Regiospecific Incorporation of Bromine and Iodine into Phenols Using (Trimethylsilyl)phenol Derivatives

D. S. Wilbur,* W. E. Stone,[1] and K. W. Anderson[2]

Medical Radioisotope Research (INC-3), Los Alamos National Laboratory, Los Alamos, New Mexico 87545

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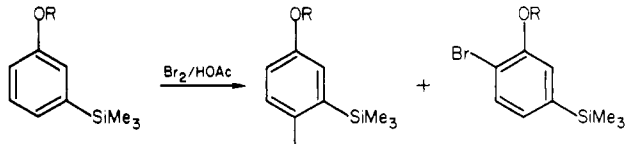
The rate of ipso electrophilic substitution in aryltrimethylsilanes is so rapid that it is possible to obtain regiospecific electrophilic halogenations in many aromatic compounds.[3,4] Indeed, it is possible to selectively obtain the ortho- and para-brominated derivatives of aromatic compounds containing deactivating, meta-directing substituents such as benzoic acids.[5] However, highly activated aromatic rings are so strongly ortho and para directing that ipso substitution of *m*-trimethylsilyl derivatives does not readily occur. For example, Hashimoto has reported[6] that bromination of *m*-(trimethylsilyl)phenol (**1**) in acetic acid



1, R = H
2, R = CH_3

3, R = H
4, R = CH_3

5, R = H
6, R = CH_3

yields the para-brominated product, 4-bromo-3-(trimethylsilyl)phenol (**3**). Likewise, Eaborn and Webster have reported[7] that the bromination of *m*-(trimethylsilyl)anisole (**2**) in acetic acid yields primarily the para-brominated adduct **4**, with none of the *m*-bromoanisole detected.

An interest in regiospecifically introducing radiohalogens into phenolic rings of potential new radiopharmaceuticals led to an investigation utilizing (trimethylsilyl)phenols. In the investigation the three regioisomeric (trimethylsilyl)phenols and the corresponding methyl ethers and acetates were used as model compounds to evaluate and optimize the reaction conditions necessary to obtain regiospecific replacement of the trimethylsilyl group by bromine and iodine and some radionuclides of these halogens. We now report on that investigation.

The three regioisomeric (trimethylsilyl)phenols were synthesized from the trimethylsilyl ethers of the corresponding bromophenols as previously described.[8,9] Reinvestigation of the bromination of these phenols using bromine monochloride generated in situ (in MeOH) from *N*-chlorosuccinimide (NCS) and sodium bromide[10] demonstrated that to some extent all of the regioisomers of the (trimethylsilyl)phenols underwent substitution by bromine without the cleavage of the trimethylsilyl functionality (as shown by GC/MS). Reaction of *p*-(trimethylsilyl)phenol yielded primarily *p*-bromophenol (80–90%), as had been previously reported for the bromination in carbon disulfide.[11] The reaction of *o*-(trimethylsilyl)phenol yielded nearly an equal mixture of *o*-bromophenol and a brominated product that contained the trimethylsilyl group. This product had a mass spectrum and ^1H NMR spectrum consistent with that of 4-bromo-2-(trimethylsilyl)phenol. Contrary to these results, reaction of *o*-(trimethylsilyl)-phenol with bromine in acetic acid reportedly yields *p*-bromophenol.[12] Reaction of *m*-(trimethylsilyl)phenol yielded one major product (>80%). This product had a mass spectrum and a ^1H NMR spectrum which indicated that bromine had substituted the aromatic ring without the loss of the trimethylsilyl group. However, from these data it was not readily apparent which of the regioisomers, para (**3**) or ortho (**5**), had been obtained.

Table I. Halogenation of (Trimethylsilyl)phenol Acetates[a]

reactant	bromination, % Br^-/NCS	bromination, % $^{82}Br^-$/NCS	bromination, % ^{77}Br/TBHC	iodination, % I^-/NCS	iodination, % $^{131}I^-$/NCS
7	92	92	78	92	86
8	96	91	60	84	87
9	92	95	76	86	79

[a] All reactions were carried out in HOAc at 60 °C. The values for the stable halogenations were obtained by UV analysis of HPLC. The values for radiohalogenations are % total activity seen on radio-HPLC.

The brominations of the three regioisomeric (trimethylsilyl)anisoles were also investigated. The (trimethylsilyl)anisoles were synthesized and reacted with the in situ generated BrCl in methanol solvent. The reactions of the *o*- and *p*-(trimethylsilyl)anisoles resulted in quantitative regiospecific conversions to the corresponding bromo compounds instantaneously at room temperature.[13] The reaction mixture from *m*-(trimethylsilyl)anisole had two major peaks by HPLC analysis (90%; 2:1 ratio), however GC/MS and ^1H NMR indicated that there was only one major component. The mass spectrum and ^1H NMR spectrum were consistent with substitution of bromine on the aromatic ring without cleavage of the trimethylsilyl group. As with the *m*-(trimethylsilyl)phenol product, the data was not sufficient to determine if the ortho- or the para-brominated product (**4** or **6**, respectively) had been obtained.

It was apparent from the previous results that more deactivation of the ortho and para positions was needed to obtain regiospecific incorporation of bromine or iodine (ipso substitution) into *m*-(trimethylsilyl)phenols. Therefore, the electron-withdrawing acetate derivatives of the (trimethylsilyl)phenols (**7–9**) were synthesized. Reaction of the acetate esters with either bromide or iodide salts and NCS in acetic acid yielded the regiospecific replacement of the trimethylsilyl group by the halide, **10–12**. The results of the halogenations are given in Table I. The acetate derivatives were extremely stable in acetic acid reaction medium with no detectable cleavage of the acetate group in 24 h at room temperature or 2 h at 60 °C. The acetate derivatives were also quite stable in MeOH; however, the iodination reactions were much slower in this solvent and the acetic acid medium was convenient as it

(1) Graduate Research Assistant, 1981–1982.
(2) Graduate Research Assistant, 1980–1981.
(3) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786.
(4) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43–57.
(5) Hashimoto, T. *Yakugaku Zasshi* **1967**, *87*, 528–529; *Chem. Abstr.* **1967**, *67*, 54206y.
(6) Hashimoto, T. *Yakugaku Zasshi* **1960**, *80*, 1399–1404; *Chem. Abstr.* **1961**, *55*, 5393.
(7) Eaborn, C.; Webster, D. E. *J. Chem. Soc.* **1960**, 179–183.
(8) Neville, R. G. *J. Org. Chem.* **1960**, *25*, 1063–1064.
(9) Speier, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 1003–1010.
(10) Wilbur, D. S.; Anderson, K. W. *J. Org. Chem.* **1982**, *47*, 358–359.
(11) Sakata, Y.; Hashimoto, T. *Yakugaku Zasshi* **1959**, *79*, 878–880; *Chem. Abst.* **1960**, *54*, 358.
(12) Hashimoto, T. *Yakugaku Zasshi* **1967**, *87*, 530–534; *Chem. Abstr.* **1967**, *67*, 54207z.
(13) Room-temperature radiobrominations ($Na^{77}Br$/TBHC/MeOH) and radioiodinations ($Na^{131}I$/NCS/HOAc) gave radiochemical yields of 80–90% for both *ortho*- and *para*-(trimethylsilyl)anisoles.

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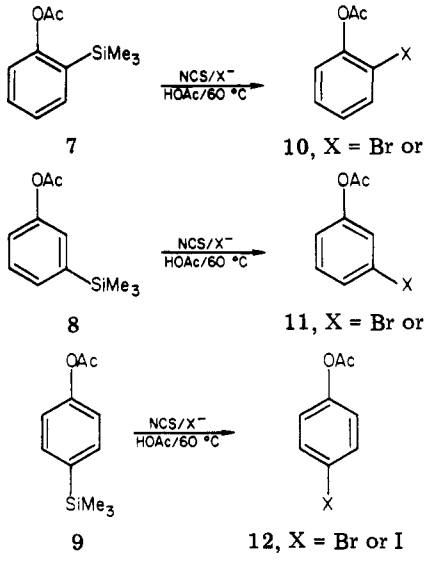

neutralized the base present in the radiohalide solutions. While the electrophilic halogenations could be carried out at room temperature, the reaction times (10–20 h) were too long for the incorporation of some desirable[14] radiohalogens (e.g., bromine-75, $T_{1/2}$ = 96 min, and iodine-123, $T_{1/2}$ = 13.3 h). Therefore, the reaction temperatures were elevated to 60 °C. At this temperature all reactions were complete within 2 h and most were complete in just 10 min. The reactions of high-specific-activity bromine-82 (0.2 Ci/mmol; $T_{1/2}$ = 35 h) were identical with those of the stable nuclides of bromine; however, as previously noted[15] the reactions of no-carrier-added[16] (nca) bromine-77 were better accomplished by using *tert*-butyl hypochlorite (TBHC) as the oxidizing agent.

Regiospecific incorporation of radiobromine or radioiodine into compounds containing phenolic rings may allow much quicker production of certain radiopharmaceuticals as less difficult separations will be needed to purify the desired products. Additionally, substitution meta to the hydroxyl group in radiohalogenated phenolic compounds may have an increased in vitro and in vivo stability, which is particularly important in radioiodinations.[17] Because of the difficulty that can be encountered in preparing or removing methyl ethers, the regiospecific substitution observed for the *o*- and *p*-(trimethylsilyl)anisoles may be most useful when the compound of interest contains an anisole ring. Syntheses of (trimethylsilyl)phenols can be readily accomplished.[18] Likewise the syntheses and subsequent removal of acetate derivatives of phenolic rings is also quite easy. While the use of (trimethylsilyl)phenols to introduce radiohalogens into the position para to the hydroxyl group may not be advantageous due to the additional syntheses involved, clearly the radiochemical yields for the ortho and meta substitution will be increased. In fact, this is the *only* method that has been demonstrated for radiohalogenation in the meta position of phenols.

Experimental Section

Materials. *tert*-Butyl hypochlorite was prepared by a literature procedure.[19] All other chemicals and solvents were obtained as reagent grade from commercial sources and were used as obtained. The ^{131}I sodium iodide was obtained from New England Nuclear in 0.1 N NaOH (~20 mCi/0.5 mL). The bromine-82 was obtained by neutron irradiation of ammonium bromide in the Omega reactor at this laboratory. The nca ^{77}Br sodium bromide was produced by 800-MeV proton irradiation of a molybdenum target as previously described.[20]

Chromatography. High-performance liquid chromatographic analyses of reaction mixtures were performed with Waters Associates 6000A pumps, U6K injector, Model 450 UV detector (at 254 nm), system controller, and data module. Separations were carried out on a Waters Radial Compression Module with a Radial Pak C-18 cartridge and elution with a solvent mixture of 50% CH_3CN/50% H_2O for phenols or 60% CH_3CN/40% H_2O for anisoles and phenol acetates. All samples were taken directly from the reaction mixture. Comparisons were made with authentic samples.

A radioactivity detection setup consisting of a 2-in. NaI crystal coupled to an Ortec power bin, high-voltage supply, rate meter, and amplifier permitted analyses of the radiohalogenation reaction. Radiochemical yields were determined from counts under peaks obtained by an Ortec counter/timer and a line printer. All peaks were corrected for background activity.

Gas chromatography was performed on a Varian Model 3700 GC using a 30-m SE-30 capillary column with FID detection and a temperature program of 60 °C (3 min) to 200 °C at 10 °C min^{-1} for phenol acetates and 5 °C min^{-1} for anisoles. The chromatograms were obtained on a Spectra-Physics 4100 plotter/integrator. Samples were taken directly from reaction mixtures when the solvent was MeOH. Reactions in HOAc were diluted with equal volumes of $CHCl_3$ and H_2O, and samples were taken from the $CHCl_3$ layer. All of the various reaction starting materials and products were separable under these conditions. Therefore, the regiospecificity of all of the reactions were checked in this manner. In addition to retention times, reaction mixtures were spiked with the various isomeric products to prove regiospecificity.

Mass Spectral Data. Mass spectral data were obtained on a Hewlett-Packard 5992 GC/MS using a 6-ft OV-101 column with a temperature program of 50 °C (4 min) to 200 °C (25 min) at 16 °C min^{-1}. Parent peaks are given for some of the reaction products to aid in characterization.

NMR Data. NMR data were obtained on the Los Alamos National Laboratory 300-MHz Bruker WM300 wide-bore instrument. The reactions which contained products that could not be identified by authentic samples were evaporated to an oil, diluted with $CHCl_3$, and washed with H_2O. After drying with $MgSO_4$ and evaporation of the $CHCl_3$ solution, the samples were dissolved in $CDCl_3$ and the NMR spectra were obtained. The values for the corresponding starting materials and bromo products were subtracted (where present) from the spectra and the remaining peaks were evaluated. All peaks are referenced to Me_4Si at 0.0 ppm.

Syntheses of (Trimethylsilyl)phenols. The bromophenols (0.58 mol) were dissolved in 150 mL of anhydrous THF, and Et_3N (0.58 mol) was added. The reaction mixtures were cooled in an ice/H_2O bath and trimethylsilyl chloride (0.58 mol) was added dropwise with stirring. The thick reaction mixtures were stirred at room temperature for 1 h, and the white precipitate was filtered. The filtrates were diluted with 100 mL of hexane, refiltered, and evaporated to colorless oils. The oils were redissolved in anhydrous THF and were used directly in the subsequent step.

The *p*- and *m*-bromosiloxybenzenes were reacted with Mg/Me_3SiCl, and the *o*-bromosiloxybenzene was reacted with Na/Me_3SiCl as previously described.[8,9] The products were fractionally distilled at 50–60 °C (35–50 μm). The silyl ethers of the para and

(14) These radionuclides are of particular interest because of their gamma decay characteristics; for example, iodine-123 has a principal gamma emission (83%) of 159 keV, which is ideal for gamma cameras currently in use, and bromine-75 is a positron emitter and may have applications in positron emission tomography.

(15) Wilbur, D. S.; Anderson, K. W.; Stone, W. E.; O'Brien, H. A., Jr. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 1171–1188.

(16) No-carrier-added terminology is used to describe radionuclide preparations that contain only one nuclide of an element, with the stable nuclide(s) present being unintentionally added through reagent contaminants, etc. In such a preparation of bromine-77, there are theoretically only ~10^{13} atoms of bromide present to react.

(17) The in vivo stability is important as free iodide can greatly increase the radiation dosage to the thyroid.

(18) Habich, D.; Effenberger, F. *Synthesis* **1979**, 841–876.

(19) Mintz, M. J.; Walling, C. "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. 5, p 1058.

(20) Grant, P. M.; Whipple, R. E.; Barnes, J. W.; Bentley, G. E.; Wanek, P. M.; O'Brien, H. A., Jr. *J. Inorg. Nucl. Chem.* **1981**, *43*, 2217–2222.

meta isomers were removed in EtOH/HCl; however, conversion of the *o*-trimethylsilyl ether to the phenol required the use of tetra-*N*-butylammonium fluoride in THF.[21]

Syntheses of (Trimethylsilyl)anisoles. The bromoanisoles were reacted with Mg turnings (1 equiv) in anhydrous THF at reflux for 6 h. Trimethylsilyl chloride (1.5 equiv) was then added, and the reaction was refluxed overnight. The reaction mixtures were worked up as previously described.[22,23] Further purification of the products for the no-carrier-added radiohalogenations was accomplished by washing with 5% NaOH solution, followed by preparative TLC using 98:2 hexane/ethyl acetate to give products that were >99.5% pure by HPLC.

Syntheses of (Trimethylsilyl)phenyl Acetates. (Trimethylsilyl)phenols (6 mmol) were reacted in a mixture of 10 mL of pyridine and 10 mL of acetic anhydride at room temperature for 3 h. Removal of the pyridine and excess acetic anhydride by vacuum distillation yielded brown residues, which were purified by Kugelrohr distillation at 30–40 °C (10–50 μm) to give colorless oils[6,11] (meta isomer solidified at room temperature, mp 25–27 °C) in 66–86% yields.

Bromination of (Trimethylsilyl)phenols and (Trimethylsilyl)anisoles. To a solution of (trimethylsilyl)phenol or (trimethylsilyl)anisole (0.06 mmol) dissolved in 1.0 mL of MeOH was added 6 mg of NaBr (0.06 mmol) and 8 mg of NCS (0.06 mmol) at room temperature. The reaction progress was followed by HPLC and found to be over within 5 min (most were over instantaneously as halogen coloration of reaction solution was not seen).

p-(Trimethylsilyl)phenol yielded 80–90% of the *p*-bromophenol with several other unidentified species present.

o-(Trimethylsilyl)phenol yielded ~48% of the corresponding bromo compound and ~43% of a compound that had an HPLC retention time (~28 min) that was much longer than that of the starting material (~16 min) or the *o*-bromophenol (~4 min). GC/MS of this unidentified species had M = 244 and M + 2 = 246, which indicated that the bromine substitution had occurred without loss of the trimethylsilyl moiety. The following ^{1}H NMR spectrum was obtained: ($CDCl_3$) δ 7.39 (1 H, d, J = 1.5 Hz), 7.28 (1 H, dd, J = 1.5 Hz, J = 8.5 Hz), 6.55 (1 H, d, J = 8.5 Hz), 0.30 (9 H, s).

m-(Trimethylsilyl)phenol yielded none of the *m*-bromophenol (HPLC retention time ~4 min) but rather a new species that had a longer retention time (20 min) than the starting materials (~11 min). GC/MS of the product had M = 244 and M + 2 = 246, which indicated that the bromine substitution had occurred without loss of the trimethylsilyl moiety. ^{1}H NMR of the major product: ($CDCl_3$) δ 7.35 (1 H, d, J = 8.6 Hz), 6.90 (1 H, d, J = 3.1 Hz), 6.68 (1 H, dd, J = 3.1 Hz, J = 8.6 Hz), 0.36 (9 H, s).

o- and *p*-(Trimethylsilyl)anisole gave nearly quantitative yields of the corresponding bromo products. None of the longer retention species were seen by HPLC.

m-(Trimethylsilyl)anisole yielded primarily two compounds (2:1 ratio), which had longer retention times (28 and 31 min) than the starting material (~15 min) by HPLC. GC/MS indicated one major product with M = 258 and M + 2 = 260, which indicated that the bromine substitution occurred without loss of the trimethylsilyl moiety. ^{1}H NMR also indicated one major product: ($CDCl_3$) δ 7.41 (1 H, d, J = 8.6 Hz), 6.98 (1 H, d, J = 3.1 Hz), 6.73 (1 H, dd, J = 3.1 Hz, J = 8.6 Hz), 0.38 (9 H, s).

Bromination and Iodination of (Trimethylsilyl)phenyl Acetates. To a solution of (trimethylsilyl)phenyl acetate (0.12 mmol) in 1.0 mL of HOAc were added either 13 mg of NaBr (0.13 mmol) or 20 mg of NaI (0.13 mmol) and 17 mg of NCS (0.13 mmol). The reaction progress was followed by HPLC. Elevation of the reaction temperature to 60 °C in a dry bath/stirrer accelerated the reactions such that they were complete within 10 min for the brominations and 1 h for the iodinations. No degradation of the products or decrease in reaction yields were observed at the elevated temperature. Results are given in Table I.

Radiobromination and Radioiodination of (Trimethylsilyl)phenyl Acetates. Bromine-82. To a solution of 10 μL of trimethylsilylphenyl acetate dissolved in 500 μL of HOAc were added 2 mg of NCS and 25 of μL (~500 μCi) of an aqueous $NH_4{}^{82}Br$ solution (10 mg/mL). The reaction solution was then placed in a dry bath/stirrer at 60 °C. The reaction progress was followed by HPLC. All reactions were found to be complete within 10 min.

Bromine-77. To a vial containing 50 μL of HOAc was added 1 μL of *tert*-butyl hypochlorite at room temperature. To this solution were added 1 μL (~400 μCi) of a $Na^{77}Br$ solution (~0.02 M $NaHCO_3/NaCO_3$ in H_2O), and quickly thereafter 10 μL of (trimethylsilyl)phenyl acetate. The reaction mixture was placed in a dry bath/stirrer at 60 °C, and the reaction was followed by HPLC. All of the reactions were found to be complete within 10 min.

Iodine-131. To a vial containing 50 μL of HOAc was added 2 mg of NCS at room temperature. To this solution were added 5 μL (~160 μCi) of a $Na^{131}I$ solution (0.1 N NaOH) and quickly thereafter 10 μL of (trimethylsilyl)phenyl acetate. The reaction mixture was placed in a dry bath/stirrer at 60 °C, and the reaction was followed by HPLC. All of the reactions were complete within 2 h. Results of the radiohalogenations are given in Table I.

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Registry No. 1, 17881-95-7; 2, 17876-90-3; 7, 85153-08-8; 8, 18001-12-2; 9, 18001-11-1; **10a**, 1829-37-4; **10a** (^{82}Br), 85153-09-9; **10a** (^{77}Br), 85153-10-2; **10b**, 32865-61-5; **10b** (^{131}I), 85153-11-3; **11a**, 35065-86-2; **11a** (^{82}Br), 85153-12-4; **11a** (^{77}Br), 85153-13-5; **11b**, 42861-71-2; **11b** (^{131}I), 85153-14-6; **12a**, 1927-95-3; **12a** (^{82}Br), 85153-15-7; **12a** (^{77}Br), 85153-16-8; **12b**, 33527-94-5; **12b** (^{131}I), 85153-17-9; Me_3SiCl, 75-77-4; *o*-bromophenol, 95-56-7; *m*-bromophenol, 591-20-8; *p*-bromophenol, 106-41-2; (*p*-bromophenoxy)trimethylsilane, 17878-44-3; (*m*-bromophenoxy)trimethylsilane, 36971-28-5; (*o*-bromophenoxy)trimethylsilane, 36601-47-5; *p*-(trimethylsilyl)phenol, 13132-25-7; *o*-(trimethylsilyl)phenol, 15288-53-6; *o*-bromoanisole, 578-57-4; *m*-bromoanisole, 2398-37-0; *p*-bromoanisole, 104-92-7; *o*-(trimethylsilyl)anisole, 704-43-8; *p*-(trimethylsilyl)anisole, 877-68-9; 4-bromo-2-(trimethylsilyl)phenol, 67044-81-9.

(21) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(22) Benkeser, R. A.; Kryiak, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 4528–4531.
(23) Eaborn, C. *J. Chem. Soc.* **1953**, 3148–3153.

Mechanism of Thio Imino Ester Formation from the Reaction of Thioamides and Thiochloroformate Esters

David Anderson, Paul Zinke, and S. L. Razniak*

Department of Chemistry, East Texas State University, Commerce, Texas 75428

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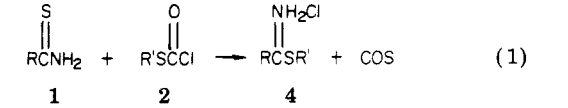
Previously we reported that thio imino esters can be prepared from thiochloroformate esters and thioamides according to the reaction:[1]



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While further examples of this reaction were studied, an induction period and a steric effect on the yield of thio imino esters were observed.[2] Introduction of bulkier

(1) Razniak, S. L.; Flagg, E. M.; Siebenthall, F. M. *J. Org. Chem.* **1973**, *38*, 2242.

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