RADIOHALOGENATION OF NON ACTIVATED AROMATIC COMPOUNDS VIA ARYLTRIMETHYLSILYL INTERMEDIATES.

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SUMMARY

The utility of aryltrimethylsilyl derivatives to regio-specifically introduce carrier and no-carrier-added quantities of radiobromine and radioiodine into certain aromatic rings has been demonstrated. Using trimethylsilyltoluenes as a model system for aromatic rings that are not highly activated, conditions for the rapid and efficient incorporation of radio-bromine and radioiodine were found. Reaction conditions necessary for the radiobrominations were very mild; however, the slower radioiodinations required elevated temperatures or highly acidic conditions.

Key Words: Trimethylsilyltoluene, Radiobromination, Radioiodination, Bromine-77, Bromine-82, Iodine-131

INTRODUCTION

Radiohalogen-labeled compounds are of interest in radiopharmaceutical development. It is therefore of primary importance that methods be available for introducing radiohalogens into a variety of types of compounds, in specific positions. For compounds containing aromatic rings it is generally accepted that the best position to radiohalogenate is on the aromatic ring. This preference arises from the fact that aryl-halogen bonds are usually more stable than other carbon-halogen bonds. Thus, the radiobromine will probably be less labile in vivo.

At present there are several methods of introducing radiohalogens into highly activated aromatic rings (e.g. phenols and anilines) in very high specific activity (1); however, only a few methods have appeared in the literature for introducing radiohalogens into less activated aromatic rings with high

specific activity. Particularly noteworthy is the in situ generation of a
radiobrominating agent produced by the oxidation of bromide-77 with tetrafluoro-
N-chlorosuccinimide (TFNCS).(2) Radiobromination of toluene in trifluoroacetic
anhydride (TFAA) with this method yielded a 2:3 mixture of ortho- and para-
[77Br]-bromotoluene in 52% radiochemical yield within 30 minutes reaction time.
Similarly, radioiodination of toluene in TFAA using TFNCS and iodine-123 yielded
a 1:2 mixture in 60% radiochemical yield after 10 hours reaction time (3).
Unfortunately, for practical laboratory radiohalogenation of compounds this
method has two drawbacks; all experiments must be conducted in a dry box and a
mixture of radiohalogenated compounds arises. The only other methods reported
for radiohalogenating aromatic rings that are not highly activated, which might
yield high specific activity compounds, involve the decomposition of diazonium
salts (4) or triazine analogs (5,6,7) of aromatic compounds in the presence of
bromide or iodide salts. While these methods are regiospecific, yielding only
one aryl position radiohalogenated, they have not been demonstrated for no-
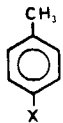carrier-added reactions.

Dissatisfaction with the present methods of radiohalogenating non activated
aromatic rings led to an investigation of another method. It has been known for
over three decades that aryltrimethylsilyl compounds will react with the electro-
philic halogens, bromine and iodine, to yield arylhalides (9); however, this
method has not previously been utilized to introduce radiohalogens into aromatic
compounds. The trimethylsilyl moiety has been shown to impart a reactivity
enhancement such that even aromatic rings that contain the highly deactivating
nitro (10) and carboxylic acid (11) substituents will react. Additionally, the
rate of electrophilic ipso substitution (12) is so rapid that a single regio-
isomer is obtained in the halogenations. Since the aryltrimethylsilyl inter-
mediates are often easily synthesized (13), an investigation to determine if
they could be used to regiospecifically introduce radiohalogens (bromine-82,
bromine-77 and iodine-131) into aromatic rings was carried out. To simplify
the evaluation of the reaction parameters, a model compound study employing

the three trimethylsilyl regioisomers of toluene; ortho-trimethylsilyltoluene

(o-TMST, 1), meta-trimethylsilyltoluene (m-TMST, 2), and para-trimethylsilyl-

toluene (p-TMST, 3) was carried out. The trimethylsilyltoluenes can be consi-

dered model compounds for alkyl substituted aromatics, a moiety that is found in

many pharmaceuticals. The results of that investigation are reported herein.

RESULTS AND DISCUSSION

Halogenations with Stable Nuclides

Halogenation reactions of aryltrimethylsilanes have been carried out in

carbon tetrachloride (10,14,15), methanol (16), and acetic acid (17,18) using

iodine monochloride and bromine. In those investigations, the halogenating

agents were added to the reaction mixtures; however, for radiohalogenations

it is most desirable to generate the radiohalogenating species in situ from

their salts (19). Therefore, our initial studies dealt with the electrophilic

cleavage of the trimethylsilyltoluenes (TMSTs) 1-3 by halogenating agents

(nonradioactive) generated in situ. Reactions of the TMSTs were investigated

in methanol, ethanol, water, and acetic acid as the bromide and iodide salts

were soluble in these solvents (20). Some reactions were also carried out with

the above solvents in combination with CCl_4. The reaction progress of the

halogenations was followed by HPLC and capillary GC using the three bromo-

toluenes 4-6 or three iodotoluenes 8-10 as standards for retention time compar-

isons. Additionally, the three chloro isomers of toluene 12-14, as well as

benzyl bromide 7 and benzyl chloride 11, were used to evaluate the percentages

of side reactions occurring. The presence of benzyl iodide 15 was checked by

GC-MS. Reaction times of five minutes and one hour were used throughout the

investigation to demonstrate the relative rates of the reactions, but other

reaction times were also checked to show completion of the reaction.

X = Si(CH$_3$)$_3$	1	2	3	
X = Br	4	5	6	7
X = I	8	9	10	11
X = Cl	12	13	14	15

Reactions of TMSTs with reagents that produce electrophilic brominating species in situ, were carried out to evaluate which methods gave the highest yields in the shortest time (Table I). Analyses of the product mixtures demonstrated that the reactions were completely regiospecific with no observable chloro side products, 12-15. The facility of this reaction is clearly demonstrated, considering the fact that toluene reacted under identical conditions (as shown in Table I) to yield benzyl bromide 7 as the only product. Reactions of N-bromosuccinimide (NBS) or NBS/chloride were clearly much slower than the reactions of the electrophilic brominating agents formed from the oxidation of bromide ion by N-chlorosuccinimide(NCS) or tert-butylhypochlorite(TBHC). The electrophilic brominating species produced from NCS/Br$^-$ is most likely BrCl (21). This same species should be generated from NBS/Cl$^-$; however, the solubility of lithium chloride ion makes its generation much slower. Indeed, the results of the reaction of NBS and NBS/Cl$^-$ are similar enough to state that it is probably the NBS that is the electrophilic brominating species in both reactions. The reactions with TBHC/Br$^-$ may also have BrCl as the electrophilic brominating species, but it could potentially be tert-butylhypobromite. The two reactions appear to be different as the reaction of TBHC/Br$^-$ is much faster than the reaction of NCS/Br$^-$, being complete instantaneously with o-TMST and p-TMST. This difference in rate may be caused by a base catalysis and not by a difference in electrophilic halogenating agents.

Table I: Brominations with Stable Bromide[a]

	Reaction time[b]	Bromination Reagents			
		NBS	NBS/Cl⁻	NCS/Br⁻	TBHC/Br⁻
p-TMST	5 min	14	11	86	100
	1 hr	72	88	91	
m-TMST	5 min	2	1	37	13
	1 hr	4	17	75	99
o-TMST	5 min	9	11	86	100
	1 hr	55	82	85	

[a]Values were obtained by GC and represent percentages of observed peaks as the brominated product; all reactions were run at room temperature in MeOH. [b]Times were measured from addition of oxidizing agent.

Iodination reactions of TMSTs were investigated using NCS and TBHC to oxidize iodide ion to an electrophilic iodinating species (presumably ICl). The reactions were observed to be much slower than the corresponding brominations; however, concentrating the reaction mixtures or heating them led to reasonable iodinated product yields at one hour reaction time (Table II). Comparison of the reaction rates with ICl in CH_2Cl_2 showed that the iodinations using *in situ* generated ICl in MeOH are much slower. However, the rate of reaction of ICl itself in MeOH also decreased by approximately 50%, leading to the conclusion that the solvent used in the reactions is very important. Reactions with NCS/I⁻ developed the deep violet color of ICl which presisted throughout the reaction, but in the reactions of TBHC/I⁻ the initial deep color quickly went to a light yellow indicating perhaps that another iodinating species is formed (presumably *tert*-butylhypoiodite).

Table II: Iodinations with Stable Iodide[a]

	Reaction Time[b]	Iodination Reagents					
		ICl[c] CH$_2$Cl$_2$	NCS/NaI[d] MeOH	NCS/NaI[e] MeOH	NCS/NaI[f] MeOH/55°	TBHC/NaI[d] MeOH	NCS/NaI[g] HOAC
p-TMST	5 min	87	<1	25	12	52	79
	1 hr	91	6	67	63	79	95
	2 hr			80		93	
	18 hr			96	80		
	68 hr					99	
m-TMST	5 min	89	N.R.	2	8		75
	1 hr		N.R.	13	25	39	79
	2 hr			25		58	
	18 hr				51		
	24 hr			74			
	68 hr					96	
o-TMST	5 min	100	<1	20	11	54	100
	1 hr		9	65	62	89	
	2 hr			78		95	
	6 hr			97			
	68 hr					100	

[a]Values were obtained by HPLC and represent percentages of observed peaks as the iodinated product; all reactions were run at room temperature except where specified otherwise. [b]Times were measured from the addition of oxidizing agents. [c]Method D. [d]Method A. [e]Method C. [f]Method B. [g]Method E.

Since the cleavages of aryltrimethylsilyl compounds are most likely electro-
philic in nature (22,23) the cleavages should be accelerated by acid (24),
therefore, iodinations were attempted in glacial acetic acid. Indeed, a large
acceleration of rate was noticed, with the reaction of NCS/I$^-$ in HOAc being
approximately equal to ICl in CH$_2$Cl$_2$. To evaluate this catalysis further,
a series of dilutions (with H$_2$O) was carried out using NCS/I$^-$ in HOAc (Figure 1).
Surprisingly, a nearly linear relationship for the percentage of iodinated
product (at 5 minute reaction time) and the concentration of acid was observed.

This same acceleration of rates was observed for brominations with NCS/Br⁻ in

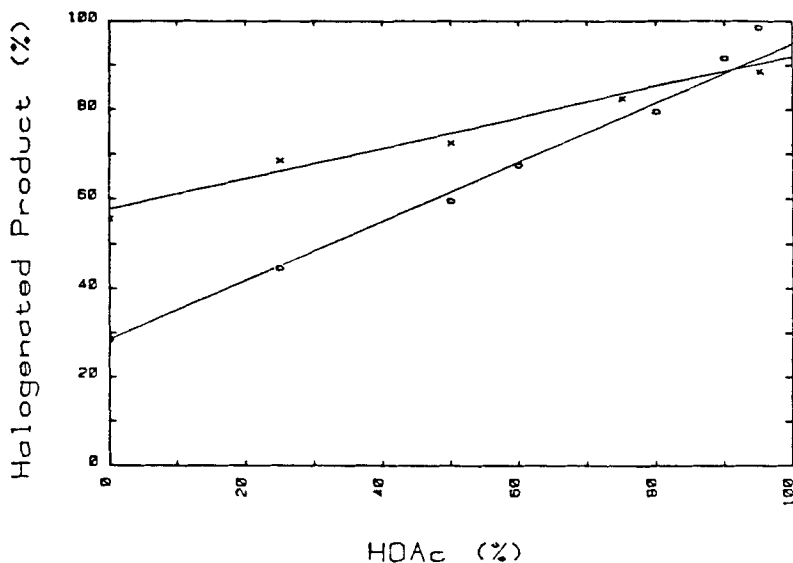HOAc, but the overall amount of catalysis was much less (Figure 1).

Figure 1.   Effect of Acetic Acid Concentration on the Percentage of Halogenated
Product at 5 Minutes Reaction Time.   (X = Bromination reactions;
0 = Iodination reactions)

Both brominations and iodinations using stoichiometric quantities of

oxidizing agents had minimal amounts of chlorinated side products, however

reactions involving no-carrier-added quantities of radiohalogens employ very

large excesses of oxidizing agents.   In these reactions, the chlorination side

reactions will most likely be appreciable and ultimately need to be separated

from the desired radiohalogenated product.   Reactions of NCS with 1-3 in MeOH

at room temperature for one hour led to no detectable quantities of chlorinated

products 12-15; however, raising the reaction temperatures to 55°C yielded 42%

of 12, 33% of 13, and 37% of 14 at one hour.   Reactions of 1-3 with NCS in HOAc

at room temperature for one hour yielded 1% of 12, 0% of 13, and 3% of 14.   When

TBHC was reacted with $\underset{\sim}{1}$-$\underset{\sim}{3}$ at room temperature yields of 52% of $\underset{\sim}{12}$, 15% of $\underset{\sim}{13}$, and 35% of $\underset{\sim}{14}$ were obtained at one hour, while the same reaction in MeOH yielded 83% of $\underset{\sim}{12}$, 49% of $\underset{\sim}{13}$, and 65% of $\underset{\sim}{14}$ in one hour.

Radiobrominations

Radiobrominations were carried out using bromine-82 and no-carrier-added (nca) bromine-77 (Table III). Bromine-82 was produced at the Omega reactor of this facility from NH_4Br and was used in stoichiometric quantities. The use of bromine-82, although not a nuclide of choice for external imaging, affords a method to evaluate radiochemical yields of low specific activity radiobrominations without using the more difficult to obtain bromine-77. Radiobrominations with bromine-82 were identical with stable brominations as expected. The use of NCS to oxidize bromide ions resulted in very good radiochemical yields.

Table III: Radiobrominations[a]

	Reaction Time[b]	Radiobromination Reagents		
		NCS/^{82}Br$^-$	TBHC/^{77}Br$^-$	TBHC/^{77}Br$^-$/TBO$^-$
p-TMST	5 min	93	46	16
	1 hr	94	52	74
	30 hr	95		
m-TMST	5 min	62	40	<1
	1 hr	80	67	46
	2 hr			46
	30 hr	82		
o-TMST	5 min	92	58	95
	1 hr	93	63	
	3 hr		62	
	30 hr	94		

[a]Values were obtained by radioHPLC and represent percentages of radioactivity that eluted at same retention time as brominated products. [b]Times were measured from the addition of oxidizing agent.

Bromine-77 was produced by spallation process at this facility and was obtained as a 0.003 M aqueous solutions of $Na_2CO_3/NaHCO_3$. The no-carrier-added reactions, unlike bromine-82, yielded products other then the desired [^{77}Br]-bromotoluenes 4-6 using NCS as the oxidizing agent. A large portion of the activity in the reactions was in radiochromatogram peaks that were also present when NCS/Na^{77}Br was reacted without the TMST. Changing the oxidizing agent to TBHC resulted in the desired reaction occurring in reasonable radiochemical yields.

The difference obtained in the nca radiobrominations of TMSTs using NCS or TBHC as oxidants is quite interesting as the same electrophilic brominating agent, bromine monochloride, might conceivably be produced in each case. It has been previously noted that the electrophilic cleavages of TMS groups appear to be different from other aromatic electrophilic substitutions in that they may go through a four-centered transition state (18), or even a six-centered transition state (23). Indeed, this reaction may be controlled to some extent by the nature of the electrophilic brominating agent and the basicity of the anion present. For example, addition of potassium tert-butoxide (TBO⁻) to the nca radiobrominations decreased the reaction product yields at five minutes (except 1), but ultimately increased the radiochemical yields of 1 and 3 in one hour reaction time. Although the use of nucleophiles has previously been described for catalysis of electrophilic TMS cleavages (25), not enough evidence is present in this study to explain the observed results.

Radioiodinations

Radioiodinations were carried out using carrier-added (ca) iodine-131 and nca iodine-131 (Table IV). To prevent iodine from changing its oxidation state (26), radioiodine is shipped in a 0.1 M NaOH solution. Although the reactions of TMSTs with carrier-added ^{131}I⁻/NCS/NaOH/55°C did occur with reasonable radiochemical yields (e.g., 78% at one hour with p-TMST), the reaction mixtures

turned very dark and the HPLC chromatograms indicated that a number of undesirable
side reactions had occurred. Therefore, a very dilute solution of p-toluenesulfonic
acid (TsOH) was used to neutralize the NaOH. In fact, reaction of ca iodine-131 in
these neutralized solutions gave very good radiochemical yields at room temperature,
but the reaction times were quite long. Further investigation demonstrated that
the reaction rates of ca iodine-131 in HOAc were appreciably faster and also gave
very good radiochemical yields.

TABLE IV: Radioiodinations[a]

	Reaction Time[b]	Radioiodination Reagents			
		[131]I(ca)/TBHC TsOH/MeOH	[131]I(ca)/NCS HOAc	[131]I(nca)/TBHC TsOH/MeOH/55°C	[131]I(nca)/NCS HOAC/60°C
p-TMST	5 min	21	81		
	20 min			8	56
	1 hr	61	97	44	72
	2 hr	75		48	
	6 hr			54	
	18 hr	100			74
	24 hr			60	
m-TMST	5 min	3	61		
	20 min			18	75
	1 hr	13	88	20	93
	2 hr	26		22	
	6 hr	33			
	21 hr			28	
	24 hr	70			
o-TMST	5 min	17	92		
	20 min			17	65
	1 hr	64	96	36	81
	2 hr	75		40	
	21 hr	94		55	

[a]Values were obtained by radioHPLC and represent percentages of radioactivity
that eluted at the same retention time as iodinated products. [b]Reaction times
were measured from the addition of TMST.

Reactions of nca iodine-131 were found to be so slow as to be negligable using the same reaction conditions as those used for ca iodinations. The difference in nca and ca iodinations is probably due to a kinetics problem caused by the very low concentration of iodide ion. Therefore, the reaction temperatures were raised to 55°C (for MeOH) or 60°C (for HOAc), which resulted in good radiochemical yields of the desired products.

CONCLUSIONS

Regiospecific incorporation of carried-added and no-carried-added quantities of radiobromine or radioiodine can be accomplished using aryltrimethylsilyl derivatives and in situ generated electrophilic halogenating agents. The reactions can be carried out under basic, neutral, or acidic conditions, but the rates of reaction are fastest under acidic conditions. The reactions can also be carried out using a mixture of $HOAc/CCl_4$ to limit the exposure of the TMS derivative to the acid. Oxidation of the radiohalides are preferably carried out with N-chlorosuccinimide to limit the amount of chlorinated side reaction products. However, the utility of tert-butylhypochlorite as an oxidizing agent of radiohalides has been demonstrated here for the first time and should find use in many other radiohalogenations. Radiobrominations of aromatic rings that are not highly activated can be accomplished under very mild reaction conditions in short reaction times. Although it has not been demonstrated in this study, the rate of bromination observed indicates that this reaction could also be used to introduce bromine-75 ($T_{\frac{1}{2}}$ = 98 min) into certain radiopharmaceuticals. Radioiodinations can also be carried out under mild reactions conditions, but the reaction times are quite long. When shorter reaction times are needed (i.e., for iodine-123; $T_{\frac{1}{2}}$ = 13.3 h), acidic reactions at elevated temperatures can be used. Clearly, the radiobrominations and radioiodinations using TMS derivatives are equal to, or superior to, the other methods previously described in the literature.

Even though this investigation involved only the model compounds, trimethy-
silyltoluenes 1-3, the chemistry of radiohalogenation using aryltrimethylsilyl
derivatives of potential new radiopharmaceuticals should be the same. Indeed,
the aryltrimethylsilyl derivatives of a large number of compounds of interest
could be synthesized via known procedures (13). Furthermore, these compounds
can be expected to be quite stable without storing them under an inert atmos-
phere or anhydrous conditions (22). The fact that the reactions are completely
regiospecific means that the difficult separations of radiohalogenated regioiso-
meric products often obtained by other reactions need not be carried out. Such
isomeric purity could lead to compounds directly applicable to radiopharma-
ceutical kit preparations.

Work is continuing with the syntheses of the trimethylsilyl derivatives of
some compounds of interest as radiopharmceuticals.

EXPERIMENTAL

General

The bromo- and iodotoluenes were purchased from Aldrich and were used
directly as starting materials for trimethylsilyltoluene syntheses (bromo
derivatives) and as reference compounds for GC and HPLC analysis of the reaction
mixtures. The ethanol, methanol, and water used as solvents were all HPLC grade.
Glacial acetic acid used was reagent grade. N-Chlorosuccinimide was purchased
from Aldrich Chemical Company and was used as obtained (>98%). tert-Butylhypo-
chlorite was prepared by a literature procedure (27). Trimethylsilyltoluenes
were prepared by literature procedures using THF as the solvent for Grignard
reagent formation and ethyl bromide to initiate the reaction (28,29). TMSTs
were purified by vacuum distillation (~30°C/40 micron) to >99% purity by gas
chromatography.

Analyses of the reaction mixtures were carried out by direct injection of
samples into an HPLC or GC, except in the cases where H_2O or HOAc solutions

were to be analyzed by GC. In these cases the samples were extracted with CCl_4 or CH_2Cl_2. The gas chromatograms were obtained on either a Varian model 3700 GC or Hewlett-Packard model 5710A GC, employing a 30 meter SE-30 capillary column, FID detection, and a temperature program of 60° (4 min) to 200° at 20°C/min. Only the halogenation reactions using stable halides were followed by GC and all of the TMS, bromo, chloro, and iodo derivatives could be separated, with the exception of the o-TMS and o-iodo compounds. For this reaction, analysis of the reaction mixture was performed by HPLC or on an Hewlett-Packard model 5992B GC-MS. HPLC analyses were performed on a Waters Associates HPLC system consisting of two 6000A pumps, U6K injector, Model 450 UV detector (at 254 nm), a Data Module, and a System Controller. Separations were carried out using a Waters Radial Compression Module with a Radial Pak C_{18} cartridge with a solvent mixture of 70% CH_3CN and 30% H_2O at 2 mL/minute. This system could not separate individual bromotoluene or iodotoluene isomers, but the GC system did. All reactions were analyzed by GC for regiospecificity.

Analyses of the radiolabeled compounds were accomplished by the above described HPLC using a 2-inch NaI crystal adjacent to the effluent line from the HPLC. The NaI crystal was coupled with an Ortec power bin, high voltage supply, ratemeter, and amplifier. Evaluations of the peak areas were accomplished via an Ortec counter and timer and line printer using manual counts and corrected for background activity.

Radionuclides

Bromine-82 was produced by neutron irradiation (n,γ) of ~100 mg NH_4Br (analytical grade) for 1-2 h in a sealed quartz container at a flux of 9.7×10^{12} neutrons/cm^2/sec. The irradiated sample was allowed to cool for ~24 h from end of bombardment to allow the short lived nuclides to decay. This resulted in 5-10 mCi of activity (0.5-1.0 Ci/g). The bromine-82 sample was dissolved in 5.0 mL MeOH. Aliquots of this solution were used directly.

Bromine-77 was produced by 800 MeV proton irradiation of a molybdenum target as previously described (30). The bromine-77 samples were purified by ion chromatography to yield a ~0.003 M Na_2CO_3/$NaHCO_3$ aqueous solution of sodium bromide-[77]Br. The aqueous solutions were diluted with EtOH or MeOH to aid in transfer of small quantities of activity.

Iodine-131 was purchased from New England Nuclear as a 0.1 M NaOH solution (~20 mCi in 500 µL). This sample was diluted to 5.0 mL with MeOH yielding ~4 mCi/mL at 0.02 N NaOH. For some reactions, this solution was used directly (e.g., acid catalyzed), while for others the MeOH and H_2O were removed under vacuum (~30 torr) at 55°C.

Brominations with Stable Bromide

All of the stable brominations were carried out in 10 mL of MeOH containing 0.06 M TMST. The brominating reagents (1.2 equivalents) were added to the TMST solution (as the lithium salts) followed by the oxidizing agents (1.2 equivalents). The reaction progress was followed by taking an aliquot at the desired time and placing it directly into an HPLC or GC.

Iodinations with Stable Iodide

Method A: The stable iodinations were carried out in 10 mL MeOH containing 0.06 M TMST. To the solution of TMST was added 1.2 equivents of NaI followed by 1.2 equivalents of NCS or TBHC. The reaction progress was followed by HPLC or GC.

Method B: Iodination reactions were carried out in MeOH (0.06 M TMST) as in Method A except at a reaction temperature of 55°C.

Method C: Iodinations were carried out as in Method A except using a 10 fold increase in TMST concentration (0.6 M).

Method D: Iodinations with ICl were carried out using 100 µL of TMST in 3 mL CH_2Cl_2 followed by addition of 1.0 equivalents of ICl.

Method E: Iodinations were carried out in 1 mL HOAc with 100 μL TMST

(0.60 M) using 1.2 equivalents of iodinating reagents.

Radiobrominations with Bromine-82

To a 5 mL conical bottomed vial containing 15 mg (0.15 mmole) $NH_4{}^{82}Br$

(~700 μCi) in 2.0 mL MeOH was added 29 μL (~25 mg; 0.15 mmole) trimethylsilyl-

toluene. To this stirred solution was added 24.5 mg (0.18 mmole) N-chlorosuc-

cinimide in one portion. The reaction progress was followed by radioHPLC.

Radiobrominations with nca Bromine-77

An aliquot of $Na^{77}Br$ (~200 μCi) in EtOH was evaporated under vacuum

(~30 torr) at 50°C to dryness in a 1.0 mL conical bottomed vial. To the flask

was added 100 μL of a 20 μL/mL solution of trimethylsilyltoluene in absolute

EtOH. To this stirred solution was added 2 μL of tert-butylhypochlorite.

The reacton progress was followed by radioHPLC.

Radioiodinations with ca Iodine-131 in MeOH

To a vial containing 2.45 mL of a 0.02 M p-toluenesulfonic acid (TsOH) in

MeOH solution was added 24 mg (0.16 mmole) NaI. To the resultant solution

was added 22 μL (~20 mg; 0.18 mmole) tert-butylhypochlorite. The reaction

solution turned dark brown (ICl color) upon addition but quickly went to a

light yellow color with a white precipitate present (presumably NaCl). A 50-μL

solution of nca Na ^{131}I (~125 μCi) in MeOH (0.02 M NaOH) was added followed

by 30 μL (~26 mg; 0.16 mmole) TMST. The reaction progress was followed by

radioHPLC.

Radioiodinations with ca Iodine-131 in HOAc

To a stirred solution of 21 mg NaI (0.14 mmole) in 500 μL glacial HOAc

was added 30 mg NCS (0.23 mmole). To the resultant dark colored solution was

added 50 µL of a Na^{131}I solution (0.1 M NaOH; ~200 µCi), followed by 50 µL of

TMST (43 mg; 0.27 mmole). The reactions were light yellow at 5 minutes and

colorless at one hour reaction time. The reaction progress was followed by

radioHPLC.

Radioiodinations with nca Iodine-131 in MeOH

To a vial containing 100 µL of a 0.02 M TsOH solution in MeOH was added

2 µL tert-butylhypochlorite. To this solution was added 50 µL of a nca Na ^{131}I

solution in MeOH (0.02 M NaOH), followed by 3 µL TMST. The reaction solution

was capped tightly and placed in a dry bath at 55°C. The reaction progress

was followed by radioHPLC.

Radioiodinations with nca Iodine-131 in HOAc

To a vial contining 500 µL glacial HOAc was added (with stirring) 20 mg

NCS; 50 µL of a Na^{131}I solution (0.1 N NaOH - ~200 µCi); and 50 µL of neat TMST

in rapid succession. The reaction solution was then placed in a dry bath at

60°C. The reaction progress was followed by radioHPLC.

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8. Another labeling procedure, isotopic exchange reactions, does not usually yield high specific activity products since equilibrium conditions occur, but an exception may be radiofluorination (fluorine-18; $T_{1/2}$ ≅ 110 min.) due to its extremely high maximum specific activity of 1.7 x 10^9 Ci/mol. (see: Cacae F., Speranza M., Wolf A. P., and Fowler J. S.-J Label. Compds. Radiopharm. 18:1721-1730 (1981)).

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12. Ipso-substitution occurs at a ring carbon that has a substituent other than hydrogen; in the described reactions it occurs at the carbon bearing the silyl group.

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19. Radiohalogens are generally received as halide salts and the in situ conver-
     sion to electrophilic halogenerating agents in our hands has generally given
     much better radiochemical yields than distillation procedures. In situ
     generation is also more convenient with less danger of radiochemical contam-
     ination.

20. An attempt was made to use THF as a reaction solvent but no reaction occurred.
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