Synthesis of Highly Functionalized 2-(Substituted biphenyl) Benzimidzoles *Via* Suzuki-Miyaura Cross Coupling Reaction

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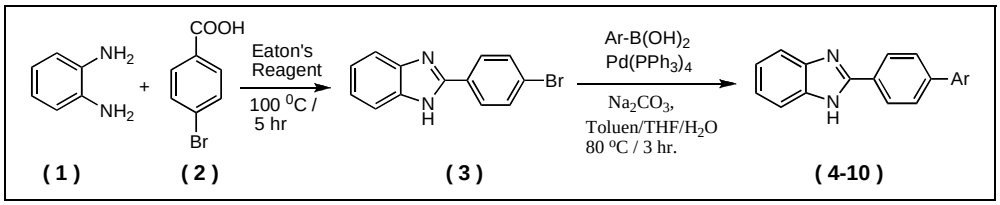

A facile and convenient method for the synthesis of highly functionalized 2-(substitutedbiphenyl) based benzimidazoles has been reported by the application of Suzuki-Miyaura cross coupling reaction.

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INTRODUCTION

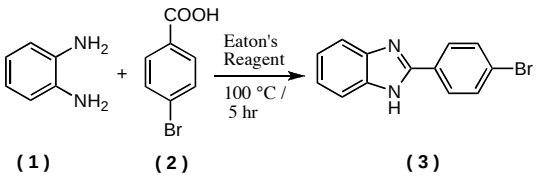
Benzimidazoles generally come under the group of broad spectrum anti-helmintic agents useful against veterinary parasites and also possess medicinal importance [1]. Further, its nucleus is also a constituent part in the naturally occurring Vitamin-B_{12} and its derivatives [2]. Benzimidazole moiety provides an interesting theme for the synthesis of various biologically active compounds [3] and the biological activities of the latter are very well documented as well [4]. Of the hundreds of derivatives tested, those therapeutically have useful modifications at 2- or 5-position of the benzimidazole ring system [5-8]. Some of them like thiabendazole, mebendazole and albendazole are widely used as anti-helmintic drugs [9]. In this communication, we wish to report our results towards the synthesis of some novel and functionalized 2-(substituted-biphenyl) based benzimidazoles by the utilization of Suzuki-Miyaura cross coupling reaction.

RESULTS AND DISCUSSION

We have been interested in the synthesis of 2-(substi-tutedbiphenyl) based benzimidazoles in connection with our on-going project on benzimidazole derivatives of potential biological activities [10]. Literature survey revealed that there are only a couple of methods available for the synthesis of 2-biphenylbenzimidazoles, the first one, by the condensation of *o*-phenylenediamine (OPDA) with 4-phenylbenzaldehyde to get the Schiff's base and oxidative cyclisation of the latter with $Cu(OAc)_2$ giving the title compounds [11]. Secondly, from the reaction of OPDA with polymer-esterified biaryl aldehydes, prepared from polymer bound aryl halides and formyl benzene boronic acids [12], where the required aldehyde was synthesized by the cross-coupling reaction of 4-Iodobenzoic acid with 4-formylbenzene-boronic acid. However, in case of the reaction on a solid support, one requires specifically different formyl boronic acids, which restricts the applicability of this method for generating libraries for biological screening. The third method is in three steps starting with Suzuki coupling of the haloaryl carbo-nitriles with formylboronic acids and coupling the latter with diamines to obatain the benzimidazoles [12b]. This is clear indication of the fact that there is no general and useful methodology for the synthesis of these title compounds. In recent times, Suzuki-Miyaura cross coupling reaction has gained wide acceptance as a very useful methodology for the synthesis various natural and non-natural products [13].

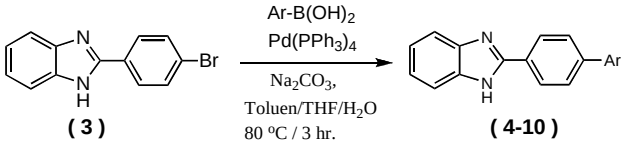
Previously, we have reported the synthesis of functionalized dibenzylglycine derivatives *via* Suzuki-Miyaura cross coupling reaction [14]. In continuation of our work on Suzuki-Miyaura cross coupling reactions, the present paper describes the application of the latter reaction to generate a convenient route for the synthesis of the title compounds. Hence, in this regard, OPDA (**1**) was reacted with 4-bromobenzoic acid (**2**) in the presence of Eaton's Reagent [15] (1:10 mixture of phosphorous pentoxide - methanesulfonic acid, an efficient and convenient alternative to PPA for cyclodehydration reactions) at 100 °C 5 hr, followed by a simple work up yielding the known 2-(4-bromophenyl)benzimidazole (**3**) [16], which was previously reported by the PPA mediated cyclisation of compound (**1**) with compound (**2**) (Scheme-1).

Scheme-1



The advantage with the use of Eaton's reagent in place of conventional dehydrating agent polyphosphoric acid (PPA) is that Eaton's reagent can be easily handled and since it is a mobile colorless liquid. Further, the excess reagent can be easily destroyed by simple addition of water to the reaction mixture or by an aqueous solution of sodium bicarbonate. Compound (**3**) was then treated with phenylboronic acid (Ar = Ph) under Suzuki-Miyaura cross coupling conditions to obtain the known 2-biphenylbenzimidazole (**4**)[12] in 78 % yield (**Scheme-2**). Similarly, the reaction of compound (**3**) was then extended with other substituted aryl boronic acids and the physical properties of the products (**5-10**) thus obtained are summarized in **Table-1**.

Scheme - 2



(3) (4-10)

In conclusion, we have demonstrated that highly functionalized 2-substitutedbiphenyl based benzimidazoles could be conveniently synthesized from 3 and aryl boronic acids *via* Suzuki-Miyaura cross-coupling reaction. The advantage of the present method is that starting compound 3 could be easily synthesized. The commercial availability of a wide variety of boronic acids eliminates the restriction of looking for only formyl boronic acids as in the existing method [12] makes this method a more attractive choice for the chemists working in this area. Moreover, compounds (5), (7), (8) and (9) provides access to further synthetic modifications for the dendritic cores, whose applicability is well known as hosts for molecular recognitions in biological systems.

The method described herein is useful to synthesize compounds with known pharmacophoric scaffolds, and hence is ideally suited for the generation of combinatorial libraries.

Table-1

Physical data for the synthesized compounds (**4 -10**).

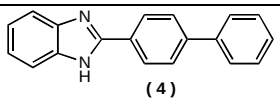
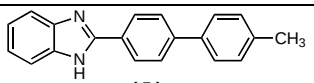
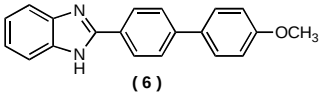
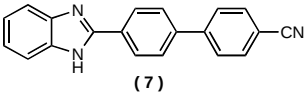
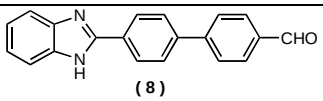
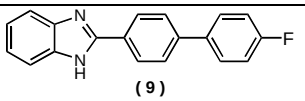
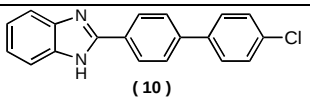
Sr. No.	Product	M.P (°C)	Yield (%)
1.	 (4)	296 -298 (Lit[12]- 296 -298)	78
2.	 (5)	280 -281	79
3.	 (6)	264 -266	81

Table 1 (continued)

Sr. No.	Product	M.P (°C)	Yield (%)
4.	 (7)	272 -274	78
5.	 (8)	269 -272	80
6.	 (9)	285 -289	78
7.	 (10)	297 -301	82

EXPERIMENTAL

Synthesis of 2-(Substitutedbiphenyl)-1*H*-benzimidazoles by Suzuki Coupling Reactions (General Procedure). To a solution of compound **4** (10 mm) in a mixture of toluene-THF mixture (1:1) was added aryl boronic acid (12 mm), anhydrous sodium carbonate (12 mm) and water (2 ml). The reaction mixture was then degassed for 20 min and the tris(triphenylphosphine) (10 mol%) was added and the reaction mixture was heated to 70-80 °C for several 3-4 h till the starting material disappears on tlc. The solvent from the reaction mixture was concentrated under vacuum, dichloromethane (20 ml) was added and the layers were separated, washed with water, brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude products, which were purified either by crystallization using appropriate solvent systems or by column chromatography.

2-(4'-*p*-Toluylphenyl)-1*H*-benzimidazole (5). This compound was obtained as an off-white solid (ethyl alcohol); ^{1}H nmr ($CDCl_3$-DMSO-d6): δ 1.77 (s, 3H), 6.57 (dd, *J* = 6.2 & 2.6Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 7.6Hz, 3H), 7.10 (d, *J* = 8.0 Hz, 3H), 7.63 (d, *J* = 8.0 Hz, 2H); 13C-nmr ($CDCl_3$-DMSO-d6)(100 MHz): 20.94, 111.17, 118.79, 122.44, 126.55, 126.79, 127.06, 128.92, 129.52, 136.83, 137.31, 141.76, 151.39; ms: m/z: 285 (M^+) ; *Anal*. Calcd. for $C_{20}H_{16}N_2$ C, 84.48; H, 5.67; N, 9.85. Found: C, 84.06; H, 5.55; N, 9.92.

2-(4'-*p*-Anisylphenyl)-1*H*-benzimidazole (6). This compound was obtained as an off-white solid (ethyl alcohol); ^{1}H nmr ($CDCl_3$-DMSO-d6): δ 3.71 (s, 3H), 6.85 (d, *J* = 9.2Hz, 2H), 7.12 (dd, *J* = 6.0 & 3.2Hz, 2H), 7.44 (d, *J* = 9.2Hz, 2H), 7.52-7.55 (m, 4H), 8.15 (d, *J* = 8.4Hz, 2H). **^{13}C** nmr ($CDCl_3$-DMSO-d6) (100 MHz): 55.36, 114.37, 122.70, 123.04, 126.93, 127.61, 128.08, 128.48, 131.95, 132.36, 142.67, 151.11, 159.65; ms: m/z: 301 (M^+); *Anal*. Calcd. for $C_{20}H_{16}N_2O$, C: 79.98; H: 5.37; N: 9.33. Found: C: 79.68; H: 5.08; N: 9.11.

2-(4'-(4-Cyanophenyl)phenyl)-1*H*-benzimidazole (7). This compound was obtained as an pale yellow solid (ethyl alcohol); ^{1}H-nmr ($CDCl_3$-DMSO-d6): δ 7.16 (dd, *J* = 6.0 & 2.8Hz, 2H), 7.55 (dd, *J* = 6.0 & 2.6Hz, 2H), 7.64-7.70 (m, 6H), 8.24 (d, *J* = 8.4Hz, 2H). ^{13}C nmr ($CDCl_3$-DMSO-d6) (100 MHz): 111.02, 115.16, 118.73, 122.54, 127.46, 127.50, 127.58, 130.42, 132.58, 139.99, 144.53, 151.04. ms: m/z: 296 (M^+); *Anal*. Calcd. for

$C_{20}H_{13}N_3$, C: 81.34; H: 4.44; N: 14.23. Found: C: 81.24; H: 4.09; N: 14.11.

2-(4'-(4-Formylphenyl)phenyl)-1*H*-benzimidazole (8). This compound was obtained as an off-white solid (ethyl alcohol); ^{1}H nmr ($CDCl_3$-DMSO-d6): δ 7.18-7.27 (m, 2H), 7.56 (m, 1H), 7.68 (m, 1H), 7.98-8.01(m, 6H), 8.32 (d, J = 8.34). 13C-nmr ($CDCl_3$-DMSO-d6)(100 MHz): 115.8, 122.8, 123.46, 127.60, 127.92, 129.56, 131.40, 136.80, 138.90, 145.08, 146.82, 152.10, 191.89; ms: m/z: 298 (M^+); *Anal*. Calcd. for $C_{20}H_{14}N_2O$ C, 80.52; H, 4.73; N, 9.39. Found: C, 80.16; H, 4.42; N, 9.42.

2-(4'-(4-Fluorophenyl) phenyl)-1*H*-benzimidazole (9). This compound was obtained as an off-white solid (ethyl alcohol); ^{1}H-nmr (DMSO-d6): δ 7.21-7.37 (m, 4H), 7.61 (brs, 2H), 7.81-7.88 (m, 4H), 8.26 (d, *J* = 8.2Hz, 2H), 12.97 (s, 1H). ^{13}C nmr ($CDCl_3$-DMSO-d6) (75 MHz): 115.90, 116.19, 122.37, 127.23, 127.31, 128.89, 129.00, 129.33, 135.93, 140.43, 151.10, 160.72, 163.96; ms: m/z: 289 (M^+); *Anal*. Calcd. for $C_{19}H_{13}FN_2$, C: 79.15; H: 4.54; N: 9.72. Found: C: 79.02; H: 4.49; N: 9.68.

2-(4'-(4-Chlorophenyl)phenyl)-1*H*-benzimidazole (10). This compound was obtained as an off-white solid (ethyl alcohol); ^{1}H-nmr (DMSO-d_6/TMS): δ 7.22 (s, 2H), 7.55-7.68 (m, 4H), 7.80-7.90 (m, 4H), 8.29 (d, *J*=7.8Hz, 2H), 13.03 (s, 1H); ^{13}C nmr (DMSO-d_6/TMS): δ 111.60, 122.00, 122.84, 127.25, 127.34, 128.68, 129.20, 129.67, 132.98, 138.26, 140.08, 151.00; ms: m/z: 304 (M^+); *Anal*. Calcd. for $C_{19}H_{13}ClN_2$, C, 74.88; H, 4.30; N, 9.19; Found: C, 74.89; H, 4.47; N, 9.17.

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