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One-step synthesis of 2-arylbenzothiazole ('BTA') and -benzoxazole precursors for in vivo imaging of β-amyloid plaques

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Abstract—We report the simple and efficient synthesis of 2-arylbenzothiazoles ('BTA') and 2-arylbenzoxazoles by direct coupling of benzothiazoles or benzoxazoles with aryl bromides. This method permits direct one-step access to precursors of radiolabeled BTA-1 and BTA-2 and their 6-methoxy analogues, used for in vivo imaging of β-amyloid plaques with positron emission tomography (PET).

Alzheimer's disease (AD) is a member of a heterogeneous family of diseases referred to as amyloidosis, including type II diabetes, variant Creutzfeldt-Jakob disease, painful joints associated with long-term hemodialysis, and rare cases of hereditary insomnia.[1] In all of these disorders, proteins that are normally soluble are converted into insoluble aggregates that can form intractable and frequently toxic deposits in skeletal muscular tissue and in organs such as heart, liver, and brain.[2] In vivo biomarkers of amyloid deposits in the brain would be useful to identify and follow individuals at risk for AD and to assist the evaluation of new anti-amyloid therapies under development.[3,4] A large number of radiolabeled compounds have been investigated as radioactive amyloid agents[5–11] for imaging amyloid plaque by positron emission tomography (PET). The 2-arylbenzothiazole (BTA) derivatives represent one of the most promising families.[8,12] The reported synthesis of 2-arylbenzothiazoles have commonly used one of two methods: condensation of *ortho*-amino thiophenols with substituted aldehydes, carboxylic acids, acyl chlorides, or nitriles;[12] or Jacobson's cyclization of thiobenzanilides mediated by potassium ferricyanide.[12] Yields from these methods are relatively low and the condensation method also has the limitation of a readily oxidizable sulfur group. Recently, Majo et al.[13] reported Suzuki cross-coupling between 2-bromobenzothiazoles and boronic acids or esters however, the moderate to low yield and scarcity of commercially available boronic acids/esters limit the use of this reaction despite the remarkable advantage of a one-step synthesis. The same year, Yokooji et al.[14] reported the direct arylation of thiazoles with aryl bromides in the presence of $Pd(OAc)_2/P(t\text{-}Bu)_3$ and they extended this reaction to a very small number of benzothiazoles. In this letter, we describe extending the potential application of the direct coupling between benzothiazole **1** or 6-methoxybenzothiazole **2** and aryl bromides with the objective of a one-step synthesis of precursors to radiotracers for imaging amyloid plaques in vivo.

Benzothiazole **1** or 6-methoxybenzothiazole **2** was reacted at 150 °C in a sealed tube with aryl bromide in DMF in the presence of $Pd(OAc)_2$, Cs_2CO_3, and CuBr with $P(t\text{-}Bu)_3$ as ligand[19] yielding after 1–3 h of reaction the desired 2-arylbenzothiazole in 66–84% yield (Table 1). In contrast with the Suzuki cross-coupling, this method permitted direct synthesis in good yield of 2-(2,4-dimethoxyphenyl)benzothiazole **5f** and its 6-methoxy analogue **5m**. This reaction allows us to obtain in good yield and in one-step (no protection of the nitrogen required) the BTA-1 and BTA-2 precursors (**5b** and **5c**) as well as their 6-methoxy analogues (**5h** and **5i**). Reaction of the 4-bromo-*N*-Boc protected aniline led to the deprotected compound by thermal cleavage of the *N*-Boc group as the major product. To conclude this work

Keywords: 2-Arylbenzothiazole; BTA; 2-Arylbenzoxazole; Amyloid plaques; Palladium; Direct coupling.
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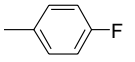
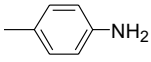
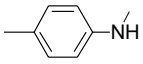
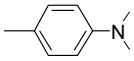
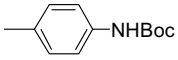
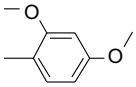
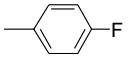
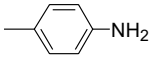
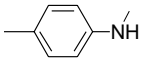
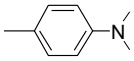
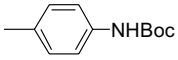
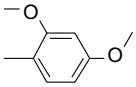
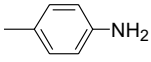
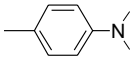
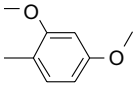
Table 1. Direct coupling of **1**–**3** with aryl bromides

Benzazole	Aryl bromide	Product	Yield[a]	Suzuki yield[b]
1		**5a**	79	48
1		**5b**[c]	68	—
1		**5c**[c] BAT-1	71	—
1		**5d** BAT-2	78	—
1		**5b** (NH_2) **5e** (NHBoc)	63 8	—
1		**5f**	84	0
2		**5g**	71	54
2		**5h**[c]	66	35
2		**5i**[c] 6-OMe-BAT-1	78	—
2		**5j** 6-OMe-BAT-2	78	—
2		**5h** (NH_2) **5k** (NHBoc)	68 10	— 55
2		**5m**	77	—
3		**5n**[c]	70	
3		**5o**	72	
3		**5p**	64	

The reaction was carried out using $Pd(OAc)_2$-P(*t*-Bu)$_3$ (0.05 and 0.1 equiv to benzothio- or benzoxazole), Cs_2CO_3 (1 equiv) and CuBr (0.2 equiv) in DMF, sealed tube at 150 °C for 1 h unless otherwise noted.[19]

[a] Yield refers to pure isolated product.

[b] Previously published yield shown here for comparison.[13]

[c] Reaction time was extended to 3 h.

we investigated the possible application of this methodology to the synthesis of 2-arylbenzoxazoles, even though the synthesis of such compounds is well described in the literature by other synthetic means (oxidative cyclization of phenolic Schiff's bases[15,16] or coupling of 2-aminophenols with carboxylic acids[17,18]). In the same manner as benzothiazole, benzoxazole **3** react with aryl bromide to provide after 1 h at 150 °C the desired 2-arylbenzoxazole (Table 1).

In summary, we report a simple and efficient synthesis of 2-arylbenzothiazoles and 2-arylbenzoxazoles using a

direct palladium-catalyzed arylation of benzothiazoles or benzoxazoles with aryl bromides. This methodology permits the direct synthesis of precursors to radiotracers for the imaging of amyloid deposit in vivo and allows the development of a large library of 2-aryl-benzothiazoles.

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19. Typical experimental procedure: A suspension of benzothiazole or benzoxazole (1.21 mmol, 1 equiv), aryl bromide (1.45 mmol, 1.2 equiv), dry Cs_2CO_3 (1.21 mmol, 1 equiv), CuBr (0.24 mmol, 0.2 equiv), $Pd(OAc)_2$ (0.06 mmol, 0.05 equiv) and P(*t*-Bu)$_3$ (0.12 mmol, 0.1 equiv) in DMF (10 mL) was heated under argon with stirring in a sealed tube at 150 °C for 1–3 h (Table 1). After cooling, the reaction mixture was diluted with EtOAc and washed several times with H_2O, dried over Na_2SO_4, concentrated under vacuum, and flash column chromatographed (silica gel/hexane:EtOAc, 98:2 to 80:20 or CH_2Cl_2/hexane/EtOAc, 5:4:1).