Tetrahedron 69 (2013) 2081–2086

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Site-selective Suzuki–Miyaura reactions of 2,6-dichlorobenzoxazole

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ARTICLE INFO

Article history:
Received 1 August 2012
Received in revised form 25 October 2012
Accepted 6 November 2012
Available online 13 November 2012

Keywords:
Benzoxazole
Site-selectivity
Palladium
Catalysis
Suzuki–Miyaura reaction

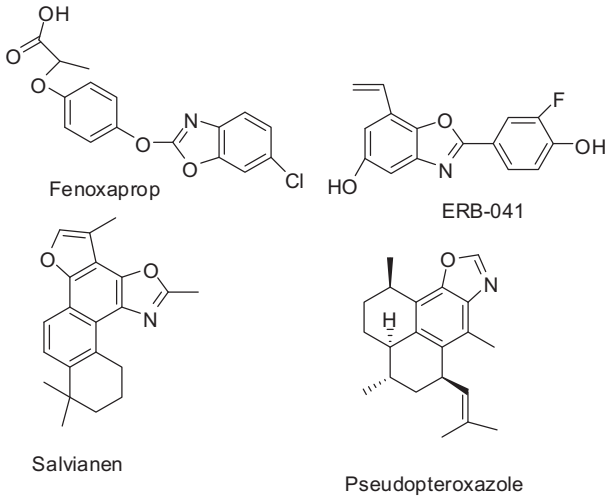
ABSTRACT

Suzuki–Miyaura reactions of 2,6-dichlorobenzoxazole provide a convenient access to arylated benzoxazoles. The reactions proceed with excellent site-selectivity in favour of position 2, due to electronic reasons.

1. Introduction

The benzoxazole moiety is an important structural motif in many biologically active natural products and pharmaceutical compounds. Examples include pseudopteroxazole and salvianen (Scheme 1).[1,2] Benzoxazoles also represent important molecules in medicinal chemistry.[3] Previous reports revealed that substituted benzoxazoles, such as the herbicide fenoxaprop, possess diverse chemotherapeutic activities, including antibiotic,[4] antimicrobial,[5–8] antiviral[9] and antitumour activities.[10,11] The 2-aryl-6-hydroxybenzoxazole ERB-041 represents an oestrogen receptor-β agonist.[12]

Traditional methods for the synthesis of substituted benzoxazoles include the oxidation of aromatic amines with persulfate and condensation of *ortho*-aminophenols with aldehydes.[13,14] Recently, general methods for the copper-catalyzed intramolecular C–O coupling reaction of 2-haloanilides were reported.[15] Nagasawa et al. reported that 2-arylbenzoxazoles and 2,6-diarylbenzoxazoles can be prepared by copper-catalyzed intramolecular oxidative C–O coupling of benzanilides.[16] Palladium catalyzed multi-component reactions of aryl halides, isocyanides and aminoalcohols have also been used for the synthesis of benzoxazoles.[17]



Scheme 1. Benzoxazoles in biologically active compounds.

In recent years, site-selective Pd catalyzed cross-coupling reactions have attracted considerable attention.[18,19] Herein, we report a new approach to arylated benzoxazoles by site-selective Suzuki–Miyaura cross-coupling reactions of commercially available 2,6-dichlorobenzoxazole (**1**) with arylboronic acids.

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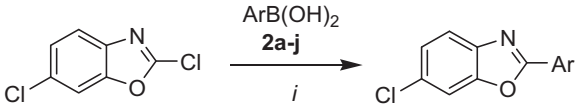
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.021

The Suzuki–Miayura reaction of commercially available 2,6-dichlorobenzoxazole (**1**) with 1.2 equiv of arylboronic acids **2a**–**j** afforded the 2-aryl-6-chlorobenzoxazoles **3a**–**j** in 72–90% yields with very good site-selectivity (Scheme 2, Table 1). The reactions



Scheme 2. Synthesis of **3a**–**j**. Reagents and conditions: i, **1** (1.0 equiv), **2a**–**j** (1.2 equiv), $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (aqueous solution, 2 M), 1,4-dioxane, 80 °C, 6 h.

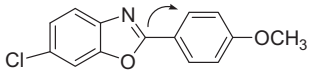
Table 1
Synthesis of **3a**–**j**

2,3	Ar	% (**3**)[a]
a	3,5-$Me_2C_6H_3$	90
b	4-EtC_6H_4	81
c	4-(MeO)C_6H_4	90
d	3-FC_6H_4	83
e	4-ClC_6H_4	88
f	Ph	90
g	2,3,4-$(MeO)_3C_6H_2$	80
h	3-MeC_6H_4	87
i	4-$^tBuC_6H_4$	72
j	4-$(F_3C)C_6H_4$	83

[a] Yields of isolated products.

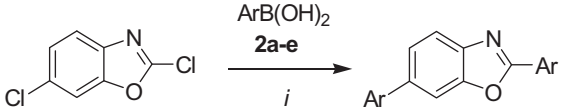
were carried out under standard conditions for Suzuki–Miyaura reactions: $Pd(PPh_3)_4$ (3.0 mol %) was employed as the catalyst and an aqueous solution of K_2CO_3 was used as the base (dioxane, 80 °C, 6 h). Very good yields were obtained for both electron rich and poor arylboronic acids. During the optimization, it proved to be important to carry out the reactions at 80 °C. A higher temperature resulted in the formation of significant amounts of diarylated products.

The structure of product **3c** was unambiguously confirmed by HMBC correlation between carbon atom C-2 of the benzoxazole moiety with the *ortho* hydrogens of the attached *p*-methoxyphenyl group (Scheme 3).



Scheme 3. Important HMBC correlation of compound **3c**.

The Suzuki–Miyaura reaction of **1** with 2.2 equiv of various arylboronic acids **2a**–**e** afforded the 2,6-diarylbenzoxazoles **4a**–**e** in 75–89% yields (Scheme 4, Table 2). The reactions had to be carried out at a higher temperature (120 °C) as compared to the synthesis of products **3**. Very good yields were obtained for products derived from both electron rich and poor arylboronic acids.



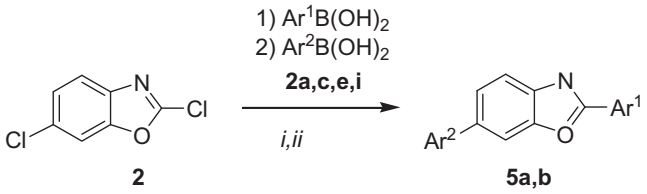
Scheme 4. Synthesis of **4a**–**e**. Reagents and conditions: i, **1** (1.0 equiv), **2a**–**e** (2.2 equiv), $Pd(PPh_3)_4$ (26 mg, 6 mol %), K_2CO_3 (aqueous solution, 2 M), 1,4-dioxane, 120 °C, 8 h.

Table 2
Synthesis of **4a**–**e**

2	4	Ar	% (**4**)[a]
a	**a**	3,5-$Me_2C_6H_3$	89
b	**b**	4-EtC_6H_4	88
c	**c**	4-(MeO)C_6H_4	88
d	**d**	3-FC_6H_4	75
e	**e**	4-ClC_6H_4	75

[a] Yields of isolated products.

The one-pot reaction of **1** with two different arylboronic acids was next studied. The reaction of **1** with 1.2 equiv of an arylboronic acid and subsequent addition of a second arylboronic acid (1.2 equiv) afforded the 2,6-diarylbenzoxazoles **5a**,**b** containing two different aryl groups in good yields (Scheme 5, Table 3). During the optimization, it proved to be important to carry out the first step at 80 °C and the second step at 120 °C. It also proved to be important to add a fresh portion of catalyst together with the second arylboronic acid. The structure of **5b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[20]



Scheme 5. Synthesis of **5a**,**b**. Reagents and conditions: i, 1) **1** (1.0 equiv), $Ar^1B(OH)_2$ 1.2 equiv), $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (aqueous solution, 2 M), 1,4-dioxane, 80 °C, 6 h; 2) $Ar^2B(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (aqueous solution, 2 M), 120 °C, 8 h.

Table 3
Synthesis of **5a**,**b**

2	5	Ar^1	Ar^2	% (**5**)[a]
e,**a**	**a**	4-ClC_6H_4	3,5-$Me_2C_6H_3$	84
i,**c**	**b**	4-$^tBuC_6H_4$	4-(MeO)C_6H_4	72

[a] Yields of isolated products.

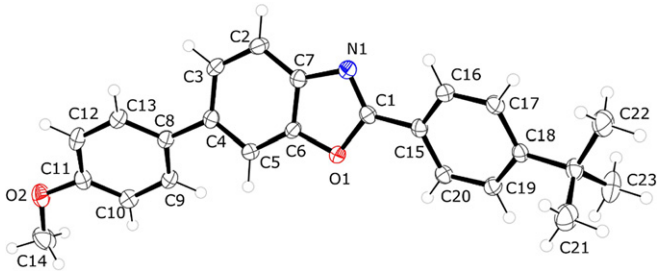


Fig. 1. Crystal structure of **5b**.

The site-selectivity in favour of position 2 can be explained by the fact that carbon C2 is more electron deficient than carbon C6 (Scheme 6). Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient position.[18,19]

We have reported a new approach to arylated benzoxazoles by site-selective Suzuki–Miyaura cross-coupling reactions of commercially available 2,6-dichlorobenzoxazole with arylboronic acids. The reactions proceed with excellent site-selectivity in favour of position C-2, which is more electron deficient than position C-6.