

## Site-specific Bromination of Aromatic Compounds: a Rapid Method for Radiobromine Labelling

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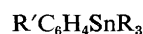
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[<sup>82</sup>Br]Bromobenzene and [<sup>82</sup>Br]-*p*-bromoanisole have been synthesized in less than 5 min by treatment of the aryltin derivative with ammonium [<sup>82</sup>Br]bromide, chloramine-T, and HCl in EtOH-H<sub>2</sub>O at 0 °C.

The synthesis of organic substances labelled with short-lived radionuclides such as those required for positron emission tomography (PET)<sup>1</sup> [e.g. <sup>18</sup>F (*t*<sub>1/2</sub> 110 min), <sup>75</sup>Br (*t*<sub>1/2</sub> 97 min)], places two stringent demands on the synthetic method, namely that it should be rapid and result in high yield with respect to incorporation of the radionuclide. We recently reported the use of aryltin derivatives as precursors of radiofluorinated aromatic compounds<sup>2</sup> and have now extended that approach to the rapid synthesis of brominated aromatic compounds *via* the cleavage of aryl-tin bonds by sodium bromide or ammonium bromide and chloramine-T. For convenience we chose to use commercially available [<sup>82</sup>Br]NH<sub>4</sub>Br (*t*<sub>1/2</sub> 35.4 h), † a gamma-emitting radionuclide, to prove feasibility.

Although there has been a general paucity of methods for 'no-carrier-added' radiobromination of aromatic compounds a few methods<sup>3-5</sup> have been described recently which rely on the production of an electrophilic bromine species by oxidation of bromide ions. Unfortunately these methods lack the required site specificity when applied directly to aromatics; however, we now demonstrate that this problem can be overcome by using aryltin reagents as substrates. It is well known that aromatic compounds can be readily stannylated<sup>6,7</sup> and there is ample precedent for cleavage of aryl-tin bonds by electrophiles such as halogens<sup>6</sup> under conditions such that alkyl-tin bonds are cleaved more slowly than their aryl-tin counterparts.<sup>8</sup>



- (1) R = Bu<sup>n</sup>, R' = H
- (2) R = Bu<sup>n</sup>, R' = *p*-OMe
- (3) R = Ph, R' = H

Reaction of tributylphenyltin (1), *p*-tributylanisyltin (2), or tetraphenyltin (3) with an equimolar amount of NaBr, two equiv. of chloramine-T and 1M HCl in EtOH-H<sub>2</sub>O (2:1) at 0 °C for 15 min gave the corresponding brominated compounds in 86, 95, and 48% chemical yields respectively (based on g.l.c.). THF-H<sub>2</sub>O as the solvent was found to give poorer yields. The reactions of (1) and (3) gave no detectable amounts (g.l.c.-FID detection) of benzene, the side-product which would result from HCl cleavage; however some chlorobenzene (<2%) was detected. The production of only the *para*-isomer of bromoanisole from (2) proved that this bromination procedure is site-specific; it was shown that under these reaction conditions HCl alone did not cleave the aryl-tin bond.

Reactions of (1), (2), and (3) with [<sup>82</sup>Br]NH<sub>4</sub>Br were performed in 1M HCl in EtOH-H<sub>2</sub>O (2:1) with 10<sup>-3</sup> M chloramine-T at 0 °C for 5 min and gave radiochemical yields of 96, 95, and 38%, respectively. These yields were determined after extraction of the product with hexane and subsequent h.p.l.c. analysis of the hexane layer. Less than 2% of the initial activity remained in the aqueous layer and for (1) and (2), near quantitative amounts of the injected activity appeared at the appropriate product peak; however for (3) only 49% of this activity was due to bromobenzene. Study of aliquots removed from the reaction mixtures over a 30 min period showed that all three reactions were essentially complete after 5 min.

† [<sup>82</sup>Br]NH<sub>4</sub>Br was purchased from New England Nuclear Canada, Lachine, Quebec.

It seems probable that the low yields for the formation of bromobenzene from (3), which parallels the findings of our earlier fluorination study,<sup>2</sup> are due at least in part to the poor solubility of (3).

Given both the speed and the high selectivity of the cleavage of aryl-tin bonds in the presence of alkyltin groups, this route should be generally applicable for radiobromination of other aromatic compounds. With regard to PET chemistry, we draw attention to the fact that the 5 min reaction period is not a limiting factor even when using a relatively short-lived isotope such as <sup>75</sup>Br (*t*<sub>1/2</sub> 97 min) and that very high specific activity labelling should be obtainable.

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