Aromatic Radiobromination without Added Carrier

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p-Bromo-*N,N*-dimethylaniline, bromobenzene, and *p*-bromobenzoic acid labelled with ^{77}Br or ^{80m}Br have been prepared by radiobromodestannylation at no-carrier-added levels of radiobromine.

The halogens have a number of medically attractive radioisotopes; previous work has focused primarily on radioiodination, and to a lesser extent radiofluorination. The development of positron emission computed tomography has led to increased interest in radiopharmaceuticals labelled with a positron-emitting isotope of bromine (*i.e.*, ^{75}Br). The use of aryltrialkyltin compounds as precursors of radioiodinated,[1,2] radiofluorinated,[3] and, more recently, radiobrominated[4] aromatic compounds is an attractive synthetic approach because of both the facility and the regiospecificity of the halodestannylation.

We report the use of radiobromodestannylation in the production of aromatic compounds labelled with ^{77}Br and ^{80m}Br. We have determined the effect of no-carrier-added levels of radiobromine, and the effect of aromatic substitution *para* to the trialkyltin group on radiochemical yields.

The radioisotopes used in this study, ^{77}Br ($t_{1/2}$ = 55.8 h) and ^{80m}Br ($t_{1/2}$ = 4.4 h), were produced at the Argonne National Laboratory cyclotron: the ^{77}Br was produced *via* the $^{75}As(\alpha,2n)$ reaction,[5] and was obtained at a concentration of 0.1 $\mu Ci\ \mu l^{-1}$; the ^{80m}Br was produced in a gas target assembly[6] *via* the $^{82}Kr(d,\alpha)$ reaction. In the latter case, ^{81}Rb and ^{82m}Rb are co-produced,[6] and were removed from the target rinsings by using a cation-exchange resin column. The effluent was made basic and evaporated in a stainless-steel beaker (to retain ^{80m}Br as the bromide) to a concentration of 0.1 $\mu Ci\ \mu l^{-1}$ of ^{80m}Br.

$RC_6H_4SnBu^n_3$

(**1**) R=*p*-NMe_2
(**2**) R=H
(**3**) R=*p*-CO_2H

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Table 1. Radiochemical yields (%).

para-substituent	NMe_2		H		CO_2H	
isotope	^{77}Br	^{80m}Br	^{77}Br	^{80m}Br	^{77}Br	^{80m}Br
10 nmol carrier-added	70	65	80	70	20	25
no-carrier-added	60	35	70	30	20	10

The radiobromodestannylations of the aryltin compounds (**1**), (**2**), and (**3**) were performed at room temperature in closed glass vials. A two-phase solvent system of $CHCl_3$–H_2O was used in the following reactions: 1 μmol of the aryltin compound in 20 μl $CHCl_3$ with (a) 10 μl of no-carrier-added [$^{77,80m}Br$]bromide with and without 10 nmol carrier NaBr, (b) 10 μl of 5% NaOCl, and (c) 10 μl glacial acetic acid with (**2**) and (**3**) or 0.02 M acetic acid with (**1**). These reaction mixtures were vigorously shaken for 15 min (the optimal reaction time), and 1 M $Na_2S_2O_3$ (10 μl) was added.

The products were isolated by reverse-phase h.p.l.c. (u.v. λ 254 nm and radiochemical detection) under the following eluant conditions: i, MeOH–H_2O (4:1), 0.1 M in ammonium acetate; ii, MeOH–H_2O (7:3); iii, MeOH–H_2O–$MeCO_2H$ (5:4:1), 1 mM in HCl. These conditions allowed the separation of the desired radiobrominated products [$^{77,80m}Br$]-*p*-bromo-*N,N*-dimethylaniline, [$^{77,80m}Br$]bromobenzene, and [$^{77,80m}Br$]-*p*-bromobenzoic acid from the corresponding chlorinated by-products. The radiobrominated products were collected, the associated activities counted with a gamma-well scintillation counter, and the decay-corrected isolated radiochemical yields calculated based on starting [$^{77,80m}Br$]bromide (Table 1).

Reducing the carrier NaBr from 10 nmol to the no-carrier-added levels decreased the radiochemical yields, as would be expected. However, this effect is more marked in the case of ^{80m}Br: adventitious carrier bromine is present in the solution of ^{77}Br at levels approaching our carrier-added levels,[7] thereby reducing the above mentioned effect.

Deactivation by the electron-withdrawing *p*-carboxy-group

is evident from the yields in Table 1. However, the reciprocal effect expected for the electron-releasing *p*-dimethylamino-group is not seen. This is likely to be due to the differing acidity of the reaction mixture of (**1**) *versus* those of (**2**) and (**3**). Acid conditions were necessary for the reaction, but the maximum radiochemical yield for (**1**) was obtained with dilute acetic acid, while the maxima for (**2**) and (**3**) were obtained with glacial acetic acid. This difference is due to the basicity of the amine group in (**1**), which becomes protonated below pH 5, and hence strongly deactivating.

In summary, we have shown radiobromodestannylation to be a useful route for the preparation of aryl bromides labelled with ^{77,80m}Br at the no-carrier-added level. In spite of the adverse effect of the electron-withdrawing *p*-carboxy-group, useful radiochemical yields of isolated, chromatographically pure, labelled materials were obtained. In addition, the reaction time from end-of-batch to isolated radiobrominated product is less than 25 min. This fact, coupled with the similarities between ^{80m}Br and ^{75}Br (methods of production[8]‡ and half-lives: 4.4 h and 1.6 h, respectively), indicates this reaction will be useful in the preparation of radiopharmaceuticals labelled with ^{75}Br, an isotope useful for positron emission tomography.

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‡ Both isotopes are produced in a gas target assembly (see ref. 6): ^{80m}Br *via* the ^{82}Kr(d,α) reaction; ^{75}Br *via* the ^{78}Kr(p,α) reaction.

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