SYNTHESIS OF TRITIATED BROMOBENZENE DERIVATIVES

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SUMMARY

The synthesis of ^{3}H-bromobenzene, ^{3}H-o-bromotoluene, ^{3}H-o-bromobenzonitrile, ^{3}H-o-bromobenzotrifluoride is reported. The method involves exchange-tritiation of the appropriate anilines in heptafluorobutyric acid, followed by diazotization and either reduction or Sandmeyer coupling of the diazonium salt.

Key words: ^{3}H-bromobenzene, ^{3}H-o-bromotoluene, ^{3}H-o-bromobenzonitrile, ^{3}H-o-bromobenzotrifluoride

INTRODUCTION

Bromobenzene is a potent hepatotoxin and an important model compound for investigating the mechanisms of tissue injury by chemicals and drugs. It appears that the toxicity is due to an enzymatically formed arene oxide metabolite of bromobenzene, rather than to bromobenzene itself.[1] The epoxide metabolite in turn reacts indiscriminately with and becomes covalently bound to important cellular nucleophiles, thus disrupting cellular function. We have observed that *in vivo* the toxicity of bromobenzene is subject to marked substituent effects, being greatly increased or decreased, respectively, by electron-withdrawing or -donating substituents.[2] In order to investigate the biochemical basis for this substituent effect, we required several radiolabeled bromobenzene derivatives. In this paper we report convenient syntheses for tritiated derivatives of several bromobenzenes bearing both electron-withdrawing and electron-donating substituents; the specific activities obtained are in the 1-10 mCi/mmole range.

RESULTS AND DISCUSSION

The basic method involves exchange tritiation[3] of an appropriately substituted aniline derivative, followed by diazotization and either reduction or coupling of the diazonium compound, as illustrated in the scheme. As shown

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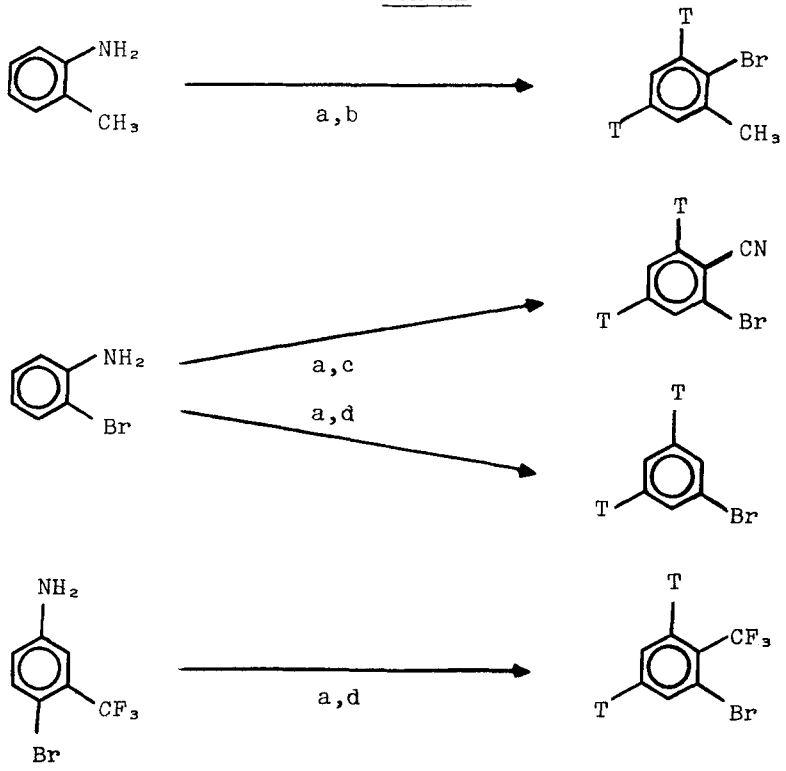
in the preceeding communication,[3] the exchange takes place almost exclusively ortho and para to the amine function. Attempts to exchange ortho-aminobenzotrifluoride, or its acetamide deravative, with D or T in HFBA always met with failure. This was evidently due to solvolysis of the CF_3 group, as previously observed with ortho and para CF_3-substituted phenols.[4] CF_3 groups meta to amine and phenol functions are stable, however, as indicated in the scheme.

This method represents a facile way to introduce tritium into specific positions in aromatic rings. The amine grouping which activated the ring toward electrophilic exchange, and directs the course of the reaction, can later be converted into a variety of other functionalities (H, -SR, halogen, CN, etc.) through relatively efficient aryldiazonium ion reactions.

SCHEME



Reagents: a) $C_3F_7CO_2H/^3H_2O$ followed by $HCl/NaNO_2$; b) CuBr; c) KCN/CuCn; d) H_3PO_3/18-crown-6/Cu_2O.

EXPERIMENTAL SECTION

Tritium oxide (5 Ci/g) was obtained from New England Nuclear Corp., and heptafluorobutyric acid was obtained from Aldrich.

o-Bromoanaline-^{3}H. o-Bromoaniline (400 mg, 2.32 mmole), heptafluorobutyric acid (600 mg, 2.78 mmole), and ^3H_2O (0.025 ml, 5 Ci/gram) were heated at 165° in a screw capped culture tube for 5 days. The cooled contents of the tube were transferred to a separatory funnel and partitioned between 2 ml saturated aqueous sodium bicarbonate and 2 ml pentane. Extraction of the pentane solution with dilute HCl, basification with saturated aqueous sodium bicarbonate, re-extraction into pentane, drying and evaporation of the pentane solution afforded 120 mg (30%) of tritiated o-bromoaniline. The original pentane solution remaining from HCl extraction was dried, evaporated, and the residue saponified in 5% KOH in ethanol for 2 hours. The solvent was evaporated and the residue (largely o-bromoheptafluorobutyranilide) was extracted with pentane. Evaporation of the pentane afforded an additional 260 mg (65%) of tritiated o-bromoaniline. The two crops were combined. and examined for purity by thin layer chromatography (silica gel, 25% ethyl acetate in Skellysolve B) and gas chromatography (1/8" x 10' 5% DC-550 on silanized chromosorb W, 140°, carrier 35 ml/min). Gas chromatography indicated the purity of this material to be in excess of 95%. The specific activity was determined to be 8.2 mCi/mmole.

o-Bromobenzonitrile-^{3}H. o-Bromoaniline-^{3}H (163 mg, 0.95 mmole, 8.2 mCi/mmole) was dissolved in 5 ml 15% aqueous HCl, and diazotized by addition of 300 mg (4.3 mmole) $NaNO_2$ at 0°. The *pH* of this solution was then adjusted to 5 with K_2HPO_4. A solution of CuCn was prepared[5] from 5 g $CuSO_4$ and heated to 60°. To the hot CuCn solution was added dropwise the solution of the diazonium salt. The mixture was extracted several times with pentane and the combined pentane extracts were washed with water, dried, and evaporated. The dark, oily residue was purified by sublimation to afford 120 mg (70%) o-bromobenzonitrile. Gas chromatographic analysis, using the conditions described for o-bromoaniline, revealed the product to be 100% pure. The specific activity was determined to be 8.2 mCi/mmole.

Bromobenzene-^{3}H. To a mixture of 2 ml HCl and 20 ml water was added 300 mg (1.74 mmole) o-bromoaniline-^{3}H (8.2 mCi/mmole) and o-bromoaniline (900 mg, 6.97 mmole). The solution was cooled to 0° and diazotized by the addition of a solution of 800 mg (11.6 mmole) NaNO in water, the temperature being kept near 0°. Fluoboric acid (2 ml, 12 mmole) was then added, and the

precipitate collected, washed successively with cold 5% ammonium fluoborate solution, cold methanol, cold ether, and air dried.[6] The solid obtained amounted to 620 mg (26%). This was suspended in chloroform (20 ml), and cooled in an ice bath. Forty mg of 18-crown-6,[7] 4 ml 50% hypophosphorus acid, and 30 mg Cu_2O were then added and the mixture stirred for 5 minutes. Sodium carbonate was then added until the pH was 8. The chloroform layer was washed with water and the aqueous solution backwashed with chloroform. The dried chloroform solutions were evaporated and the residue purified by column chromatography (silica gel, pentane). There was obtained 284 mg (75%) of bromobenzene-^{3}H (2.01 mCi/mmole) which was homogenous to thin layer and gas chromatography, as described above.

o-Toluidine-^{3}H. o-Toluidine (390 mg, 3.64 mmole), heptafluorobutyric acid (660 mg, 3.08 mmole), and ^3H_2O (0.01 ml, 5 Ci/g) were heated at 160° in a screw capped culture tube for 5 days. Workup as described for o-bromoaniline afforded 350 mg (90%) of tritiated o-toluidine, which was shown to be more than 95% pure by thin layer and gas chromatographic procedures detailed above. The specific activity was determined to be 10.76 mCi/mmole.

o-Bromotoluene-^{3}H. To a mixture of 5 ml of 10% HBr and 5.0 ml water was added 270 mg (2.52 mmole) of o-toluidine-^{3}H (2.82 mCi/mmole). The solution was cooled to 0° and diazotized by the addition of a solution of 520 mg (7.6 mmole) sodium nitrite in water, the temperature being kept near 0°. A solution of CuBr was prepared[8] from 5 g $CuSO_4$ and heated to 60°. To the CuBr solution was added dropwise the solution of the diazonium salt. The mixture was heated at 60° for 20 minutes, cooled, and extracted with pentant. The pentane extracts were washed with water, dried, and the pentane evaporated. The residue was purified by column chromatography (silica gel, pentane) to afford 188 mg (70%) of o-bromotoluene-^{3}H. The purity of the material was determined by gas chromatographic analysis, using the conditions specified for o-bromoaniline, and was found to be better than 95%. The specific activity was 2.8 mCi/mmole.

o-Bromobenzotrifluoride-^{3}H. o-Bromobenzotrifluoride (from PCR, Inc.) was nitrated and reduced to 2-bromo-5-aminobenzotrifluoride according to the procedure of McBee, et al.[9] The latter amine (135 mg) was then heated with 200 µl HFBA and 10 µl ^3H_2O at 140° for 10 days. Workup as described above yielded 91 mg of pure material, which was then diazotized in 10 ml of 5% H_2SO_4 with 60 mg $NaNO_2$. The diazotized aniline was then treated with 2.5 mmoles of H_3PO_4 added over a 30 minute period. After warming to room

temperature the mixture was extracted with pentane, which yielded after drying and careful evaporation, 72 mg (78%) of o-bromobenzotrifluoride (sp. act. 0.614 mCi/mmole).

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