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Radiobromination of Aromatic Compounds by Cleavage of Aryl-Tin Bonds*

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Radiobrominated compounds have been proposed as useful tools in studies of nuclear medicine and biochemistry particularly as receptor binding radiopharmaceuticals. Although a variety of reports have been published on bromination methods, most of these techniques have limitations. These methods usually rely on the direct electrophilic bromination of aromatic compounds using bromide oxidized *in-situ* with an oxidant such as chloramine-T (CAT) or N-chlorosuccinimide (NCS). These methods usually produce low yields and/or mixtures of ring isomers.

It is well known that aryl-tin bonds can be cleaved selectively by electrophilic halogenating agents in the presence of alkyl-tin bonds. Following this fact, we synthesized a series of aryl-tin compounds by first metallating the appropriate bromo- or iodo-precursors, via lithium-halogen exchange with *n*-BuLi, and subsequent transmetallation using tri-*n*-butyltin chloride. All of the tin substrates were brominated with "cold" NaBr, to determine chemical yields, and then with $NH_4{}^{82}Br$ and NCA $Na^{77}Br$ to determine radiochemical yields at different levels of specific activity. Both chloramine-T (CAT) and N-chlorosuicinimide (NCS) were used as oxidants in this study. Bromination chemical yields ranged from 78.8% to 96.9% with reaction times ranging from 5—35 minutes. In general, the bromination rates with NaBr/NCS were rather slow and yields lower than those with NaBr/CAT. The yields from reactions employing CAT/NaBr/HCl were shown to be very dependent upon the concentration of HCl.

A stimulation phenomena was observed when using NaBr/CAT, with no HCl, when the mixtures were cooled to dry ice temperature. Yields increased from about 10% before cooling to 40% after cooling as seen in the glc chromatogram. This affect was seen for all of the tin substrates and may reflect an increase in concentration of reagents into the ethanol portion of the solvent mixture as the aqueous component freezes.

Radiobromination reactions with ^{82}Br gave excellent results with average radiochemical yields being greater than 90%. Again, reactions utilizing CAT/HCl were faster than reactions using NCS. When NCS was employed the reaction times were, as expected, shorter for the highly activated systems than for any of the other substrates. Times ranged from 5 minutes for the veratrole and anisole systems to 45 minutes for the chloro derivative. Two control reactions were performed whereby fluorobenzene and toluene were brominated under the same conditions as used for the stannylated

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substrates. After 5 minutes using CAT/HCl only 33% and 5% of the para-fluoro products were detected. Running these reactions for a longer time only caused the yield to decrease, in the case of fluorobenzene, and to increase only slightly for the toluene derivative.

Reactions with NCA^{77}Br also gave very high radiochemical yields. Under the conditions used in these reactions there was no apparent difference in reaction rates when using either NCS or CAT. This may have been due to the higher concentration of substrate and the higher molar ratio of tin substrate to oxidant and bromide. All radiochemical yields except that of the chlorinated compound were 90% or higher. For the chlorinated compound NCS/HOAc gave the best results with a yield of 82%. The chromatogram reveals an unidentified impurity component making up 18% of the total yield.