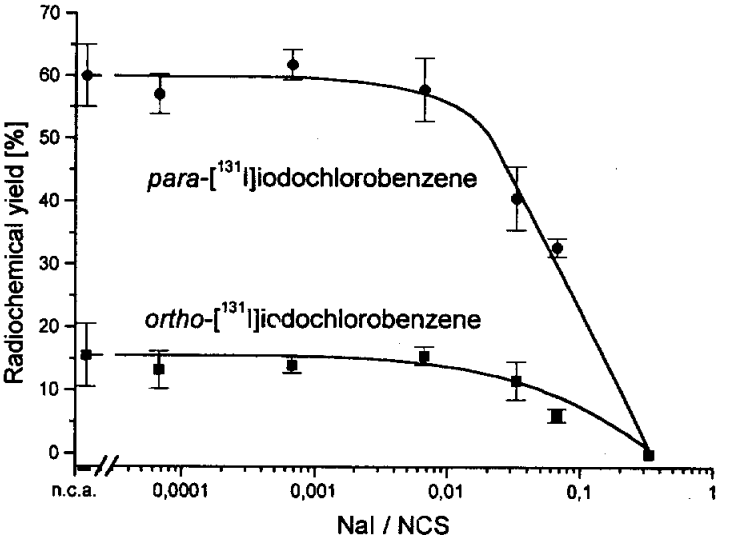


Figure 6: Dependence of the radiochemical yield of *ortho*- and *para*-[^{131}I]iodochlorobenzene on added carrier iodide
reaction conditions: 15 µmol NCS, 0.5 mmol chlorobenzene, Na^{131}I, 0.5 mL triflic acid, 15 min at RT

Radioiodination of monosubstituted arenes

The influence of electronic activation or deactivation of the aromatic ring in the electrophilic substitution was studied for the n.c.a. radioiodination of monosubstituted arenes (substituents X = OH, OMe, Me, H, Cl, $CONH_2$, CO_2H and NO_2) and is shown in Table 1.

Table 1: Radiochemical yields of selected monosubstituted arenes [a]

	Substituent	Radiochemical yield [%]	Positional selectivity [%]
1	OH	64.7 ± 4	35/65 o/p
2	OCH_3	39.1 ± 5	25/75 o/p
3	CH_3	84.1 ± 7	40/40/20 o/m/p
4	H	80.6 ± 3	-
5	Cl	75.5 ± 5	20/80 o/p
6	$CONH_2$	20.5 ± 1 (24.9 ± 2) [b]	100 m
7	COOH	42.4 ± 8 (68.5 ± 4) [b]	100 m
8	NO_2	38.1 ± 1 (68.3 ± 2) [b]	100 m

reaction conditions: 0.5 mmol arene, 15 µmol NCS, n.c.a. $Na^{131}I$, 0.5 mL triflic acid; [a] reaction time 1 - 15 min at RT, [b] reaction time 1 hour at 75°C

For the strongly deactivated arenes benzamide (**6**), benzoic acid (**7**) and nitrobenzene (**8**) the *meta*-position is most activated, thus leading exclusively to the formation of *meta*-radioiodinated products (Table 1). With the exception of toluene (**3**) all weakly activated arenes and the weakly deactivated chlorobenzene (**5**) have an *ortho/para* isomer distribution typical of electrophilic substitution. The strong electrophilic nature of the *in situ* formed iodination agent, most likely protosolvated triflyl [^{131}I]hypoiodite, probably causes an unselective substitution of the weakly activated toluene (**3**), since the methyl group is the only activating substituent in Table 1 without an electronic resonance interaction with the σ-complex of the aromatic ring.

The total radiochemical yield of the strongly deactivated arenes could be increased upon heating. Thus, radioiodination of benzoic acid and nitrobenzene at 75°C led to radiochemical yields of about 68% for both radioiodoarenes. The strong electron withdrawing substituents led exclusively to *meta*-radioiodinated isomers. Furthermore, the reaction time of the strongly deactivated arenes could be shortened by heating the reaction mixture. At 75°C the maximum radiochemical yield is already obtained after 1 hour.

In the case of benzamide the unshared pair of electrons of the amide group probably interacts with the electrophilic iodinating species, thus resulting in a low radiochemical yield of about 25% even at elevated temperatures. Addition of 0.1 μmol carrier iodide in this case raised the concentration of the iodinating species and led to a significant increase of the formation of *meta*-[^{131}I]iodobenzamide up to a radiochemical yield of about 80% (data not shown here).

Substituents with a strong electron withdrawing field effect decrease the π-electron density in the phenyl ring whereas electron donating groups increase the electron density. These variances in electron density affect the ^{1}H-NMR chemical shift, especially the protons in *ortho*-position. An upfield chemical shift of the *ortho*-protons indicates a higher density of the electron cloud in the ring and thus a higher probability of electrophilic substitution. The correlation between total radiochemical substitution yields and ^{1}H-NMR chemical shifts of the *ortho* ring proton is illustrated in Figure 7.

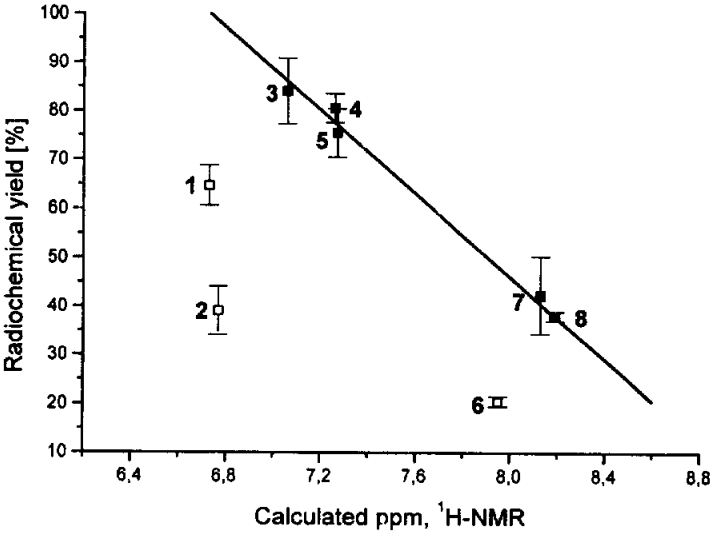


Figure 7: Correlation of total radiochemical yields with calculated ^{1}H-NMR chemical shift values of various monosubstituted arenes (□: data were not included in the calculation of regression)
reaction conditions: 0.5 mmol arene, 15 μmol NCS, n.c.a. Na^{131}I, 0.5 mL triflic acid, 15 min at RT

With the exception of phenol (**1**), anisole (**2**) and benzamide (**6**) the reaction yields can be linearly correlated [y = - 43.81 (± 1.57) x + 396.87 (± 12.65)] with the ^{1}H-NMR chemical shift of the *ortho* aryl ring proton with a correlation coefficient of $r^2 = 0.996$. From the compounds, which were used for the calculated regression line in Figure 7, toluene (**3**) gave the highest radiochemical yield of about 84% and a relatively low ^{1}H-NMR shift of the proton attached in *ortho*-position (7.06 ppm). The electron withdrawing nitro (**8**) group led to a lower radiochemical yield of about 38% due to a lower electron density in the ring resulting in a downfield ^{1}H-NMR shift of the *ortho*-proton at 8.19 ppm.

The fact that phenol (**1**), anisole (**2**) and benzamide (**6**) fall off the straight correlation line can be understood in terms of the properties of these aromatic compounds. The relatively low radiochemical yield of radioiodophenol of about 64 % indicates a decomposition of the highly activated starting compound, which is expressed by a significant decrease of the radiochemical yield of radioiodophenol after short reaction times. Radioiodination of the weakly activated anisole (**2**) only led to a radiochemical yield of 39 %, which can be explained by demethylation of the arene under the strongly acidic reaction conditions, followed by oxidative decomposition. Reasons for the low radioiodination yield of benzamide (**6**) are discussed above.

NCS/triflic acid in comparison to other electrophilic in situ radioiodination systems

In order to demonstrate the potential of the new method the radiochemical yields of several radioiodinated arenes using N-chlorotetrafluorosuccinimide (NCTFS), chloramine-T (CAT), NCS in trifluoroacetic acid anhydride (TFAA) [13] and Thallium(III)trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) [6] are compared in Table 2 with NCS in triflic acid. As expected for an electrophilic iodination mechanism, the radiochemical yields obtained by all oxidants were correspondingly dependent on the activation of the aromatic ring. However, radioiodination with NCTFS, CAT and NCS in TFAA was limited to activated benzene derivatives. Metal salts like TTFA in TFA are more efficient labelling systems, since radioiodination of activated arenes generally led to higher radiochemical yields than using N-chloroamides in TFAA and even labelling of non-activated benzene was possible with a radiochemical yield of

about 35%. However, the highest radiochemical yields could be obtained using NCS in triflic acid. Only this method allows the radioiodination of strong deactivated arenes like nitrobenzene with high radiochemical yields of about 70% at 75°C.

Table 2: Comparison of the radioiodination yields of selected arenes using various oxidizing agents

Solvent		TFAA		TFA	Triflic acid
Oxidant	NCTFS	NCS	CAT	TTFA [a]	NCS
Reaction time	4 h	4 h	10 min	15 min	5 – 60 min
Anisole	69 ± 5	72 ± 4	75 ± 8	83 ± 5	39 ± 5
Toluene	47 ± 8	30 ± 6	49 ± 8	89 ± 7	84 ± 7
Benzene	~ 4	~ 1	~ 3	34 ± 2	81 ± 3
Chlorobenzene	-- [b]	-- [b]	-- [b]	0	76 ± 5
Nitrobenzene	-- [b]	-- [b]	-- [b]	0	38 ± 1

reaction conditions: 0.5 mmol arene, 15 µmol iodination reagent, 0.5 solvent; RT
[a] 7.5 µmol arene, 6.75 µmol TTFA, 0.3 mL TFA, RT; [b] not measured

In analogy to the formation of a highly activated protosolvated triflyl [^{131}I]hypoiodite as iodination species using the NCS/triflic acid system, the oxidative reaction pathway of radioiodinations in TFAA or TFA probably leads to the formation of an intermediately formed trifluoroacetyl hypoiodite as iodination agent. *In situ* formed trifluoroacetyl hypoiodite was also postulated for the n.c.a. radioiodination of tyrosine analogues and various anisole derivatives using N-chloroamides in TFA [8, 9, 24]. Recently trifluoroacetyl hypoiodite was described as iodination agent for direct equimolar iodination [24] and radioiodination [25] of monosubstituted arenes in the presence of metal salts in TFA. Trifluoroacetyl hypobromite has been previously suggested as a bromination agent for the analogous radiobromination using NCTFS in TFAA [3, 11].

Conclusion

In conclusion, the use of NCS in triflic acid allows the direct electrophilic n.c.a. radioiodination of several activated and deactivated aromatic compounds with high

radiochemical yields. The method is simple to perform, fast and proceeds under relative mild reaction temperatures. N.c.a. radiolabelling of deactivated arenes by NCS exclusively leads to the formation of *meta*-radioiodinated isomers. Compared to other classical electrophilic radioiodination methods like chloramine-T or Iodogen™, the *in situ* oxidation of radioiodide with the NCS/triflic acid system is the first labelling procedure applicable for strongly deactivated arenes.

Thus, this new versatile method can be useful in radiopharmaceutical research, because a great number of pharmaceutically interesting compounds with a deactivated aromatic group can be directly labelled with radioiodine without preparation of a specific precursor. Of course, precursor and radioiodinated product must be stable in triflic acid. However, precursors of complex aromatic radiotracers, such as 4-methoxy-N-methylbenzamide, the basic structure of melanoma seeking tracers, the fatty acid 15-phenylpentadecanoic acid and 3-([4-phenyl-piperazin-1-yl]-methyl)-1H-pyrrolo [2,3-b]-pyridine (L-750,667), an antagonist for the dopamine D_4-like receptor, have been effectively radioiodinated using this method. Their radiosynthesis will be published elsewehre.

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