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Synthesis of Substituted Bromobenzene Derivatives via Bromoanilines. A Moderately Selective Ortho-Bromination of [^{14}C]-Aniline.

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Summary.

The synthesis of [^{14}C]-labeled bromobenzene, 2-bromophenol, 4-bromophenol, 1,2-dibromobenzene, 2-bromobenzonitrile, 2-bromotoluene, and 2-bromoanisole are reported. [^{14}C]-Aniline is selectively monobrominated to ortho- and para-bromoanilines in 5 to 3 ratio. The separated bromoanilines are diazotized and either reduced, hydrolyzed, coupled to bromide, coupled to cyanide, or coupled to carbon. 2-Bromophenol is O-methylated to 2-bromoanisole.

Key words: [^{14}C]-bromobenzene, [^{14}C]-bromophenols, [^{14}C]-1,2-dibromobenzene, [^{14}C]-2-bromobenzonitrile, [^{14}C]-2-bromotoluene, [^{14}C]-bromoanilines.

Introduction.

The hepatotoxicity of bromobenzene has been associated with the covalent binding of enzymatically generated metabolites to key cellular nucleophiles (1). These chemically reactive metabolites are believed to be either bromobenzene oxides (2,3), or bromobenzoquinones (4-7). In recent *in vivo* experiments with dual labeled [^{3}H/^{14}C]-bromobenzene, the ^{3}H to ^{14}C ratio of the protein-bound metabolites (0.5) was much lower than the substrate (1.0) or stable metabolites (0.9-1.0). These results indicate that the reactive bromobenzene metabolites which bind to protein are more highly oxidized than a bromobenzene epoxide, and are perhaps bromoquinones (4).

Since ortho-substitution modulates the hepatotoxicity of bromobenzene (1), we wished to extend our previous microsomal metabolism studies (8) with [^{3}H]-ortho-substituted bromobezene derivatives (9) to dual labeled [^{3}H/^{14}C]-substrates, to determine accurately the extent of covalent binding to protein and to determine the relative oxidation state of the covalently bound materials as determined by their ^{3}H /^{14}C ratios. For this, we needed to synthesize the ^{14}C substrates. In this paper we report methods for the conversion of [^{14}C]-aniline to the ortho- or para-substituted bromobenzene analogs illustrated in the accompanying scheme.

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Results and Discussion.

Ortho-Bromination of Aniline. Because we primarily required ortho-substituted bromobenzenes, a route that preferentially produced 2-bromoaniline from aniline was sought. There are few reliable methods

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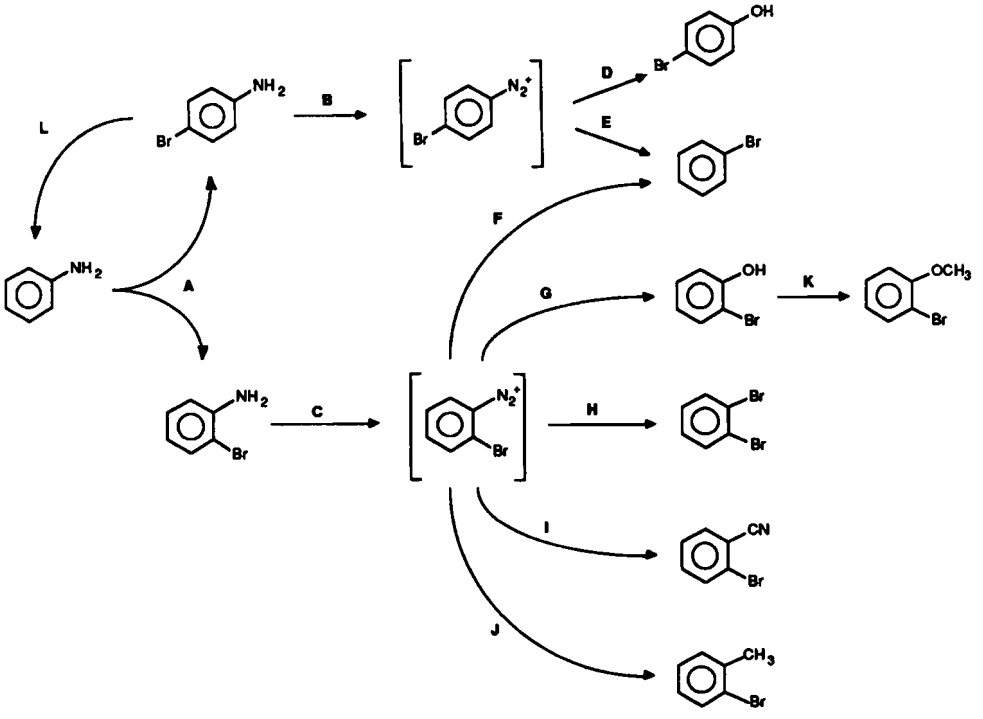

A. NBS / benzene; 16 h, 25 °C. **B, C.** $NaNO_2$ / H^+ / H_2O ; 5 min, 5 °C. **D, G.** (B,C) in H_2SO_4; H_2SO_4 / Na_2SO_4 / H_2O; 135 °C. **E, F.** (B,C) in H_3PO_2; CH_2Cl_2 / Cu_2O ; 3 h, 5 °C. **H.** (C) in HBr; CuBr / KBr; 1 h, 30 °C. **I.** (C) in H_2SO_4; CuCN / KCN / Na_2CO_3; 10 min, 60 °C. **J.** (C) in H_2SO_4; $NaBF_4$, lyophilize; CH_3CN / $Pd(OAc)_2$ / Me_4Sn; 2 h, 25 °C. **K.** CH_2N_2 / Et_2O; 16 h, 25 °C. **L.** Et_3N / H_2CO, Pd(C) ; 16 h, 50 °C.

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for the direct monobromination of reactive aromatic amines (10). Generally , electrophilic aromatic substitution of aniline by bromine or NBS leads to para-mono-, di-, and tri-bromoanilines (for example, see 11). Some brominating reagents such as, dioxane perbromide (12), dimethylsulfoxide dibromide (13), or 2,4,4,6-tetrabromocyclohexa-2,5-dienone (14), monobrominate anilines, but lead predominantly to para-bromination. Other procedures involve bromination of N-derivatized anilines. For example, acetanilide reacts with bromine or NBS in acetic acid to produce 2- and 4-bromoacetanilide in a 4 to 21 ratio (15), and anilinotrimethylsilane reacts with NBS in carbon tetrachloride to yield 2- and 4-bromoanilinotrimethylsilane in a 5 to 92 ratio (16). Thus o-bromoaniline is not easily made directly from aniline.

Several potential routes to 2-bromoaniline involved blocking the para-position of the aniline moiety by removable functional groups, (e.g. Iodo or nitro , 17). Unfortunately, in the bromination of both 4-iodoacetanilide and 4-iodoanilinotrimethylsilane, an exchange of the para-iodo-substituent with bromine

(i.e., bromodeiodination) was observed. Para-nitration of acetanilide, ortho-bromination, nitro reduction, and reductive diazotization to 2-bromoaniline proved unfeasible because of amide hydrolysis during reduction of 2-bromo-4-nitroacetanilide with stannous chloride (18) leading to 2-bromo-1,4-phenylenediamine. Lastly, sulfonation of aniline, ortho-bromination, and desulfonation of 2-bromo-4-sulfanilic acid in boiling water (19) was feasible, but we found sulfanilic acids to be extremely difficult to purify.

A report indicating 2.4 to 1 ortho- to para- product ratios for the chlorination of aniline by N-chlorosuccinimide in benzene (20) prompted an evaluation of the analogous bromination reaction. The room temperature reaction of aniline (0.2-1.0 g) with 0.95 eq of NBS in dry benzene over 16 h reproducibly generated: 2-bromoaniline (50%), 4-bromoaniline (30%), and recovered aniline (13%). Trace amounts 2,4-dibromoaniline were occasionally detected as a contaminant of 2-bromoaniline isolated by gravity silica chromatography (< 1% by GC). Mass spectral analysis also indicated the presence of trace amounts of a tribromoaniline. Various trials established that for optimum production of 2-bromoaniline, the NBS to aniline ratio should be 0.95 to 1, because higher ratios produced 2,4-dibromoaniline and 2,4,6-tribromoaniline at the expense of 2-bromoaniline. Silica gel gravity chromatography efficiently separated 2-bromoaniline from 4-bromoaniline and aniline. Aniline and 2-bromoaniline, but not 4-bromoaniline, codistill with the chromatographic solvent unless a Vigreux distillation head is used. This property was exploited to separate aniline from 4-bromoaniline by distilling the combined fractions through a short path distillation head. Aniline codistills with the solvent and is recoverable by extraction into aqueous HCl. We believe this to be the only known example of direct and selective ortho-bromination of aniline. We have not evaluated its suitability for other arylamines.

Salvage of 4-Bromoaniline as Aniline. Although NBS bromination in benzene was moderately regioselective for 2-bromoaniline, 4-bromoaniline was a significant side product (30%). We had specific needs for bromobenzene and 4-bromophenol and therefore developed procedures for their preparation from 4-bromoaniline. However, if economy requires, a reductive salvage procedure for the recovery of 4-bromoanline as aniline is possible. 4-Bromoaniline reacts with triethylammonium formate over 5% palladium on carbon (21) to produce aniline quantitatively as determined by GLC assay. Simple isolation procedures involving gravity-flow silica chromatography easily afforded 65% isolated yields of aniline.

Bromobenzene. Either 2- or 4-bromoaniline can be reduced to bromobenzene by diazotization and reduction with hypophosphorous acid (22). Two unexpected advantages of this two-step preparation of bromobenzene were higher overall yields and cleaner product profiles. For example, a mixture of 2- and 4-bromoaniline afforded bromobenzene in 75% overall yield from aniline and required only bulb-to-bulb distillation as purification, whereas the direct Sandmeyer coupling reaction afforded bromobenzene in 35% crude yield and required preparative HPLC for purification, mainly because of the presence of di- and tribromobenzenes as determined by GC/MS (see following discussion).

1,2-Dibrombenzene. 1,2-Dibromobenzene was prepared in 37% overall yield by direct Sandmeyer coupling of 2-bromobenzenediazonium bromide to cuprous bromide (23). Like the analogous reaction with benzenediazonium bromide, this reaction produced a complicated product profile, and consequently required preparative HPLC for purification . A minor side product isolated with 1,2-dibromobenzene was an unidentified tribromide, suggesting the generation of a brominating agent under these reaction conditions. The use of aged cuprous bromide increased this side product, and should be avoided. HPLC indicated two other side products; bromobenzene at 11% of the radioactivity, and an unknown (not 2-bromophenol) at

7%. Urea was added to the diazonium solution prior to coupling to eliminate excess nitrite, which improved isolated yields slightly.

2-Bromotoluene. A synthesis of 2-bromotoluene involving ortho-methylation of acetanilide with palladium acetate/methyl iodide (24), hydrolysis, diazotization, and coupling to bromide was evaluated, but afforded 2-bromotoluene in only 7% overall yield from aniline. An apparently simpler, albeit chemically complicated, one-pot approach involved palladium-catalyzed methylation of 2-bromobenzenediazonium fluoroborate with tetramethyl tin (25). 2-Bromobenzenediazonium fluoroborate, suspended in dry acetonitrile, reacted with an excess of tetramethyl tin (9 fold) and palladium acetate (10 mol%) to produce a 41% yield of 2-bromotoluene by HPLC assay. Analytical reverse phase HPLC demonstrated a large number of UV peaks, and thus 2-bromotoluene was finally purified by preparative C_{18} HPLC in 25 % isolated yield.

2-Bromoanisole. 2-Bromophenol reacted with a 20 fold excess of diazomethane to produce an 85% crude yield of 2-bromoanisole accompanied by numerous UV-active impurities. One of these peaks was unreacted 2-bromophenol. Acid and base extracts, and a bulb-to-bulb distillation eliminated 2-bromophenol and the majority of the UV impurities, but failed to remove three other minor radioactive contaminants. Thus preparative C_{18} reverse phase HPLC was necessary for purification of 2-bromoanisole.

Summary. The synthesis of several *ortho*-substituted bromobenzenes needed in ^{14}C-labeled form for metabolism studies has been accomplished. The crucial step as far as radiochemical efficiency is concerned was the development of a simple effective method for the regioselective *ortho* bromination of [^{14}C]-aniline. The resulting 2-bromoaniline was then converted using classical diazonium ion chemistry (adapted for small-scale operations) to ^{14}C-labeled bromobenzene, 2-bromotoluene, 1,2-dibromobenzene, 2-bromobenzonitrile, 2-bromophenol and 2-bromoanisole.

Experimental.

U-[^{14}C]-Anilinium sulfate (47.4 mCi/mmol) was obtained from a commercial source. Palladium acetate and sodium fluoroborate were purchased from Alpha Corp. Diazald, tetramethyl tin and NBS were purchased from Aldrich Chemical Co. NBS was recrystallized from water. Cuprous bromide (26), cuprous cyanide (27), and cuprous oxide (28) were prepared shortly before use.

N-Bromosuccinimide Bromination of Aniline. An aqueous stock solution of anilinium sulfate (3.76 mCi/mmol) was reacted with KOH and extracted with three 20 ml portions of methylene chloride. The combined extracts were concentrated by distillation through an air cooled Vigreux column (15 cm). As the extract volume was reduced to less than 5 ml, 20 ml of benzene was added to azeotrope water from the residue. NBS (1.23 mmol) was added to a solution of aniline (4.85 mCi,1.30 mmol) in 25 ml of freshly distilled dry benzene. After stirring for 16 h at room temperature, the solution was diluted with 50 ml of hexanes and succinimide-derived solids were filtered off. The filtrate was concentrated by Vigreux distillation and the residue chromatographed on 35 g of silica gel solvated in hexane, and eluted sequentially with hexane (200 ml), 5% v/v ethyl acetate in hexane (200 ml), 10% v/v ethyl acetate in hexane (200 ml), and 20% v/v ethyl acetate in hexane (400 ml). Three compounds were detected by TLC of the fractions (40% v/v ethyl acetate in hexane on silica gel): 2-bromoaniline (Rf 0.67), 4-bromoaniline (Rf 0.42), and aniline (Rf 0.38). The latter two compounds were not well resolved by gravity silica gel chromatography and were combined. Fractions (15 ml each) were pooled, distilled to residues and evaluated by HPLC as described below. During distillation, aniline was removed from 4-bromoaniline by codistillation with chromatographic solvent through a short path head. 4-Bromoaniline was slightly red in color and was

sublimed at 0.05 mm Hg. After these procedures, aniline, 2-bromoaniline and 4-bromoaniline were better than 99% pure by chemical (UV) and radiochemical (Ramona-LS flow-through) HPLC assay. The anilines were converted to their hydrochlorides and stored as aqueous solutions. Isolated yields were 2-bromoaniline (2.53 mCi, 52%), 4-bromoaniline (1.50 mCi, 31%), and recovered aniline (0.75 mCi, 15%).

Bromobenzene. An aqueous solution of 2-bromoanilinium hydrochloride (3.23 mCi, 3.76 mCi/mmol, 0.859 mmol) was evaporated to near dryness and dissolved in 4.5 ml of hypophosphorous acid (50%). Sodium nitrite (2.58 mmol in 1 ml of water) was added slowly over 3 min to this suspension stirred at 5 °C. After 3 min, methylene chloride (5 ml) and cuprous oxide (1.72×10^{-2} mmol, 2 mol% catalyst) were added in one portion. After 3 h at 5 °C, the methylene chloride phase was separated and the aqueous phase extracted twice with 6 ml portions of methylene chloride. The organic phases were combined, dried over sodium sulfate, and filtered. After concentrating by Vigreux distillation, the residue was bulb-to-bulb distilled at 0.05 mm Hg. Isolated yield of bromobenzene was 1.98 mCi, 60%.

2-Bromophenol. An aqueous solution (3.85 ml) of 2-bromoanilinium hydrochloride (1 mCi, 3.76 mCi/mmol, 0.266 mmol) was mixed with 0.18 ml of sulfuric acid for 3 min. This solution was stirred at 5 °C, and sodium nitrite (0.319 mmol in 1 ml water) was added slowly over 3 min. After 5 min, urea (1.06 mmol) was added to consume excess nitrite. The cold diazonium solution was added slowly via syringe to a boiling mixture of 9.5 ml water, 5.8 ml sulfuric acid, and 3.6 g of sodium sulfate, at a rate to maintain the distillation pot temperature at 130-135 °C. 2-Bromophenol steam distilled in 10 to 15 ml of water. The steam distillate was extracted with three 15 ml portions of methylene chloride and the combined extracts were concentrated by distillation. The residue was bulb-to-bulb distilled at 0.05 mm Hg to yield 2-bromophenol (0.779 mCi, 78%).

4-Bromophenol. 4-Bromophenol was prepared by procedures identical to those described for 2-bromophenol, except the residue from steam distillation was sublimed at 35 °C and 0.05 mm Hg to yield 4-bromophenol (0.879 mCi, 88%).

1,2-Dibromobenzene. An aqueous solution (5 ml) of 2-bromoanilinium hydrochloride (0.70 mCi, 1.0 mCi/mmol) was dissolved in 5 ml of hydrobromic acid (30%) and evaporated to near dryness. An additional 5 ml of hydrobromic acid and 5 ml of water were added to dissolve this residue and the solution was cooled to 5 °C. Sodium nitrite (0.80 mmol, in 1 ml of water) was added slowly over 3 min to this stirred solution. After 5 min, an ice-cold urea solution (0.14 mmol in 1.0 ml water) was added to consume excess nitrite. The resulting diazonium solution was added slowly to a stirred solution of freshly prepared cuprous bromide (0.70 mmol), and potassium bromide (2.68 mmol) in 10 ml of HBr (3.7 mmol) and 2 ml of water at 5 °C. After 30 min, the reaction was warmed to room temperature (30 °C) for 1 h, and extracted twice with 15 ml portions of pentanes. The extracts were combined, extracted with 5% aqueous NaOH, concentrated by Vigreux distillation, and the residue bulb-to-bulb distilled at 0.05 mm Hg to produce a colorless liquid.

HPLC assay of this material indicated that it consisted of 84% 1,2-dibromobenzene (0.34 mCi) with two other radioactive components of 7 and 11% each. This material was further purified by preparative C_{18} reverse phase HPLC as described below. The fraction collected at 22 min was saturated with NaCl and extracted four times with 40 ml portions of methylene chloride. The extract was concentrated by Vigreux distillation to give a clear colorless residue (0.26 mCi, 37%).

2-Bromobenzonitrile. An aqueous solution (7 ml) of 2-bromoanilinium hydrochloride (0.90 mmol, 1 mCi/mmol) was mixed with 1 ml of 10% v/v aqueous sulfuric acid (1.7 mmol) for 2 min, and cooled to 5 °C. Sodium nitrite (1.20 mmol in 1 ml of water) was added dropwise over 3 min to this solution. After 5 min, the diazonium solution was added slowly to a stirred freshly prepared solution of cuprous cyanide (1 mmol),

potassium cyanide (5 mmol), and sodium carbonate (4 mmol) in 10 ml of water at 60 °C. After 10 min, the reaction was diluted with 20 ml of water, and 2-bromobenzonitrile steam distilled from the reaction pot in 20 ml of water. The steam distillate was twice extracted with 10 ml portions of methylene chloride, the extracts combined and concentrated by Vigreux distillation, and the residue sublimed at 35 °C and 0.05 mm Hg.

Reverse phase HPLC of this material indicated one UV and radioactive component, but silica TLC showed trace impurities. Purification by preparative TLC (1 mm silica gel, 254 fluorescent indicator, 35% ethyl acetate/hexane v/v) separated 2-bromobenzonitrile from two minor impurities. The major compound (Rf 0.6) was located by UV visualization, scraped from the plate, the silica extracted with four 10 ml portions of methylene chloride, and the combined extracts concentrated by Vigreux distillation. Recovery from TLC was 85% and overall isolated yield was 0.33 mCi, 37%.

2-Bromotoluene. 2-Bromoaniline (0.50 mCi, 1.0 mCi/mmol) was dissolved with 1.15 ml of 10% v/v aqueous sulfuric acid (2.0 mmol) and cooled to 5 °C. Sodium nitrite (0.6 mmol in 1 ml of water) was added drop-wise over 3 min to this stirred solution. After an additional 3 min solid sodium fluoroborate (2 mmol) was added to the solution, the mixture warmed to room temperature for 15 min, and lyophilized to a dry residue (3 h). The residue was suspended in 5 ml of freshly distilled dry acetonitrile and reacted with tetramethyltin (1 ml, 7.2 mmol) and palladium acetate (0.05 mmol, 10 mol % catalyst). After 2 h, the mixture was extracted with four 10 ml portions of methylene chloride, the extracts combined, and concentrated by Vigreux distillation.

HPLC evaluation of this residue (0.40 mCi total) indicated four radioactive and UV compounds with 2-bromotoluene as 42% of the detectable counts (0.208 mCi by assay). Acid and base extraction, and bulb-to-bulb distillation of this extract did not eliminate these contaminants. Purification was performed by C_{18} reverse phase HPLC as described below. 2-Bromotoluene eluted at 42 min. The methanol/water solution from preparative HPLC was extracted four times with 20 ml portions of pentanes, the organic extracts combined and concentrated to a residue by Vigreux distillation. The isolated yield was 0.124 mCi, 25%.

2-Bromoanisole. A solution of Diazald (N-methyl-N-nitroso-p-toluenesulfonamide, 3.0 mmol), in diethyl ether, was added drop-wise to a stirred solution of sodium hydroxide (22 mmol in 4 ml of methanol/water, 1:1 v/v) at 60 °C. The diazomethane was continuously distilled into an ice-cold receiver containing a solution of 2-bromophenol (0.150 mCi, 1.0 mCi/mmol) dissolved in 6 ml of ether. The resulting solution was stirred for 16 h at room temperature. Excess diazomethane was consumed by the addition of sufficient acetic acid to eliminate color. The solution was diluted with 10 ml of pentanes and extracted with 5 ml of ice-cold 10% w/v aqueous sodium hydroxide. The organic layer was concentrated to a residue by Vigreux distillation. The residue (0.144 mCi) consisted of four compounds by HPLC, with 2-bromoanisole as 89% of the detectable counts (0.128 mCi, 85% assayed yield).

Bulb-to-bulb distillation of the residue at 0.50 mm Hg reduced the UV impurities but not the radioactive contaminants. Purification was performed by C_{18} reverse phase HPLC as described below. 2-Bromoanisole eluted at 30 min. The methanol/water solution of 2-bromoanisole from preparative HPLC was extracted four times with 20 ml portions of pentanes, the organic extracts combined and concentrated to a residue by Vigreux distillation. Isolated yield was 0.094 mCi, 63%.

GC Assays. Chromatographic conditions on OV-17 (glass packed column, 6 ft x 2 mm I.D., 20 ml /min carrier) were 115 °C for the first 40 min followed by a linear temperature gradient from 115 ° to 200 °C over 14 min. Retention times (min) in order of elution follow: bromobenzene, 1.4; aniline, 2.3; 2-bromophenol, 3.2; 1,2-dibromobenzene, 7.9; 2-bromoanisole, 9.2; 2-bromoaniline, 10.2; 2-bromobenzonitrile, 15.6; 4-

bromophenol, 16.4; 4-bromoaniline, 18.3; 2,6-dibromoaniline, 29.3; 2,4-dibromoaniline, 47.5; and 2,4,6-tribromoaniline, 52.8.

HPLC Assays. Chromatographic conditions on a 10 μ Alltech C_{18} column (4.6 x 250 mm) at 1.5 ml/min were isocratic elution for 15 min with 30% methanol/water, followed by a linear gradient from 30 to 90% methanol/water over 30 min, and an isocratic hold at 90% methanol/water for 5 min before recycling. The initial solvent composition must be held for 15 min if 2- and 4-bromoaniline are to be resolved from each other. Radioactivity was detected by a Ramona LS flow through monitor equipped with a 0.6 ml glass flow cell and upper and lower discriminator channels set at 400 and 2, respectively, for the detection of ^{14}C radioactivity. Retention times (min) in order of elution follow: aniline, 8.9; 2-bromophenol, 25.3; 2-bromoaniline, 25.6; 4-bromoaniline, 26.0; 4-bromophenol, 29.3; 2-bromobenzonitrile, 30.7; 2-bromoanisole, 35.9; 2,6-dibromoaniline, 37.1; 2,4-dibromoaniline, 37.7; bromobenzene, 37.7; 2-bromotoluene, 42.0; 1,2-dibromobenzene, 42.7; and 2,4,6-tribromoaniline, 44.4. Preparative purifications of 1,2-dibromobenzene, 2-bromotoluene, and 2-bromoanisole were performed on a 10 μ Whatman C_{18} Magnum 9 (10 mm x 60 cm) column at 4 ml/min using an isocratic mobile composition of 40% methanol/water for 10 min followed by linear gradient from 40 to 90% methanol/water over 15 min, and an isocratic hold at 90% methanol/water for 30 min before recycling. Fractionations by HPLC were accomplished on the basis of ^{14}C radioactivity by collecting directly from the Ramona LS flow through detector.

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