Straightforward synthesis of PET tracer precursors used for the early diagnosis of Alzheimer's disease through Suzuki-Miyaura cross-coupling reactions

Maité SYLLA-IYARRETA VEITIA, Guillaume BORT and Clotilde FERROUD

Laboratoire de Transformations Chimiques et Pharmaceutiques, ERL CNRS 3193, Conservatoire national des arts et métiers, 2 rue Conté, 75003 Paris maite.sylla@cnam.fr

INTRODUCTION

In the last 20 years, the research on Alzheimer's disease (AD), focused on the development of different therapeutic approaches and diagnostic techniques to detect the pathology at an early stage. The "amyloid hypothesis" suggest that Aβ plaques appear in the brain 10 to 20 years before the clinical symptoms of AD. Various molecular imaging radiolabelled tracers have been reported for the early diagnosis of AD. Among them, the **Pittsburgh Compound-B 1** ([^{11}C]PIB, Figure 1), a carbon-11 radionuclide marker of Aβ plaques, is currently the most widely used positron emission tomography (PET) tracers in preclinical and clinical trials for the diagnosis of AD.[1-3]

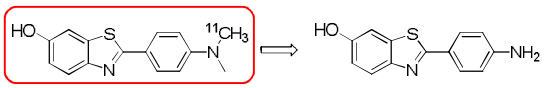
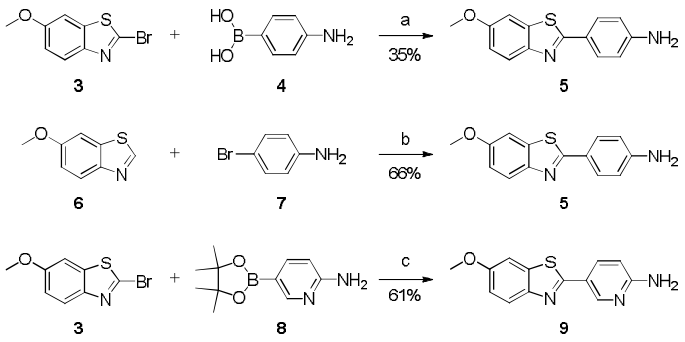


Figure 1 Chemical structures of [^{11}C]PIB **1** used for the *in vivo* imaging of AD and the precursor **2** used for the radiosynthesis.

The commonly used method for the synthesis of the precursor **2** of [^{11}C]PIB requires the protection of the phenolic function or the use of a nitro group as precursor of the amine function. It involves a five-step synthesis with quite low overall yields ranging from 24 to 39% involving a Jacobson's oxidative cyclization of substituted thiobenzanilides.

Few improved syntheses of substituted 2-arylbenzothiazoles which could be used as precursors for the radiosynthesis of [^{11}C]PIB are reported in the literature (Scheme 1). [4-5]



Scheme 1 a: $Pd_2(dba)_3.CH_2Cl_2$, K_2CO_3, DME-water, 100 °C, 6 h. b: $Pd(OAc)_2$, P(*t*-Bu_3, Cs_2CO_3, CuBr, DMF, 150 °C, 1 h. c: $Pd(dppf)Cl_2.CH_2Cl_2$, K_2CO_3, DMF, 80 °C, 2 h.

[1] Huang, Y.; Mucke, L. *Cell* **2012**, *148*, 1204; [2] Vallabhajosula, S. *Semin. Nucl. Med.* **2011**, *41*, 283; [3] Svedberg, M. M.; Rahman, O.; Hall, H. *Nucl. Med. Biol.* **2012**, *39*, 484. [4] Majo, V. J. *et al Tetrahedron Lett.* **2003**, *44*, 8535-8537; [5] Alagille, D. *et al. Tetrahedron Lett.* **2005**, *46*, 1349; [6] Johnson, A. E *et al . J. Neurochem.* **2009**, *108*, 1177.

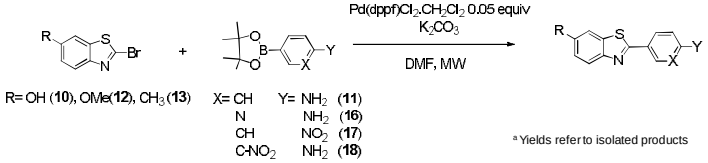
RESULTS

We developed a direct synthesis of the precursor **2** of [^{11}C]PIB from commercially available reagents, by a Suzuki-Miyaura coupling reaction. The one-step cross-coupling implied the use of the unprotected 2-bromo-6-hydroxybenzothiazole **10** and 4-aminophenylboronic acid pinacol ester **11** [6]

Scheme 2 Suzuki-Miyaura coupling reaction conditions leading to the precursor **2** of the radiochemical tracer [^{11}C]PIB **1**.

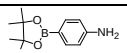
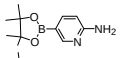
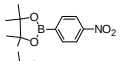
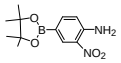
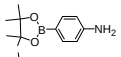
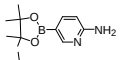
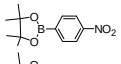
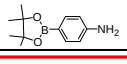
These Suzuki-Miyaura conditions were successfully extended to the synthesis of several 2-arylbenzothiazole and 2-pyridinylbenzothiazole derivatives.

Considering the results obtained under thermal conditions, the Suzuki cross-coupling reactions were undertaken under controlled microwave activation.

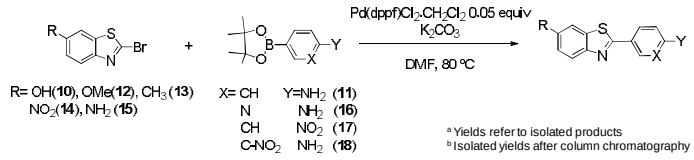


R= OH (**10**), OMe(**12**), CH_3(**13**) X= CH Y= NH_2 (**11**); N NH_2 (**16**); CH NO_2 (**17**); C-NO_2 NH_2 (**18**)

[a] Yields refer to isolated products

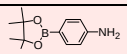
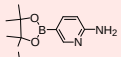
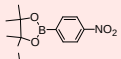
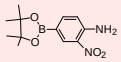
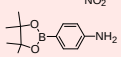
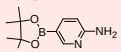
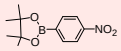
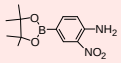
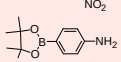
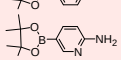
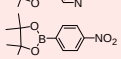
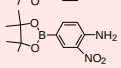
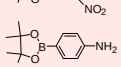
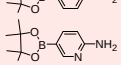
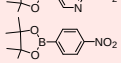
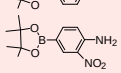
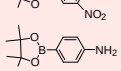
Entry	Aryl halide	Boronic acid pinacol ester	Conditions	Product	Yield [a] (%)	HPLC purity (%)
1	**10** (OH)		10W, 60°C, 15 min	**2**	93	94
2	**10**		10W, 60°C, 15 min	**19**	92	99
3	**10**		10W, 60°C, 15 min	**20**	87	96
4	**10**		10W, 60°C, 15 min	**21**	85	96
5	**12** (OMe)		50W, 60°C, 15 min	**5**	98	77
6	**12**		50W, 150°C, 15 min	**9**	68	88
7	**12**		50W, 60°C, 15 min	**22**	96	91
8	**13** (Me)		50W, 80°C, 15 min	**24**	84	81

[6] Bort G. , Sylla Iyarreta-Veitia M. , Ferroud C. *Tetrahedron* **2013**, *69*, 7345-7353



R= OH(**10**), OMe(**12**), CH_3(**13**) NO_2(**14**), NH_2 (**15**) X= CH Y=NH_2 (**11**); N NH_2 (**16**); CH NO_2 (**17**); C-NO_2 NH_2 (**18**)

[a] Yields refer to isolated products
[b] Isolated yields after column chromatography

Entry	Aryl halide	Boronic acid pinacol ester	Time (h)	Product	Yield (%)[a]	HPLC purity (%)
1	**10** (OH)		1.5	**2**	94	92
2	**10**		1.5	**19**	95	99
3	**10**		1.5	**20**	70	99
4	**10**		1.5	**21**	98	99
5	**12** (OMe)		3	**5**	97	89
6	**12**		6	**9**	98	96
7	**12**		1.5	**22**	78	95
8	**12**		2	**23**	99	95
9	**13** (Me)		1.5	**24**	99	87
10	**13**		12	**25**	82	93
11	**13**		5	**26**	64	99
12	**13**		1	**27**	97	92
13	**14** (NO_2)		2	**28**	74	64
14	**14**		2	**29**	13[b]	62
15	**14**		1	**30**	60[b]	99
16	**14**		1	**31**	78	87
17	**15** (NH_2)		4	**32**	70	95

CONCLUSIONS

- We have developed an efficient and rapid synthesis of the precursor of the widely used radionuclide [^{11}C]PIB, a PET tracer employed for the *in vivo* imaging of AD.
- The high yields (68-98%) and short reaction times provided by the microwave-assisted Suzuki-Miyaura cross-coupling are decisive advantages.
- The unprotected phenol and amine functions are well tolerated by these coupling conditions, which makes this synthesis a very straightforward route to get the precursor of the [^{11}C]PIB and other derivatives.

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