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Synthesis and iodination of methyl 4-tri-n-butylstannylbenzoate, *p*-(methoxycarbonyl)phenylmercuric chloride and *p*-(methoxycarbonyl)phenylboronic acid

Mark D. Hylarides, D. Scott Wilbur, Stephen W. Hadley, and Alan R. Fritzberg

NeoRx Corporation, Seattle, Washington (U.S.A.)

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Abstract

Synthesis of methyl 4-tri-n-butylstannylbenzoate (**1**) was accomplished by reaction of methyl 4-bromobenzoate with hexabutylditin and palladium catalyst. Transmetallation of **1** with mercuric acetate yielded the corresponding arylmercuric acetate **4** which was readily converted to aryl mercuric halides **2a** and **2b**. Reaction of arylmercuric bromide **2b** with diborane or catecholborane produced arylboronic acid **3** in high yield. Iodinations of **1**, **2a** and **3** were studied using *N*-chlorosuccinimide/NaI at the 10% and 100% stoichiometric amounts of NaI with $Na^{125}I$ added to monitor the course of the reaction.

Introduction

The application of radiohalogenated monoclonal antibodies to diagnosis, staging, and therapy of cancer is being studied [1,2]. Direct radiohalogenation of the antibodies can be deleterious to their ability to bind to antigens on tumor cells owing to possible damage brought about by the reaction conditions. However, radiohalogen labeling of antibodies in two steps, where a small molecule is radiohalogenated in one step, followed by reaction of the small molecule with the protein in a second step, has proven to be a less damaging method of labeling [3]. In addition, introduction of radiohalogens via direct radiohalogenation results in susceptibility to in vivo dehalogenation owing to structural similarities to thyroid hormones.

Part of our studies regarding radiolabeled antibodies have been directed at the preparation of radioiodinated antibodies that do not undergo in vivo deiodination. To accomplish this goal we have been investigating the use of small molecules which would be generally reactive with a number of radiohalogens and also reactive with proteins. To facilitate the incorporation of radiohalogens into the small protein-reactive molecules, organometallic intermediates have been investigated. The use of

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organometallic intermediates such as arylstannanes [4,5], organoboranes [6], organomercury [7], organosilanes [8], organosilicates [9], organothallium [10], and organogermanes [11] to incorporate radiohalogens into aromatic positions of organic compounds is well documented. However, the question of which organometallic intermediate could be more generally applied and have the best chemical properties for our applications has not been adequately addressed.

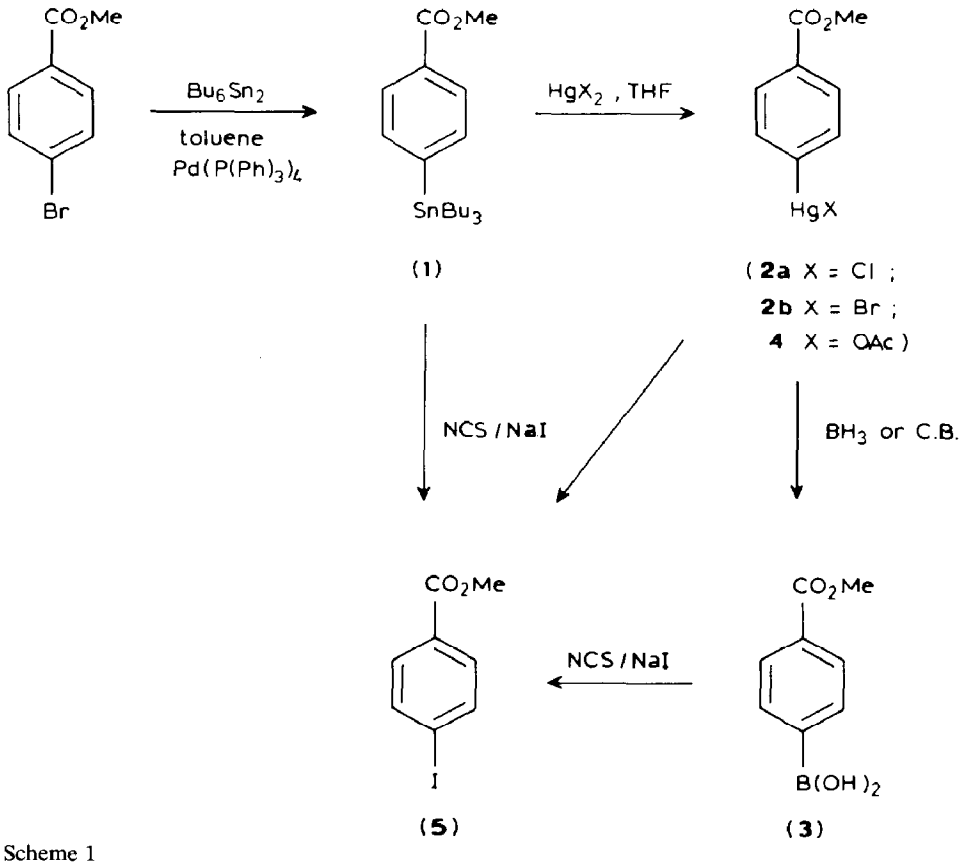
A comparison of the iodination/radioiodination of three organometallic derivatives of methyl benzoate was carried out to evaluate the relative merits of each. Radioiodination reactions were initially carried out at 100% stoichiometric amount of NaI/$Na^{125}I$. The reactions were then repeated at the 10% stoichiometric level to more closely mimic use of iodine-131, a radiohalogen of therapeutic interest. The compounds, methyl *p*-tri-n-butylstannylbenzoate (**1**), *p*-(methoxycarbonyl)phenylmercuric chloride (**2a**), and *p*-(methoxycarbonyl)phenylboronic acid (**3**), were chosen as models for benzoates containing protein reactive "activated esters". Described herein is the synthesis of compounds **1**–**3** and the results of some iodination studies with the compounds.

Results

The syntheses (Scheme 1) involved initial preparation of methyl *p*-tri-n-butylstannylbenzoate (**1**) in 88% yield from methyl *p*-bromobenzoate by treatment with excess hexabutylditin and tetrakis(triphenylphosphine) palladium in refluxing toluene [12]. Compound **1** had previously been prepared by reaction of methyl *p*-iodobenzoate with hexabutylditin and tetraammonium fluoride in benzene [13]. Subsequent transmetallation of **1** with mercuric acetate, mercuric chloride or mercuric bromide [14] produced arylmercuric acetate **4** or arylmercuric halide **2a** or **2b** in high yields. Arylmercuric halides were also conveniently prepared by treatment of **4** with aqueous KCl or KBr. The synthesis of mercuric acetate **4** had been reported earlier, however, no experimental detail was presented [15]. Additionally, an earlier reported synthesis of **2a** involved refluxing 4-chloromercuribenzoic acid with methanolic HCl for 1 week [16].

Arylboronic acid **3** was prepared in high yield by two methods. The first involved treatment of **2** with a ten-fold excess of diborane in THF [17] followed by aqueous hydrolysis. The use of less reactive catecholborane [18] was then studied in an effort to minimize the introduction of a large excess of hydride, as employed in the diborane procedure. In each case high yields of arylboronic acid **3** were obtained.

The iodination/ radioiodination of **1**, **2** and **3** using *N*-chlorosuccinimide (NCS) and NaI in 10% HOAc/90% MeOH was studied using three different methods. The first method involved addition of one equivalent of NaI to the solution of NCS (one equivalent) with **1**, **2** or **3**. The progress of the reaction (i.e., generation of methyl *p*-iodobenzoate (**5**)) was monitored by use of a high performance liquid chromatography (HPLC) instrument equipped with a UV detector. Product yield was calculated by HPLC analysis of a solution of **5** of known concentration. Iodination of **1** proceeded in 90% yield within 15 min at 25 °C. In contrast, compounds **2** and **3** produced only 15–20% of **5** under the same conditions. In each of the two latter reaction mixtures, polar species were initially generated which decreased in amount over time as more of the desired product formed.



Scheme 1

To further study the reaction kinetics and the characteristics of these polar byproducts, radioiodination reactions of **1**, **2** and **3** were performed at the 100% and 10% stoichiometric levels of NaI with added $Na^{125}I$ and one equivalent of NCS. Reaction progress was monitored by an HPLC instrument equipped with both UV and radiometric detectors. At the 100% stoichiometric amount of $NaI/Na^{125}I$, the yield of aryliodide **5** from arylstannane **1** was 98% after 15 min (based on the consumption of radioiodine). Conversely, even after 20 h radioiodination of arylmercuric chloride **2a** had afforded only a 40% yield of **5**. This yield did, however, increase to 60% after 72 h. A labeled polar compound was again observed early during the course of the reaction which appeared to be converted to **5** over time. Radioiodination of arylboronic acid **3** under similar conditions produced **5** in 60% radiochemical yield in 3 h. A more polar species comprised the remaining 40% of the radioactivity. After 20 h, a 70% yield of radioiodinated product was observed which did not further increase with additional time. When the reaction was performed in the presence of excess NaOAc the same radiochemical yield was obtained. Interestingly, when the reaction was repeated using two equivalents of NCS, a 96% radiochemical yield of **5** was obtained after 24 h.

Radioiodination of arylstannane **1** at 25 °C for 20 min with a 10% stoichiometric amount of $NaI/Na^{125}I$ gave a 98% yield of **5**. The radioiodination of arylboronic acid **3** was also quite facile since a quantitative radiochemical yield of **5** was

obtained after 20 min at 25 °C. In contrast to the iodinations of **1** and **3**, the rate of reaction of arylmercuric chloride **2a** was substantially slower. After 20 min, a 30% yield of **5** was obtained which was accompanied by a polar compound comprising 60% of the total radioactivity. HPLC analysis of the reaction mixture after 3 h showed that the yield of **5** had increased to 89% with a proportionate decrease in the percentage of the labeled polar species.

Experimental

Melting points were obtained on a MeltTemp Apparatus and are uncorrected. All ^{13}C and ^{1}H NMR spectra were obtained using a Varian Gemini 200 MHz instrument. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Solvents, including anhydrous toluene, and reagents were obtained from commercial sources and used as received. Anhydrous THF was obtained by distillation from Na/benzophenone. Sodium [^{125}I] iodide in 0.1 *N* NaOH solution was purchased from NEN DuPont and used as obtained. For the radioiodination reactions, HPLC analyses were performed using a Spectra Physics Model 8800 pump equipped with a Beckman Model 160 UV detector at 254 nm and a Beckman Model 170 radioisotope detector. Data from the HPLC was collected and analyzed using a computer (Dynamic Solution Integrator software package). The progress of the reactions was monitored by an HPLC instrument fitted with a Whatman C_{18} reversed phase column, using an isocratic solvent system (65% A, 35% B, flow 1.0 ml/min). Solvent A was 98% acetonitrile with 2% of a 1% HOAc/H_2O solution. Solvent B was a 90% solution of 1% HOAc/H_2O and 10% acetonitrile mixture. The product profile was analyzed by UV and radiometric detectors. In each case, the radiolabeled product peak coeluted with non-radioactive methyl *p*-iodobenzoate at 4.5 min.

*Preparation of p-tri-n-butylstannyl benzoate (**1**)*

Methyl 4-bromobenzoate (5 g, 23 mmol) was dissolved in 100 ml of anhydrous toluene. The resulting solution was degassed by bubbling nitrogen through the solution. Hexabutylditin (27.3 ml, 54 mmol) was added via syringe, followed by addition of tetrakis(triphenylphosphine)palladium (0.27 g, 0.23 mmol). Following these additions the solution was refluxed for 24 h. After removal of the solvent under reduced pressure, the crude product was applied to a silica gel chromatographic column. The excess hexabutylditin was eluted first from the column using hexane. Compound **1** was isolated from the column by elution with 10% ethyl acetate/90% hexane. After removal of the solvents under reduced pressure, 8.6 g (88% yield) of **1** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): 0.91 (t, 3H, *J* 7 Hz), 1.07(t, 2H, *J* 7 Hz); ^{13}C NMR 9.47, 13.47, 27.19, 28.92, 51.92, 128.55, 129.75, 136.60, 149.88, 167.79. IR ($CDCl_3$, cm^{-1}): 2800–2950, 1725, 1260. MS (CI): 429(8.2%), 428(10.2%), 427(51.9%, 426(22.2%), 425(40.3%), 424(16.6%), 423(22.2%), for parent *M* + H; Similar pattern at 391–399 (*M* + H − CH_3OH); 365–373 (*M* + H − butane).

*Preparation of p-(methoxycarbonyl)phenylmercuric acetate (**4**)*

To a solution of **1** (0.42 g, 0.99 mmol) in 7 ml of dry THF was added 0.32 g (1.0 mmol) of mercuric acetate in 7 ml dry THF. The mixture was allowed to stir at

room temperature for 12 h. After removal of the THF under reduced pressure, the white solid was suspended in hexane and filtered. The solid was then washed extensively with hexane to give 0.32 g (82% yield) of **4** as a white powder, m.p. 181–183°C. ^{1}H NMR (DMSO-d_6): 1.94(s, 3H), 3.85(s, 3H), 7.58(d, 2H, *J* 8 Hz), 7.89(d, 2H, *J* 8 Hz); ^{13}C NMR: 23.15, 52.10, 128.56, 129.19, 137.56, 166.72, 157.17; IR (KBr, cm^{-1}): 1660, 1680, 1580, 1260, 1100; MS (CI): 399(4.5%), 398(1.8%), 397(15.9%), 396(8.3%), 395(13.6%), 394(9.9%), 393(5.5%) for *M* + H; 333–339 (*M* + H − CH_3OH); 198–206 (Hg^0).

*Preparation of p-(methoxycarbonyl)phenylmercuric chloride (**2a**)*

To a suspension of **4** (0.16 g, 0.41 mmol) in 2.0 ml THF was added 10 ml of 3% KCl solution. The resulting suspension was allowed to stir at room temperature for 1.5 h. The white product was filtered off and washed extensively with hexanes to yield 0.12 g (79%) of **2a**, m.p. 253–254°C. ^{1}H NMR (DMSO-d_6): 3.83(s, 3H), 7.61(d, 2H, *J* 8 Hz), 7.86(d, 2H, *J* 8 Hz); ^{13}C NMR: 52.17, 128.60, 129.12, 137.26, 137.43, 166.79; IR (KBr, cm^{-1}): 2700–2950, 1730, 1280; MS (CI): 375(19.5%), 374(17.3%), 373(46.3%), 372(43.7%), 371(41.8%), 370(34.0%), 369(20.0%) for *M* + H; 341–33 (*M* + H − HCl); 206–198 (Hg^0).

*Preparation of p-(methoxycarbonyl)phenylmercuric bromide (**2b**)*

To a solution of **1** (0.30 g, 0.70 mmol) in 5 ml dry THF was added 0.25 g (0.70 mmol) of mercuric bromide. The resulting white suspension was allowed to stir for 2 h at room temperature. The white product was filtered and washed thoroughly with hexane to remove the butyltin byproducts. Arylmercuric bromide (0.21 g) was obtained as a white powder in 71% yield, m.p. 235–236°C. ^{1}H NMR (DMSO-d_6): 3.83(s, 3H), 7.61(d, 2H, *J* 8 Hz), 7.87(d, 2H, *J* 8 Hz), IR (KBr, cm^{-1}): 1740, 1290.

*Preparation of p-(methoxycarbonyl)phenylboronic acid (**3**)*

Method A. To a suspension of **2b** (75 mg, 0.18 mmol) in 5 ml dry THF was added 1.8 ml (1.8 mmol) of 1.0 *M* $BH_3 \cdot$ THF solution. The resulting grey suspension was allowed to stir for 1 h at which time the reaction was quenched by the careful addition of 1.0 ml water. The resulting suspension was filtered through Celite filter aid to remove elemental mercury. After removal of the solvents under reduced pressure, the white solid was dissolved in 30 ml 10% THF/90% ethyl acetate and the solution extracted once with water. After drying over anhydrous $MgSO_4$ and removal of the solvents under reduced pressure 23 mg of arylboronic acid **3** was obtained in 67% yield as a white solid, m.p. 232–234°C, reported m.p. 230–233°C [19]. ^{1}H NMR (DMSO-d_6): 3.84(t, 3H), 7.72(d, 2H, *J* 8 Hz), 7.94(d, 2H, *J* 8 Hz); ^{13}C NMR: 52.03, 128.13, 138.70, 177.58; IR (KBr, cm^{-1}): 1700, 1450, 1280; MS (EI): 135(M^+ − $B(OH)_2$), 120(M^+ − 60).

Method B. To a suspension of **2b** (75 mg, 0.18 mmol) in 5 ml dry THF was added 0.36 ml (0.36 mmol) of 1.0 *M* catecholborane/THF solution. The mixture was allowed to stir for 1 h at which time the reaction was quenched with the careful addition of 1.0 ml H_2O. The resulting suspension was filtered through a bed of Celite filter-aid followed by removal of the solvents under reduced pressure. The residual white solid was suspended in ethyl ether and filtered to remove residual catechol. After extensive washing of the solid with ethyl ether 30 mg of **3** was obtained as a white solid in 94% yield. The melting point and spectral data obtained were identical to that previously described.

Iodination / radioiodination procedures

A. 100% stoichiometric amount of NaI / $Na^{125}I$. To a solution of 2.77 μmol of **1** (1.2 mg) in 0.5 ml MeOH was added 415 μl (2.8 μmol) of a 1.0 mg/ml NaI in MeOH solution to which was added 1.0 μl (20 μCi) of a $Na^{125}I$ solution. Acetic acid (150 μl) was then added to the reaction mixture followed by the addition of 440 μl (3.3 μmol) of a 1.0 mg/ml solution of NCS in MeOH. The reaction mixture was allowed to stir at 25 °C and reaction progress was monitored by HPLC analysis of approximately 2.0 μl of the solution at various time intervals.

Radioiodination of the methanolic suspensions of 2.77 μmol of **2** (1.0 mg) or **3** (0.5 mg) was carried out in like manner. However, prior to addition of NaI, HOAc and NCS solutions, the methanolic suspensions of **2** or **3** were placed in an ultrasonic bath for 1 min.

B. 10% stoichiometric amount of NaI / $Na^{125}I$. The procedure was identical to the aforementioned except that 41.5 μl (0.28 μmol) of NaI + 1.0 μml (20 μCi) $Na^{125}I$ was added.

Conclusion

Transmetallation reactions are highly efficient for the conversion of arylstannanes to arylmercuric derivatives and for conversion of arylmercuric halides to arylboronic acids.

Although not demonstrated, the reaction conditions are generally mild enough to accommodate a "protein-reactive" activated ester on the aromatic ring. Catecholborane was compared to diborane for the conversion of arylmercuric halide to arylboronic acid. Unlike diborane, a large excess of catecholborane is not required; thus, this procedure may have a more general application in organic synthesis.

Radioiodination of arylstannanes, arylmercuric halides, and arylboronic acids proceeds efficiently at the 10% stoichiometric level of NaI/$Na^{125}I$ using NCS in 10% HOAc/90% methanol. While quantitative radiochemical yields were obtained within 20 min with the arylstannane and arylboronic acid, the arylmercuric halide required three hours to achieve a good radiochemical yield. At the 100% stoichiometric level, the arylstannane was different from the others, since a quantitative product yield was obtained within one hour. In the reactions of **2** and **3** labeled polar compounds were generated along with product. One polar species generated in the arylboronic acid reaction appeared quite stable with time, but was converted to product when additional NCS was added. The polar compound generated from the arylmercuric chloride reaction slowly disappeared as product was formed. The exact chemical nature of these polar byproducts; however, has not been determined.

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