Tetrahedron Letters 54 (2013) 213–216

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Palladium-mediated conversion of *para*-aminoarylboronic esters into *para*-aminoaryl-$^{11}$C-methanes

Valdemar L. Andersen [a,b,c,d,†], Matthias M. Herth [a,b,c,d,†], Szabolcs Lehel [b], Gitte M. Knudsen [c,d], Jesper L. Kristensen [a,d,*]

[a] Department of Drug Design and Pharmacology, School of Pharmaceutical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, Copenhagen 2100, Denmark
[b] PET and Cyclotron Unit, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen 2100, Denmark
[c] Neurobiological Research Unit, Copenhagen University Hospital, Juliane Maries Vej 24, Copenhagen 2100, Denmark
[d] Center for Integrated Molecular Brain Imaging (CIMBI), Juliane Maries Vej 24, Copenhagen 2100, Denmark

ARTICLE INFO

*Article history:*
Received 9 July 2012
Revised 17 October 2012
Accepted 1 November 2012
Available online 10 November 2012

*Keywords:*
Cross-couplings
PET
Carbon-11
Methyl iodide
Palladium

ABSTRACT

Cross-couplings are an alternative to conventional $^{11}$C-methylations which are generally employed in PET tracer synthesis. Therefore, we set out to develop a general procedure for the synthesis of *para*-$^{11}CH_3$ labeled aromatic amines from the corresponding *para*-aminoarylboronic esters in the presence of free amines. Aryl boronic esters containing primary, secondary, and tertiary amines were successfully converted into corresponding labeled methyl derivatives in sufficient radiochemical yield to apply this method for tracer development. This procedure was applied to the labeling of CIMBI-712, a promising candidate for the in vivo imaging of the 5-HT$_7$ receptor in the CNS.

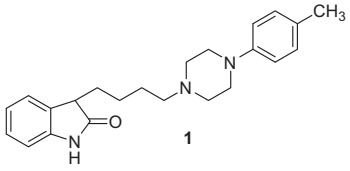


Positron emission tomography (PET) is widely used as a tool to image biological processes in the body. For example, it allows the imaging of neuroreceptors and transporters in vivo. Since its discovery in 1976, $^{11}$C-methylation of amines and hydroxy-groups via [$^{11}$C]$CH_3I$ has been the most commonly used strategy for obtaining $^{11}$C-labeled PET tracers.[1] The disadvantage of this approach is twofold. Firstly, the presence of an *N*-methyl- or methoxy- group in the ligand is necessary for the synthesis of a viable precursor. Secondly, its applicability to various functional groups often makes time consuming protection/deprotection a necessity. Therefore, different $^{11}$C-labeling strategies have been developed.[1] For example, cross-couplings via [$^{11}$C]$CH_3I$ have been carried out to broaden scope, and in recent years, mainly the Stille reaction was applied in PET chemistry, even though examples where the Suzuki reaction has been used for $^{11}$C-radiolabeling have appeared in the literature.[2,3]

Both the Stille and the Suzuki reactions have advantages and disadvantages. In general, the reactivity in a Stille reaction is higher and therefore gives faster reaction rates. However, in PET chemistry the very large excess of the precursor causes the concentration of this to remain constant during the labeling step, and the reactions can be considered pseudo-first-order.[4] Therefore, the higher reactivity in a Stille reaction does not play a key role. Thus, a direct comparison of reactivities in preparative synthetic organic chemistry and radiochemistry can be misleading.

The Stille reaction is not dependent on the presence of a base. This is an advantage when working with compounds that are unstable under basic conditions. On the other hand, the Suzuki reaction uses less toxic reagents compared to the tin species applied in the Stille reaction. When a radiolabeled compound is to be used in vivo, non-toxic reagents and precursors are preferable. Therefore, we believe that the Suzuki reaction is the superior alternative for PET tracer production.

The use of the Suzuki reaction in PET chemistry has received limited attention. A review in 2011 described the various endeavors using the Suzuki reaction as a tool to insert $^{11}$C-labeled




1

**Figure 1.** Structure of CIMBI-712.

* Corresponding author.
*E-mail address:* jekr@farma.ku.dk (J.L. Kristensen).
† Equally contributed.

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.001

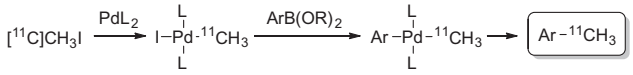


**Figure 2.** Oxidative addition of [$^{11}$C]MeI followed by transmetallalation and reductive elimination upon addition of the boronic substrate.

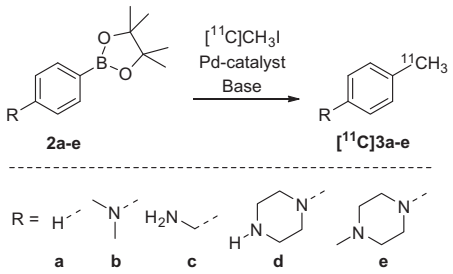
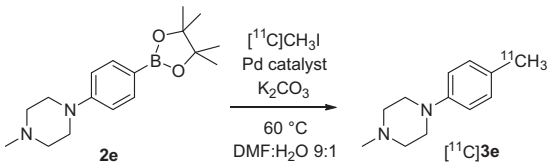


**Figure 3.** Model compounds portraying different amines encountered in PET tracers.

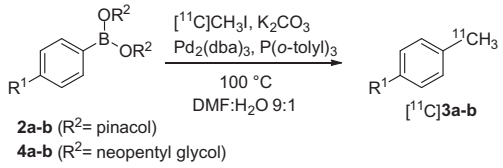
**Table 1**
Effect of different Pd-systems on the RCY[a]



| Entry | Pd-catalyst | RCY (%) |
|---|---|---|
| 1 | $Pd(PPh_3)_4$ | 9 |
| 2 | $Pd(PPh_3)_2Cl_2$ | 0 |
| 3 | $Pd(dppf)Cl_2$ | 0 |
| 4 | $Pd_2(dba)_3$ + P(*o*-tolyl)$_3$ | 49 |

[a] Reaction was carried out with 40 equiv of boronic ester, 1 equiv of Pd-catalyst, 2 equiv of ligand, and 2 equiv of base.

**Table 2**
Impact of the ester species on the RCY[a]



| Entry | $R^1$ | $R^2$ | (RCY) (%) |
|---|---|---|---|
| 1 | H | pinacol | 71 |
| 2 | H | neopentyl glycol | 72 |
| 3 | $N(CH_3)_2$ | pinacol | 59 |
| 4 | $N(CH_3)_2$ | neopentyl glycol | 58 |

[a] See Table 1 for the reaction conditions.

carbonyl groups or methyl groups.[5] Additionally, it remarks that the insertion of [$^{11}$C]methyl groups has received no further attention, and a literature search only revealed two separate investigations on this subject. The Suzuki reaction has been investigated by Hostetler et al.[6] and Doi et al.[7] using either microwave or conventional heating. Previously the Suzuki reaction has been used to label [ω-$^{11}$C]palmitic acid[2] and [$^{11}$C]dehydropravastatin.[3] The applicability toward amine-containing compounds is still

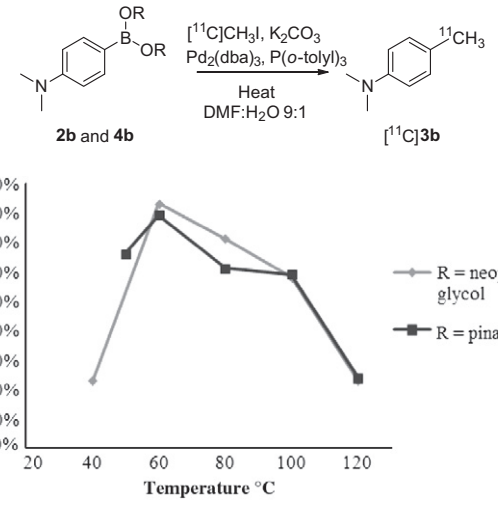


**Figure 4.** Impact of the reaction temperature on the RCY.

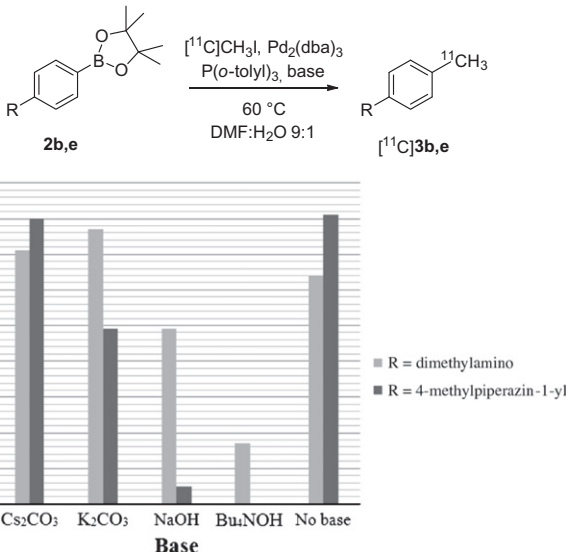


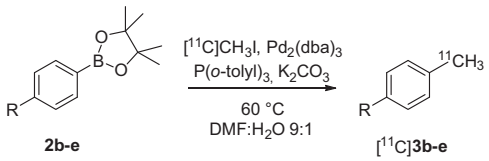
**Figure 5.** Impact of base on the RCY.

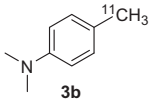
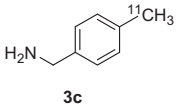
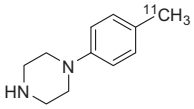
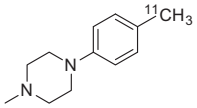
unknown and competing alkylation of the nitrogen could, in principle, be detrimental, as [$^{11}$C]$CH_3$I is known to react readily with amines. The possibility of applying the Suzuki reaction to these compounds is of great interest as many biologically active compounds contain amines.

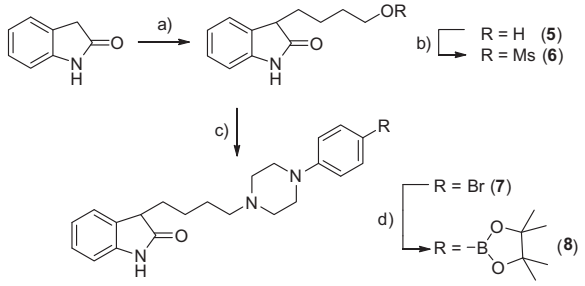
An example is the (phenylpiperazinyl-butyl)oxindoles developed by Volk et al. as selective 5-HT$_7$ antagonists.[8] Recently, we developed a promising compound within this chemical class, CIMBI-712, see Figure 1.[9] Its selectivity profile makes it a prime candidate for PET applications, ideally setup to be labeled via the Suzuki reaction of the corresponding aryl boronic derivative.

As Hostetler et al.[6] and Doi et al.[7] reported, the reaction between an aryl boronic derivative and [$^{11}$C]$CH_3$I is a stepwise process, see Figure 2: first the oxidative addition, then the transmetallation, and finally reductive elimination. Thus, the palladium-carbon-11-complex can be formed quantitatively before the aryl boronic precursor is added. Thus, $^{11}$C-Suzuki reactions can be thought of as palladium-mediated rather than catalyzed as the Pd-catalyst is used in large excess compared to [$^{11}$C]$CH_3$I. This led us to hypothesize that *N*-$^{11}$C-methylation of amines should only be

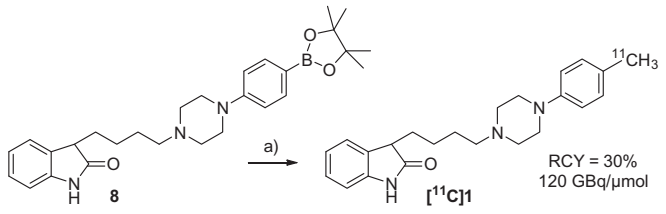
**Table 3**
Comparison of the impact of conventional heating and microwave irradiation on the RCY




| Entry | Product | RCY (%) conventional heating | RCY (%) MW heating |
|---|---|---|---|
| 1 |  **3b** | 77 | 54 |
| 2 |  **3c** | 82 | 5 |
| 3 |  **3d** | 64 | 77 |
| 4 |  **3e** | 49 | 86 |




**Scheme 1.** Reagents and conditions: (a) 1,4-butanediol, Raney-Nickel, 200 °C, 12 h, 70%; (b) $MeSO_2Cl$, $Et_3N$, THF, −78 °C to rt, 2 h; (c) 1-(4-bromophenyl)piperazine, $Na_2CO_3$, 130 °C, 55%; (d) bis(pinacolato)diboron, Pd(dppf)$Cl_2$, KOAc, 1,4-dioxane, 100 °C, 12 h, 54%.




**Scheme 2.** Radiosynthesis of [$^{11}$C]CIMBI-712. Reagents and conditions: (a) [$^{11}$C]$CH_3I$, $K_2CO_3$, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, 60 °C, DMF:$H_2O$ (v:v 9:1).

observed to a minor degree. Therefore, the aim of this study was to develop a procedure in which compounds containing unprotected amines could be labeled via the Suzuki reaction, and eventually apply this procedure to the labeling of CIMBI-712.

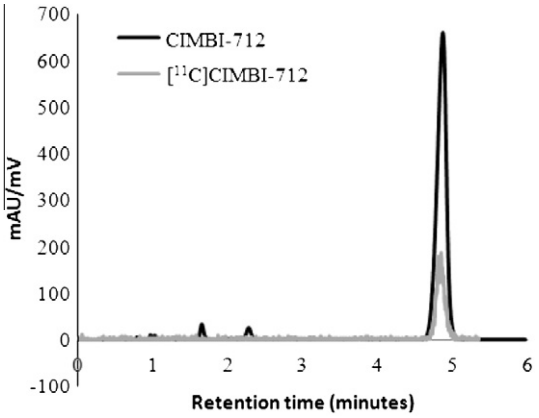



**Figure 6.** HPLC chromatograms of [$^{11}$C]CIMBI-712 and CIMBI-712.

Primary, secondary, and tertiary amines are commonly observed moieties in various PET tracers. Therefore, the possibility to label model compounds bearing such motifs was investigated, see Figure 3. Reference compounds and precursors were either purchased or synthesized using standard procedures, see Supplementary data.

In general, the choice of the palladium-catalyst (Pd-ligand) affects the chemical yields quite dramatically.[10] Therefore, the impact on radiochemical yields (RCY) of four different Pd-ligand systems, was tested (Table 1). In accordance with the findings of Doi et al.,[7] $Pd_2(dba)_3$ combined with P(*o*-tolyl)$_3$ was found to be the most efficient Pd-ligand system (Table 1).

The reactivity of the organoboron species of the precursors also influences the transmetallation in Suzuki couplings. Therefore, two different ester moieties were tested. The neopentyl and corresponding pinacol ester precursors displayed no impact on the RCY (Table 2).

Optimization of the reaction temperature was carried out using 4-(dimethylamino)phenylboronic esters. A range of temperatures was set from 40–120 °C for the neopentyl glycol based ester and 50–120 °C for the pinacol based ester (conditions shown in Table 1). The labeling of both compounds was highly affected by the reaction temperature. The RCY increased until 60 °C and decreased afterward for both compounds (Fig. 4). This is possibly due to the decomposition of $PdIL_2$[11] $CH_3$.

Furthermore, the Suzuki reaction is dependent on a base and therefore, the effect of the utilized base was investigated. $Bu_4NOH$, NaOH, $K_2CO_3$, $Cs_2CO_3$, and the absence of a base were all tested (conditions shown in Table 1). The RCYs varied from 17–77%. Strong bases showed the lowest yields. Surprisingly, the radiosynthesis without an additional base resulted in rather high RCYs of 64% and 81%, respectively. This demonstrates that amine-containing compounds can provide suitably basic conditions for $^{11}$C-Suzuki reactions. However, $Cs_2CO_3$ and $K_2CO_3$ provided the highest yields in our set-up and are thus preferable (Fig. 5).

To summarize, the standard conditions for $^{11}$C-Suzuki cross-couplings are as follows: $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ (1:2) in DMF is added to the trapped [$^{11}$C]MeI and stirred at 60 °C for 2 minutes. The aryl boronic ester and base are then added and the mixture is heated at 60 °C for 5 minutes (see supporting information for full details). Using these conditions *p*-[$^{11}$C]tolylmethanamine ([$^{11}$C]**3c**), 1-(*p*-[$^{11}$C]tolyl)piperazine ([$^{11}$C]**3d**), and 1-methyl-4-(*p*-[$^{11}$C]tolyl)piperazine ([$^{11}$C]**3e**) were labeled starting from their respective precursors **2c–e** with RCYs ranging from 49–82%.

Hostetler et al. demonstrated the use of microwave (MW) irradiation as a way of increasing the RCYs in $^{11}$C-Suzuki reactions.[6]

Therefore, we applied MW conditions for labeling compounds **3b–e**. Instead of 5 minute conventional heating, 3 minutes of MW heating were applied. Changes in the RCY were variable. [$^{11}$C]**3d** and [$^{11}$C]**3e** showed moderately increased RCYs, whereas reduced RCYs for [$^{11}$C]**3c** and [$^{11}$C]**3b** were observed (Table 3).

CuI has previously been used to increase yields of Suzuki reactions.[11] As such [$^{11}$C]**3c** and [$^{11}$C]**3e** were obtained using CuI in 1:1 ratio with the respective boronic ester, but without improved RCYs.

We then utilized the protocol to prepare CIMBI-712, a potential 5-HT$_7$ PET tracer, see Figure 1.

The precursor was prepared via a four-step synthesis starting from oxindole (Scheme 1). 3-(4-Hydroxybutyl)-indolin-2-one (**5**) was formed by a Raney-Nickel catalyzed reaction between oxindole and 1,4-butanediol.[8] The resulting alcohol was then converted into the corresponding mesylate **6**[8] and reacted with 1-(4-bromophenyl)piperazine to give 3-{4-[4-(4-bromophenyl)piperazin-1-yl]butyl}indolin-2-one (**7**). Finally, the boronic ester **8** was formed via Miyaura borylation.

Labeling of **8** via the devised standard method (Scheme 2) followed by preparative HPLC purification (Fig. 6) yielded the labeled compound [$^{11}$C]**1** with a radiochemical purity $\geqslant$98% in 30% RCY at the end of synthesis, with a typical specific activity of 120 GBq/μmol. Labeling using $Cs_2CO_3$ was also attempted but was unsuccessful. We are currently evaluating CIMBI-712 as a PET tracer, and the results will be reported elsewhere.

In conclusion, a set of standard conditions for $^{11}$C-labeling via the Suzuki reaction has been identified. Using these conditions it was possible to label compounds containing primary, secondary, and tertiary amines without competing alkylation at these amino groups. Finally, these conditions were used to label [$^{11}$C]CIMBI-712, a potential new 5-HT$_7$ PET tracer.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.001.

## References and notes

1. Allard, M.; Fouquet, E.; James, D.; Szlosek-Pinaud, M. *Curr. Med. Chem.* **2008**, *15*, 235–277.
2. Hostetler, E. D.; Fallis, S.; McCarthy, T. J.; Welch, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1998**, *63*, 1348–1351.
3. Ijuin, R.; Takashima, T.; Watanabe, Y.; Sugiyama, Y.; Suzuki, M. *Bioorg. Med. Chem.* **2012**, *20*, 3703–3709.
4. Chang, R. Physical Chemistry for the Chemical and Biological Sciences; University Science Books, 2000.
5. Pretze, M.; Grosse-Gehling, P.; Mamat, C. *Molecules* **2011**, *16*, 1129–1165.
6. Hostetler, E. D.; Terry, G. E.; Burns, H. D. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 629–634.
7. Doi, H.; Ban, I.; Nonoyama, A.; Sumi, K.; Kuang, C.; Hosoya, T.; Tsukada, H.; Suzuki, M. *Chemistry* **2009**, *15*, 4165–4171.
8. Volk, B.; Barkoczy, J.; Hegedus, E.; Udvari, S.; Gacsalyi, I.; Mezei, T.; Pallagi, K.; Kompagne, H.; Levay, G.; Egyed, A.; Harsing, L. G.; Spedding, M.; Simig, G. *J. Med. Chem.* **2008**, *51*, 2522–2532.
9. Herth, M.; Volk, B.; Pallagi, K.; Bech, L.; Antoni, F.; Knudsen, G. M.; Kristensen, J. L. *ACS Chem. Neurosci.* **2012**. http://dx.doi.org/10.1021/cn3001137.
10. Nguyen, H. N.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
11. Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345–347.