PRACTICALLY CARRIER-FREE LABELLING OF AROMATIC COMPOUNDS WITH BROMINE-77 VIA N-CHLORO-TETRAFLUOROSUCCINIMIDE

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SUMMARY

A new method for practically carrier-free aromatic bromination has been developed using N-chloro-tetrafluoro-succinimide (NCTFS) and bromide-77. The optimum bromination conditions have been determined using toluene as a model system. In trifluoroacetic anhydride (TFA), which proved to be the best solvent, a "one-pot" synthesis with carrier-free bromide-77 gives rise to a 52 % radiochemical yield of bromotoluenes. No benzylbromide is formed. At room temperature the reaction is completed within about 30 min, the highest yields being obtained at NCTFS-concentrations of $2 \cdot 10^{-2}$ mole/l. In pure anhydride (TFA) the chlorinating side-reaction of NCTFS does not take place. The reactivity towards simple benzene derivatives (C_6H_5X, X = OCH_3, CH_3, H, F, Br, NO_2) is strongly dependent on the activation of the aromatic ring. A high ortho- and particularly para-selectivity is observed, and an electrophilic substitution process via ionic species is discussed.

Key Words: Bromination, Bromine-77, N-chloro-tetrafluorosucciminide

0362-4803/79/0616-0891$01.00

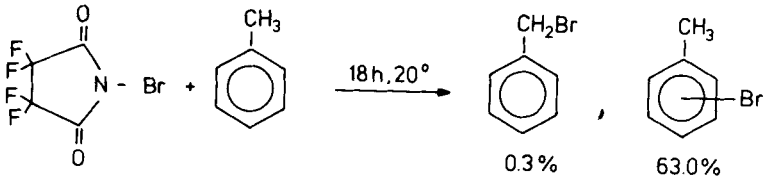
Received December 15, 1978

INTRODUCTION

For in vivo application in nuclear medicine radiohalogens are of great interest for labelling metabolites and other biomolecules. Among the neutron deficient radiohalogens used with present day gamma cameras, iodine-123 ($T_{1/2}$ = 13.3 h) and bromine-77 ($T_{1/2}$ = 56 h) have the most suitable decay properties. Bromine-77 has some advantages in comparison to iodine-123 due to the longer half-life and the stronger carbon halogen bond (1). It therefore finds increasing interest in nuclear medicine (for a review see (2)).

In the case of in vivo application toxicity and unchanged biochemical equilibrium requirements often demand high specific or carrier-free activities. Aromatic compounds are of special interest and have been brominated by various methods. The direct decay induced labelling via the krypton gas exposure technique would be a simple method with respect to carrier-free labelling. It was used by several groups but resulted mostly in poor yields (3-6). Carrier-free iodination methods such as the ^{123}ICl (7) and the $^{123}Xe/KIO_3$ method (8) have also been adapted to aromatic bromination with good results (3,9,10). The high excess of Cl_2 or $KBrO_3$ agent, however, gives rise to oxidising side reactions. The latter method is also restricted to acidic aqueous solutions and strongly activated aromatic compounds. The enzymatic bromination by chloro-peroxidase has also been applied successfully (1). Working with enzymes, however, demands sensitive biochemical methods, and pyrogen problems have to be overcome.

When searching for carrier-free brominating agents, a number of requirements should be met. Among others it should be directly preparable from bromide, which is delivered in most of the radiobromine production methods. Therefore, N-haloimides, especially succinimides, seem to be most promising. The potential of N-bromosuccinimide (NBS) to introduce single bromine atoms into organic compounds is well known (11). But also electrophilic bromination of activated aromatic compounds by NBS has been reported (12). In 1951 Henne and Zimmer prepared the tetrafluoro substituted NBS and brought it to reaction with toluene (eq. 1).



(1)

They observed a 63 % yield of bromotoluenes and only 0.3 % benzylbromide, indicating an electrophilic aromatic substitution (13).

In order to adapt the method to carrier-free bromination, the corresponding N-chloro compound, namely N-chloro-tetrafluorosuccinimide (NCTFS), was chosen as agent. Because the polyfluorinated N-halo-succinimides are very sensitive towards traces of water, carrier-free N-^{77}BrTFS could not be prepared and separated from NCTFS. We therefore employed a single step procedure using NCTFS in the presence of both the substrate and the bromide-77.

In view of the mechanistic aspects involved, in particular with respect to a possible radicalic pathway, toluene was chosen as model substrate for optimizing the reaction conditions. In order

to study selectivity and reactivity effects, simple other monosubstituted benzenes C_6H_5X (X = OCH_3, CH_3, H, F, Br, NO_2) were also used as substrates.

EXPERIMENTAL

Production of Bromine-77

Production of bromine-77 was carried out either via the $^{75}As(\alpha,2n)^{77}Br$ nuclear reaction by bombarding a thick target of copper arsenic alloy (14) with 30 MeV α-particles at the Jülich compact cyclotron CV-28. After irradiation the bromine was removed from the alloy by a dry distillation technique and collected as bromide. Alternatively, the $^{79,81}Br(d,xn)^{77}Kr(\beta^+)^{77}Br$ nuclear reaction was also used bombarding a thick target of NaBr with 80 MeV deuterons at the Jülich isochronous cyclotron (15). The krypton gas was continuously swept off the target with He-carrier gas, collected on molecular-sieve traps at 77 K, transferred into quartz vessels and allowed to decay. The details of this method and the results from the Kr-gas exposure labelling will be published elsewhere (16). The collected bromide was washed from the quartz traps and vessels with demineralised and doubly distilled water and transferred into 5 ml reaction vessels (about 0.1 - 0.5 mCi per sample). In some cases a weighed amount of NaBr was added as carrier and the aqueous solution evaporated to dryness at temperatures just below the melting point.

Bromination and Analytical Methods

A weighed amount of N-chloro-tetrafluorosuccinimide was added to the dry bromide-77 in a dry box and both were dissolved in 0.5 ml trifluoroacetic acid anhydride (TFA) containing 10 - 200 µl of the benzene derivative to be brominated. After the desired reaction time, during which the darkened vessel was kept at room temperature, 1.5 ml aqueous solution of 5 % Na_2SO_3 and Na_2CO_3 was added cautiously under ice-cooling to stop the reaction. Then 1.0 ml $CHCl_3$ containing carrier-amounts of the expected bromination products was added. After centrifugation the organic layer was separated, dryed and aliquots were taken to determine the total activity employed.

The reaction mixtures of the brominated benzenes, in particular the ortho-, meta- and para-isomers, were analysed by discontinuous radiogaschromatography on a Hewlett Packard research chromatograph 5363 A, trapping the individual peaks on charcoal (17). The separation of the brominated benzene, fluoro-, bromonitrobenzene and anisole was achieved using 4 m glas columns (3.5 mm i.d.) filled with 6 % Bentone-38 and 20 % Silicon oil or 20 % Igepal CO-880 on Chromosorb W-AW-DMCS (60 - 80 mesh) (18,19). The bromotoluenes and benzylbromide were separated on a 8 m glass column (8 mm i.d.) filled with 10 % 4,4'Azoxydianisol on Chromosorb W-AW-DMCS (60 - 60 mesh) (20). For quantitative assay each aliquot and collected peak fractions were measured in a well type Tricarb-γ-counter (Packard 5375).

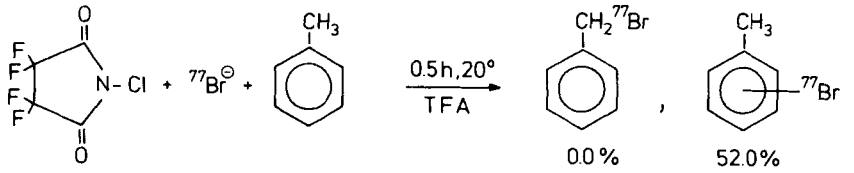
MATERIALS

The benzene derivatives (Merck, Fluka, Schuchardt), were of analytical grade and subjected to additional purification by fractional distillation. The trifluoro acetic acid and anhydride were of analytical purity grade (Merck). N-chlorotetrafluoro-succinimide (NCTFS) was prepared from the corresponding imide by adaptation of the method described for the N-bromo-compound (21). It was purified by repeated vacuum sublimation and stored in a dry box. The corresponding imide was synthesised from tetrafluoro succinicanhydride (Merck) in three steps (13).

RESULTS AND DISCUSSION

Reaction Parameters

Among ten polar, water-free solvents such as THF, DMF, DMSO etc., trifluoro acetic anhydride (TFA) proved to be the best for applying NCTFS to oxidise and introduce bromide into organic compounds in a one pot reaction. Thus, in the reaction of NCTFS and carrier-free bromide-77 with toluene in TFA, 52 % of ^{77}Br-bromo-toluenes were formed. No benzylbromide could be detected (eq. 2).



(2)

The influence of bromide-carrier added to the reaction solution on the yields is illustrated in Fig. 1.

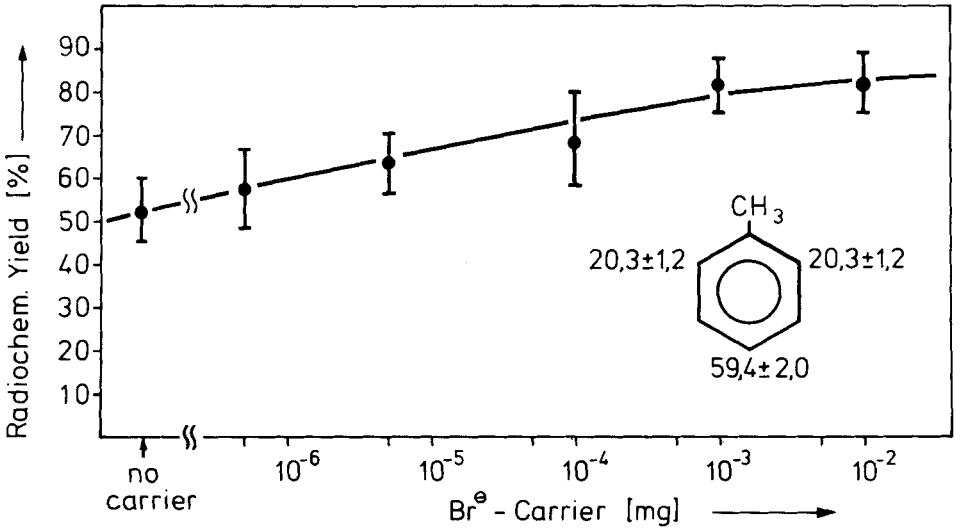


Fig. 1 Dependence of bromination yield on Br^--carrier concentration (100 µl toluene, 2 mg NCTFS, 0.5 ml TFA, 22 °C, 2 hrs reaction time).

The yield rises only by about a factor of 1.5 when the bromide concentration is varied by four orders of magnitude. If Br_2 would be formed or radical reactions would take place, the yields should be affected by the bromide carrier concentration. Obviously, the reaction mechanism does not change in the concentration range studied. The relatively small effect could also be explained by compensation of radiochemical losses at higher concentrations or by bromide impurities in the starting material. The lack of benzyl bromide formation even at high bromide concentrations also excludes radical reactions. The isomer distribution of the bromotoluenes, also shown in Fig. 1, does not change over the entire range of bromide concentration. This also supports the assumption of an unchanged mechanism.

In order to work under comparable conditions, the further studies were carried out in the presence of a constant amount of NaBr (1 µg). In Fig. 2 the influence of time and concentration of NCTFS on the bromination of toluene is shown. Both curves exhibit a saturation yield of about 82% of bromobenzene at comparable NCTFS concentration. The dependence on time indicates that the reaction is completed after about half an hour. This reaction time is short enough considering the half lives of most of the radiohalogens of interest.

To determine the dependence of radiochemical yield on the concentration of NCTFS a reaction time of two hours was chosen to ensure completion of the reaction. If this is attained, the bromination or more probably the formation of the brominating species seems to be an equilibrium reaction, being strongly dependent on the imide concentration. The high excess of imide over bromide (100 - 2000 molar) seems to be necessary to prevent losses of the carrier-free bromide. Changing the concentration of toluene from 0.2 to 4.0 molal did not affect the bromination yield, probably because of its high molecular excess. The isomer distribution (cf. Fig. 1) was not affected by changing the reaction time or the concentration of NCTFS.

Chlorination Side-Reaction

In analogy to eq. 1 direct chlorination of toluene by NCTFS can also occur as a side-reaction. The chlorination yield, however, was observed to be dependent on the concentration of trifluoro-

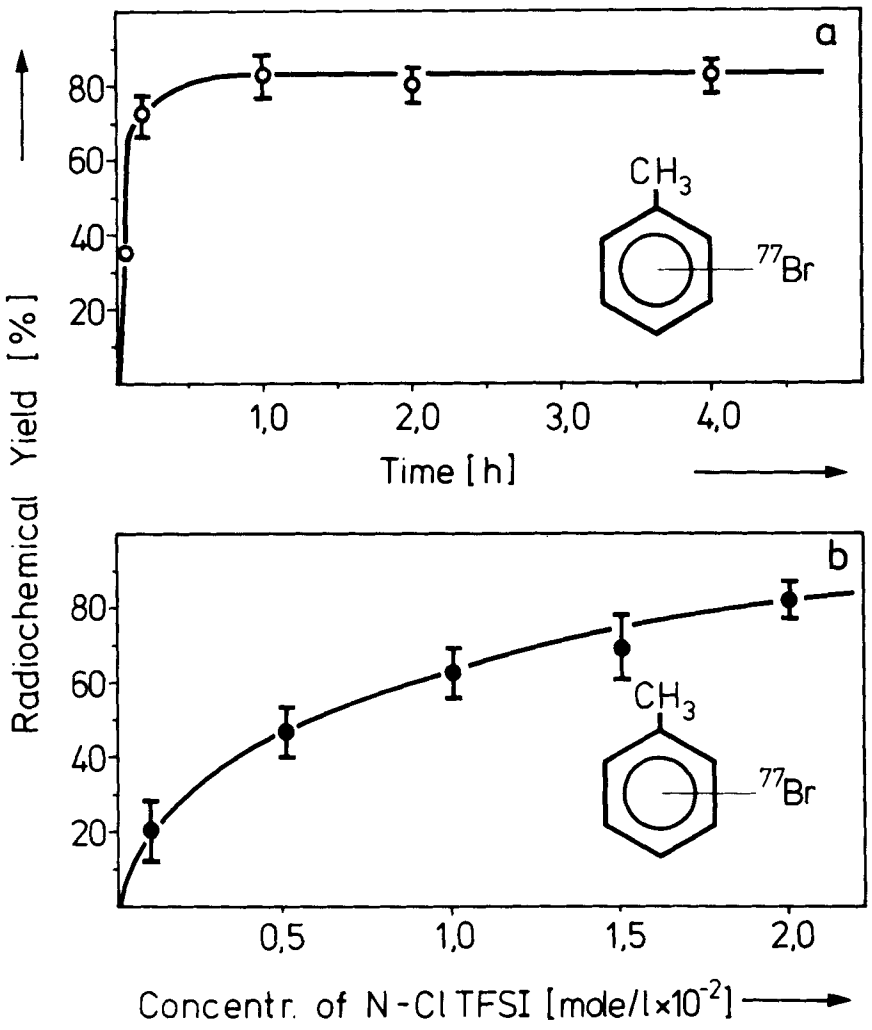


Fig. 2 Dependence of bromination yield on time (a) and concentration (b)

a) 2 mg NCTFS, 1 µg Br^--carrier, 0.5 ml TFA, 100 µl toluene, 22°C

b) 0.5 ml TFA, 100 µl toluene, 1 µg Br^--carrier, 22°C, 2 hrs reaction time.

acetic acid in the reaction mixture. Fig. 3 shows the dependence of direct chlorination and of the radiobromination yields on the trifluoroacetic acid to anhydride ratio. The yields are based on the amounts of NCTFA and bromide-77, respectively. It can be seen that radiobromination only slightly decreases, whereas the chlorination yield shows a drastic increase with increasing acid concentration. It is interesting to note that the highest chlorination yield equals that of bromination. Furthermore, the isomer distribution of the bromo- and chlorotoluenes are identical within the experimental error. Obviously, the brominating species are formed in pure anhydride whereas the corresponding chlorinating species require the presence of trifluoroacetic acid. Therefore, it can be assumed that the N-halo-imides themselves are not the halogenating agents. This is also demonstrated by the fact that N-bromotetrafluorosuccinimide (NBTFS), tracered with bromine-77, does not react with toluene in pure anhydride but only when adding the free acid. For practical use, the most important aspect is the possibility to avoid or suppress the chlorination by working in pure anhydride solution. This is a great advantage, particularly when the chloro- and bromo-compounds of complicated molecules cannot easily be separated by chromatographic methods.

Reactivity and Selectivity Towards Monosubstituted Benzenes

The results obtained in bromination of other monosubstituted benzenes derivatives are listed in Table 1. Clear ortho- and para-selectivities are observed.

With the exception of nitrobenzene only ortho- and para-products are formed. Substitution in para-position (60 - 90%) is preferred even in halobenzenes. The absolute yields of hydrogen

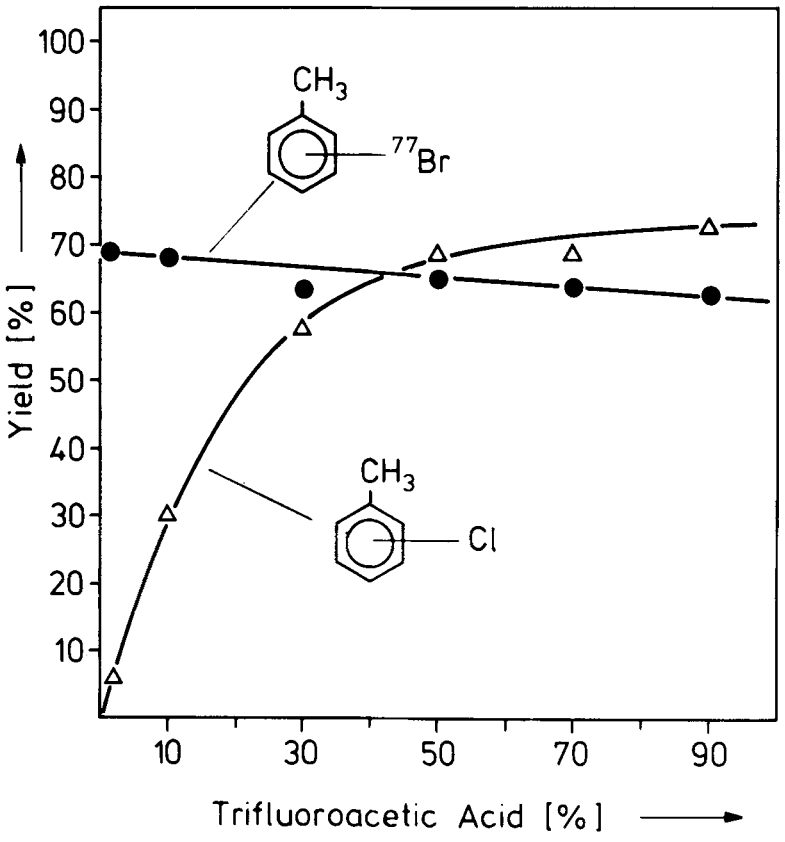


Fig. 3 Influence of the trifluoroacetic acid concentration in anhydride solvent (0.5 ml TFA, 1 µg Br^--carrier, 100 µl toluene, 1.5 mg NCTFS, 22°C, 2 hrs reaction time).

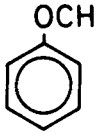
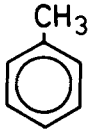
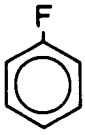
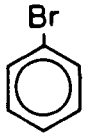
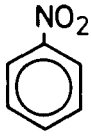
substitution are particularly high in the activated systems anisole and toluene (about 60 %). In benzene and the halobenzenes the yields are about 10 to 15 % and decrease in nitrobenzene to about 2 %. Substitution of the halogen- or other substituent groups is not observed. The drastic decrease of hydrogen substitution with decreasing activation of the aromatic nucleus and the high ortho-para selectivity suggest a strong electrophilic substitution reaction. The isomer distribution in the nitrobenzene system, however, (70 % ortho, 18 % meta and 12 % para) seems to contradict an electrophilic substitution mechanism, although the yield is expectedly low. On the other hand, this finding can hardly be explained by radical reactions. Thermal chlorine atoms, e.g. reacting in nitrobenzene (22) also exhibit a predominantly electrophilic substitution pattern (28 % ortho, 64 % meta and 9 % para). Complex formation of the reacting species with the nitro group may play a major role.

The isomer distribution found in anisol, toluene and halobenzenes are very similar to that obtained in electrophilic bromination by Br_2 in acetic acid and chlorination by Cl_2 in acetic acid, respectively (23,24). On the other hand, bromination with positively polarised bromine shows a higher ortho selectivity, e.g. BrOH ($BrOH_2^+$) in toluene (70.3 % ortho, 2,3 % meta and 27.4 % para (25)).

Brominating Species

Although the reactive brominating species cannot be identified the experimental facts concerning the mechanism can be summarised as follows:

Table 1: Radiochemical bromination-yields of benzene derivatives and relative O-, m-, p-isomer distribution (0.2 mole/l of substrate; 1.0 mg NCTFS; 0.5 mol TFA and 1 µg Br^+-carrier; 22 °C; 30 min reaction time).

Substrat	Radiochem. Yield H-Subst.	Isomer Distribution (per position)
Anisole	63.0 ± 4.6	 5.9 0.0 88.2
Toluene	62.1 ± 6.8	 20.4 0.0 59.2
Benzene	16.2 ± 1.0	——
F-Benzene	10.6 ± 2.5	 4.9 0.0 90.2
Br-Benzene	14.4 ± 2.6	 14.3 0.0 71.4
Nitro-Benzene	1.8 ± 0.3	 35.0 9.0 12.0

i) No side chain (radical) reaction can be observed

ii) The isomer distribution of the products clearly indicates an electrophilic substitution mechanism.

iii) Carrier addition of bromide has practically no influence.

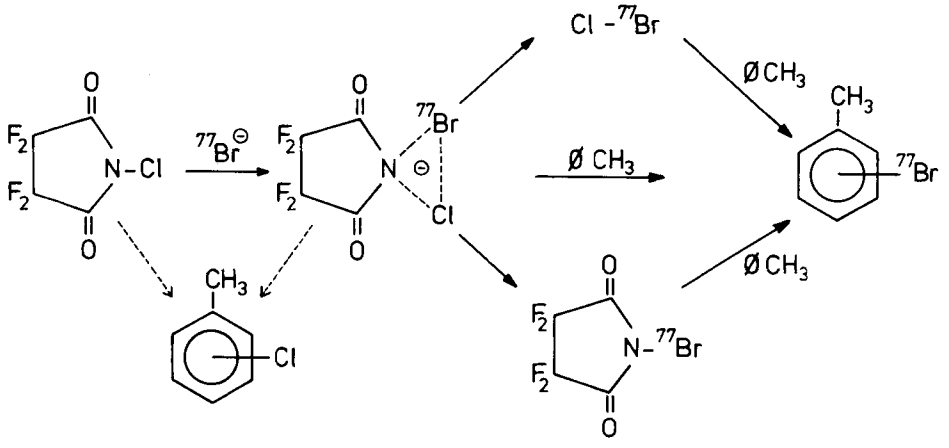


Fig. 4 Possible reaction pathways in bromination of toluene with NCTFS and bromide-77.

A hypothetical scheme for the reactions between NCTFS, ^{77}Br-bromide and toluene is given in Fig. 4. In the first interaction between bromide and the positively polarised N-Cl group a negative complex may be formed which could redissociate releasing the more electronegative chlorine or imide as anion. The resulting exchange reaction would then give rise to either ^{77}Br-NBTFS or ^{77}BrCl, both being able to brominate toluene. ^{77}Br-NBTFS, however, seems very unlikely to be the brominating species since the original N-haloimides do not react in pure trifluoroacetic anhydride (cf. Fig. 3). A contribution from ^{77}BrCl should also be

negligible due to the high instability of this compound at room temperature (26) which would give rise to a significant radical bromination at least in pure toluene. No side chain bromination of toluene was, however, observed with NCTFS in the absence of TFA, even though the absolute yields were expectedly smaller. The latter point also excludes a contribution from trifluoroacetylhypobromite, a possible electrophile formed with TFA. Considering the neseccary high excess of NCTFS (cf. Fig. 2) the formation of a brominating complex between bromide ions and NCTFS molecules which then attacks toluene molecules directly, seems to be the most likely mechanism.

Conclusion

N-chloro-tetrafluorosuccinimide is a useful reagent to introduce practically carrier-free bromine into aromatic compounds. With pure trifluoroacetic anhydride as solvent a homogeneous reaction proceeds at room temperature and chlorination is avoided. The reaction is fast and mild. In activated aromatic systems high yields are obtained with predominant ortho- and particularly para-selectivity. Radio-bromine in the form of bromide, which is delivered from most of the isotope production procedures, can be applied in a "one-pot" synthesis. A first application of the method to prepare the centrally active drug 4-^{77}Br-2,5-dimethoxyisopropylamine (28) practically carrier-free will be reported separately.

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