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Research Article

An improved synthesis of substituted [^{11}C]toluenes via Suzuki coupling with [^{11}C]methyl iodide

Eric D. Hostetler*, Garth E. Terry and H. Donald Burns
Department of Imaging Research, Merck Research Laboratories, WP44C-2, West Point, PA 19486, USA

Summary

Toluene derivatives are often found in drug-like molecules, and are therefore desirable as radiolabelled moieties. The desire for an alternate to the Stille coupling led us to investigate the feasibility of the Suzuki coupling. We have found the Suzuki coupling route to be a robust alternative to the Stille coupling for the synthesis of functionalized [^{11}C]toluene derivatives from [^{11}C]methyl iodide. The avoidance of potentially toxic tin-containing by-products is an added advantage. The products synthesized via Suzuki coupling with [^{11}C]methyl iodide were isolated in generally high yields (56–92%), with high radiochemical purity (> 95%) and specific radioactivity (> 4000 Ci/mmol) in less than 20 min following production of [^{11}C]methyl iodide.

Key Words: PET; methyl iodide; carbon-11; Suzuki coupling; microwave

Introduction

A methyl substituent on an aromatic ring is a desirable location for the introduction of carbon-11 into a potential PET tracer. The most common strategy currently utilized for synthesizing [^{11}C]toluene derivatives is via Stille coupling of the corresponding aryl trialkyltin derivative.[1] However, yields are often low, and equally significant, toxic tin by-products can be difficult to remove completely from the final product, which can be prohibitive for clinical studies. For these reasons, we have pursued the Suzuki coupling as an alternative route for the synthesis of [^{11}C]toluene derivatives. The boron-containing by-products of this reaction are considerably less toxic. Additionally, the Suzuki coupling should provide a much more robust synthetic method based on the previous success with the synthesis of [ω-^{11}C]fatty acids.[2]

*Correspondence to: E. D. Hostetler, Department of Imaging Research, Merck Research Laboratories, WP44C-2, West Point, PA 19486, USA. E-mail: eric_hostetler@merck.com

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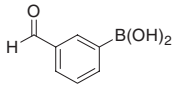
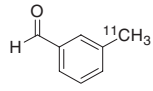
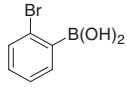
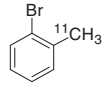
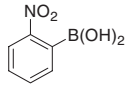
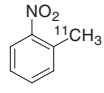
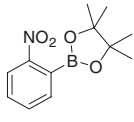
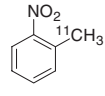
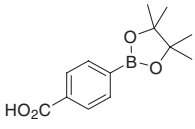
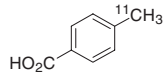
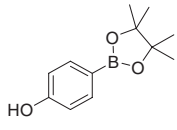
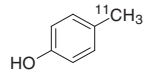
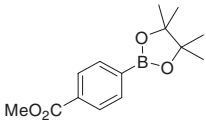
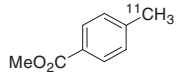
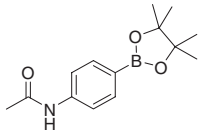
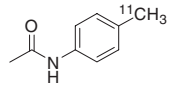
Results and discussion

Initial experiments with commercially available substituted aryl boronic esters using $Pd(PPh_3)_4$ as the catalyst provided the desired products in good yields by heating with NaOH in DMF for several minutes at 100°C. It was found that the order of reagent addition is crucial for consistently high yields. The [^{11}C]methyl iodide must be distilled into a solution of the Pd complex, and then mixed with the aryl boron species and base. Attempts at distilling the [^{11}C]methyl iodide directly into a solution containing the Pd complex, aryl boron species and base gave erratic yields, usually low, and sometimes zero. This identical observation has been noted for the Sonogoshira reaction, which is also a Pd-mediated coupling with [^{11}C]methyl iodide.[3] Presumably, the oxidative addition of [^{11}C]methyl iodide to the Pd complex must occur first when reacting tracer levels of alkyl/aryl halide. Fortunately, oxidative addition of [^{11}C]methyl iodide to the Pd complex is adequately facile such that the [^{11}C]methyl iodide can trapped in the Pd solution at 0°C and immediately transferred to the solution of reagents. While there are no literature examples of preparative-scale Suzuki coupling of iodomethane to arylboron species, the typical coupling of iodoarenes to arylboron species is done as a one-pot procedure with all reagents mixed together from the outset of the reaction. Perhaps at the tracer level, the large excess of base reacts with [^{11}C]methyl iodide faster than the Pd complex. Comparatively, iodoarenes are much more stable to base, and undergo oxidative addition to Pd complexes faster than alkyl iodides.

Initial experiments using $Pd(PPh_3)_4$ generated a substantial amount of palladium black, which often clogged the HPLC system upon injection of the quenched reaction mixture. In order to minimize the time and maximize the simplicity of the synthesis, we wished to avoid filtering the reaction before HPLC purification. Subsequently, we discovered that a minimal amount of the more stable $Pd(dppf)Cl_2$ complex was able to mediate the Suzuki coupling of [^{11}C]methyl iodide without compromising the reaction yield. By performing the reactions with a saturated solution of $Pd(dppf)Cl_2$, which is only slightly soluble in DMF, we were able to achieve maximum yields with a minimal amount of Pd complex, and the HPLC purification was not complicated by a filtering step.

Following this discovery, a series of simple functionalized aryl boronic esters and acids were subjected to standard reaction conditions to probe the utility of the reaction (Table 1). DMF was the only solvent investigated. A small number of bases were tried with the synthesis of 4′-methylacetanilide (entry 8) as a model reaction. Neither aq. KOAc nor aq. Cs_2CO_3, commonly used bases for the Suzuki coupling of aryl halides,[4] provided any desired product. Aqueous NaOH and aq. K_3PO_4 were equally efficient, but we wished to employ a milder base to prevent complications when using base-sensitive

Table 1. Suzuki couplings with [^{11}C]MeI

Entry	Precursor	Product	Condition[a]	Decay-corrected isolated yield/HPLC yield
1			a	62%/92% (n = 2)
2			b	49%/67% (n = 2)
3			a	78%/90% (n = 3)
4			a	57%/90% (n = 1)
5			c	69%/72% (n = 1)
6			a	92%/95% (n = 2)
7			a	80%/93% (n = 2)
8			a	85%/96% (n = 2)

[a] (a) 3 eq. K_3PO_4, 100°C, 50 W, 90 s; (b) 5 eq. K_3PO_4, 60°C, 50 W, 90 s; (c) 3 eq. K_3PO_4, 120°C, 50 W, 90 s.

substrates. Therefore, aq. K_3PO_4 was chosen as the base for the remainder of the substrates.

Of note is the compatibility of several base-sensitive substrates, including a methyl ester (entry 7), which is sensitive to hydrolysis, and carboxylic acid and phenol (entries 5 and 6), which possess acidic protons and are often implicated as problematic coupling partners in Suzuki reactions. Both electron-rich (entry

6) and electron-poor (entries 3–5, 7) aryl boronic esters and aryl boronic acids couple with [^{11}C]methyl iodide quickly and with good yields. A wide variety of functional groups are tolerated, including esters and halides. The effectiveness of the Suzuki coupling is not greatly diminished by ortho substituents (entries 2–4). Additionally, both aryl boronic esters (entries 4–8) and acids (entries 1–3) couple with high efficiency. The implementation of aryl boronic esters as precursors for the Suzuki coupling provides for a broader range of available precursors, allowing the synthesis of highly functionalized boronate precursors not accessible via the traditional metallation route used to synthesize aryl boronic acids.[4] Product yields are typically maximized with microwave heating for 90 s at moderate temperatures. Entry 2 gave better yields at slightly lower temperatures, possibly due to an interaction between excess palladium and the aryl bromide at higher temperatures. Entry 5 required somewhat harsher conditions for the best yields. This is not surprising considering that carboxylic acids are generally considered to thwart Suzuki couplings. Significant differences between the isolated yield and HPLC yield in some entries is likely due to product volatilization during vacuum-assisted rotary evaporation to remove organic HPLC solvents from the HPLC-purified product. This could be avoided by an alternate method of formulation, although isolated yields were still sufficiently high. Another explanation for a lower isolated yield is that unreacted [^{11}C]methyl iodide was lost due to volatilization during microwave heating of the reaction. The microwave cavity has been incorporated into the platform of a Gilson SK233 liquid handler, which facilitates the automated synthesis and purification of the desired product in less than 20 min from the end of [^{11}C]methyl iodide production. Specific activities were calculated for two syntheses of methyl ester 7, and the values (5670 and 4800 Ci/mmol) were within the range typically found for other methylated products synthesized in our laboratory.

Experimental

General

All reagents and standards were obtained from commercial sources and used as received. Solvents were anhydrous grade purchased from Aldrich and used as received. Radionuclides were produced by PETNET Pharmaceuticals, Inc. using a Siemens RDS-111 cyclotron. An N-14 gas target containing 1% oxygen was irradiated with an 11 MeV proton beam at 30 μA generating [^{11}C]CO_2. [^{11}C]Methyl iodide was synthesized by unloading [^{11}C]CO_2 from the target through stainless steel tubing directly into a G.E. Tracerlab FX_C. The reactions with [^{11}C]methyl iodide were performed using a remote-controlled, semi-automated system based on a Gilson SK233 liquid handler outfitted with a compact microwave cavity.[5] Microwave reactions were performed in a

Resonance Instruments Model 521A Microwave Cavity with integrated temperature control.

Purification and analysis of the products were performed by reversed-phase HPLC (Waters 600F pump and 600E controller) equipped with a UV detector (254 nm) and a photodiode radio detector (Pharmacia-biotech). A Waters XTerra RP18 column (7.8 × 150 mm, 5 μm) was used for preparative runs with a mobile phase gradient of 20%A 80%B to 90%A 10%B in 15 min at 3 ml/min. A = 100% MeCN; B = 95% H_2O, 5% MeCN, 0.1% TFA. Identification of all radioactive products was confirmed by co-elution with the corresponding non-radioactive compound on an analytical Waters XTerra RP18 column (4.6 × 150 mm, 5 μm) using the same HPLC conditions as for the preparative runs, but at a flow of 1 ml/min. In all cases, the radiochemical purity of the product was >95%. Specific activity was determined by quantitation of the UV response of a known amount of radioactivity injected onto the analytical HPLC column. The response of the UV detector was calibrated for mass by injection of known amounts of authentic compound. A Waters XTerra RP18 column (4.6 × 150 mm, 5 μm) was used for specific activity determinations with an isocratic mobile phase of 50%A 50%B, 1 ml/min, A = 100% MeCN; B = 95% H_2O, 5% MeCN, 0.1% TFA.

Radiochemical syntheses – general procedure

A vial was charged with 1 ml DMF, and the solvent was purged with Ar for 5 min. The starting substituted aryl boronic acid or ester (5 μmol) was dissolved in 50 μl of degassed DMF in an autosampler vial, 1.0 M aq. K_3PO_4 (15 μmol, 3 eq.) was added, and the vial was placed in the liquid handler. Pd(dppf)Cl_2 (0.1 mg) was added to the remainder of the degassed DMF, and the mixture was further purged with Ar until the solution was saturated with Pd(dppf)Cl_2, turning an orange–red color. A 250 μl aliquot of this solution was then placed in an autosampler vial and cooled by an ice-water bath in the liquid handler. [^{11}C]Methyl iodide was distilled into the Pd(dppf)Cl_2 solution. When the level of activity plateaued as measured by a photodiode detector, the solution was transferred to the solution of aryl boronic acid or ester/K_3PO_4, and then to an empty septa-capped 1 ml v-vial in the microwave cavity. The mixture was heated by microwaves for a designated time and temperature, generally 100°C for 90 s at 50 W. The reaction was quenched by the addition of 700 μl water, and the resulting solution was loaded into the autosampler's HPLC injection loop and injected onto the HPLC column. The desired product peak was collected into a flask connected to a modified rotary evaporator connected to a Teflon-membrane vacuum pump. The organic solvent was evaporated at reduced pressure with the aid of a warm water bath for less than 1 min and the remaining solvent was transferred into a sterile vial

via 1/16″ Teflon tubing. The overall synthesis time from the release of [^{11}C]MeI to the formulated product averaged less than 20 min. The decay-corrected, isolated reaction yield was determined by comparing the amount of purified product in the sterile vial to the amount of [^{11}C]MeI produced by the Tracerlab FXc, which was calculated by calibrated detectors within the synthesis module. The HPLC yield is based on the area of the product peak relative to the area of the remainder of the radioactivity on the HPLC trace.

Conclusion

The Suzuki coupling has proved to be a versatile method for the ^{11}C-labelling of a variety of functionalized toluenes. In comparison with the Stille coupling, the Suzuki coupling has several advantages. It does not generate toxic tin-containing by-products, and being a homogeneous reaction, it lends itself to high, reproducible yields and is simpler to automate. The Suzuki coupling has also been successfully used in our hands to radiolabel several highly-functionalized, drug-like molecules, which will be reported in due time.

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