Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8535–8537

TETRAHEDRON LETTERS

An efficient palladium catalyzed synthesis of 2-arylbenzothiazoles

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Received 20 August 2003; revised 17 September 2003; accepted 17 September 2003

Abstract—A novel and convergent palladium catalyzed synthesis of 2-arylbenzothiazoles has been investigated. The key step in the synthesis is a Suzuki biaryl coupling of 2-bromobenzothiazole with aryl boronic acids to provide a variety of 2-arylbenzothiazole derivatives in good yield. The synthetic utility of this methodology is demonstrated by the synthesis of 2-(4-aminophenyl)-6-methoxybenzothiazole, a PET probe precursor for the in vivo imaging of Alzheimer's disease.

2-Arylbenzothiazoles are an important class of compounds owing to their potent utility as imaging agents for β-amyloid, antitumor agents, antituberculotics, antiparasitics, calcium channel antagonists, chemiluminescent agents and also as photosensitizers.[1–7] The reported syntheses of 2-arylbenzothiazoles involve the condensation of 2-aminobenzenethiol with 4-substituted phenyl derivatives of nitrile, aldehyde, acid, acid chlorides or esters and by the use of Jacobson's cyclization of thiobenzanilides.[8–10] Other general methods include microwave mediated reaction of *o*-aminothiophenol with β-chlorocinnamaldehydes, reaction of dibenzyl disulfides with *o*-aminothiophenol, reduction of *o*,*o*′-dinitrodiphenyl disulfide, reaction of S-aryl thiobenzoate with arylhaloamines, from 1,2,3-benzodithiazole-2-oxides, radical cyclization of benzyne intermediates and Grignard reactions of arylisothiocyanates.[11–16] However, most of the above methods require multistep synthesis and therefore, we have sought to develop a convergent strategy for the synthesis of 2-arylbenzothiazoles. Our method utilizes a Suzuki cross coupling of the common intermediates 2-bromobenzothiazole (**1**) and 2-bromo-6-methoxybenzothiazole (**2**) with various aryl boronic acids/ esters as the key step (Table 1). Since a wide variety of aryl boronic acids are commercially available, or can be easily prepared from the corresponding bromides,[17] this methodology would offer a higher degree of flexibility with regard to functional groups that can be placed on the 2-aryl moiety, thereby providing a better understanding of the structure activity relationship (SAR) of the target compounds.

Benzothiazole was brominated using *n*BuLi and CBr_4 to provide corresponding 2-bromo benzothazole (**1**) in 60% yield.[18] 2-bromo-6-methoxybenzothiazole (**2**) (65%) was synthesized by Sandmayer reaction of 2-amino-6-methoxybenzothiazole by heating with isoamyl nitrite and $CuBr_2$ in presence of PEG.[19] The biaryl coupling was initially attempted with **1** and phenylboronic acid under the optimized reaction condition using $Pd_2(dba)_3$ in DME-water with aqueous K_2CO_3 to provide 2-phenylbenzothiazole (**4a**) in 50% yield.[20] Under identical conditions, coupling of **1** and **2** with 4-acetylboronic acid, 4-aminophenylboronic ester, Boc protected 4-aminophenylboronic ester, 3-thiopheneboronic acid and 2-napthaleneboronic acid provided the corresponding 2-arylbenzothiazole derivatives in moderate to good yield (Table 1). Benzothiazole derivative **4i** and its demethylated analogue are positron emission tomography (PET) probe precursors for the in vivo quantification of β-amyloid.[1,21] However, our attempts to couple 2,4-dimethoxyphenylboronic acid with **1** did not afford the desired product probably due to steric hindrance, dehydroboronation of the boronic acid and recovery of **1** was the major process observed under the optimized reaction conditions.

In summary, we have utilized a novel chemistry of 2-bromobenzothiazoles for the facile synthesis of 2-arylbenzothiazoles using Suzuki biaryl coupling. The synthetic utility of these reactions are demonstrated by the one step synthesis of 2-amino-6-hydroxybenzothazole, a potent PET probe precursor for the in vivo imaging of β-amyloid. Future work will be undertaken to develop a combinatorial version of this synthesis for the SAR of 2-arylbenzothiazoles for various pharmaceutical applications.

Keywords: boronic acid; benzothiazole; Suzuki coupling; palladium.
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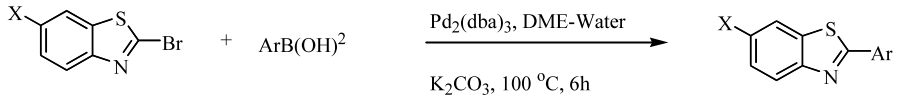
doi:10.1016/j.tetlet.2003.09.138

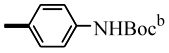
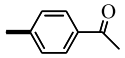
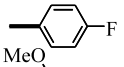
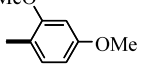
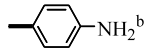
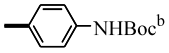
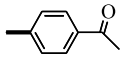
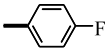
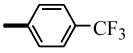
Table 1. Biaryl coupling of 2-bromobenzothazole (**1**) and 2-bromo-6-methoxy benzothiazole (**2**) with various boronic acids and esters



X= H, **1**
X = OMe, **2**

3a-i

4a-n

S. No	Aryl halide	Boronic acid	Product	Yield (%)[a]
1	**1**		**4a**	51
2	**1**	 NHBoc[b]	**4b**	40
3	**1**	 O	**4c**	72
4	**1**	 F	**4d**	48
5	**1**	MeO  OMe	**4e**	---
6	**1**	 S	**4f**	74
7	**1**		**4g**	55
8	**1**	 NH_2[b]	**4h**	35
9	**2**	 NHBoc[b]	**4i**	55
10	**2**		**4j**	58
11	**2**	 O	**4k**	63
12	**2**	 F	**4l**	54
13	**2**	 CF_3	**4m**	68
14	**2**	 S	**4n**	62

a. The yield represent the isolated yields of the product after column chromatography based on aryl bromide.

b. Pinacolate ester of the corresponding boronic acid was used for the coupling.

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20. *Typical experimental procedure for the Suzuki coupling*: A suspension of 2-bromobenzothiazole (86 mg, 0.4 mmol), thiophene-3-boronic acid (67 mg, 0.52 mmol) and $Pd_2(dba)_3$ (18 mg, 5 mol%) in 1,2-dimethoxyethane (1 mL) was deaerated and stirred under argon. Deionized water (0.1 mL) and aqueous K_2CO_3 (2 M, 400 μL, 0.8 mmol) were added to the reaction mixture and heated at 100°C for 6 h. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, passed through a short pad of celite, concentrated under vacuum and column chromatographed (97:3 hexane: ethyl acetate) to yield 2-thiophene-3-yl-benzothiazole (**4f**) as a colorless solid (65 mg) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1 H, $J=8.2$ Hz), 8.02 (m, 1 H), 7.88 (1 H, d, $J=8.0$ Hz), 7.77 (1 H, d, $J=5.0$ Hz), 7.48 (t, 1 H, $J=8.0$ Hz), 7.44 (dd, 1 H, $J=3$, 5 Hz), 7.38 (t, 1 H, $J=8.0$ Hz); HRMS: calcd. for $C_{11}H_8NS_2$ (MH^+): 218.0098 found: 218.0108; mp 110°C (lit.[22] 111.5–112.5°C).
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