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Synthesis of 2-Aryltryptamines with Palladium Catalyzed Cross-Coupling of 2-Bromotryptamines and Arylboronic Acids

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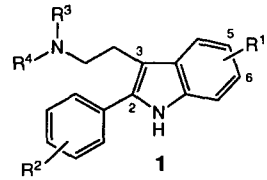
Abstract: *A versatile and high-yielding synthesis of 2-aryltryptamines employing palladium(0) catalyzed cross-coupling of 2-bromotryptamines and arylboronic acids was developed. The preparation of the intermediate 2-bromotryptamines with pyridine hydrobromide perbromide as the brominating agent, is also reported.* © 1997 Elsevier Science Ltd.

The 2-aryltryptamine (**1**) moiety is present in many natural products and medicinal chemistry targets with various biological activities. Our interest in this class of compounds led to investigations directed toward a versatile synthetic process to introduce a wide range of aryl substituents to the 2-position of the indole, potentially via a transition metal mediated aryl-indole cross-coupling. There have been limited examples of indole couplings at the 2-position reported to date. Several of them involved initial lithiation at the 2-position and hence required blocking of the indole nitrogen.[1a-d] In addition, the organolithium intermediates generated in these reactions are incompatible with many functional groups. Others utilized Stille[2] coupling conditions that would produce stoichiometric quantities of tin-containing by-products, a major drawback for industrial scale work.[3a-c] We wish to describe here a high-yielding protocol which doesn't require protection on the indole nitrogen, and which employs a modification of the Suzuki reaction with bromotryptamine **6** as the key intermediate (Scheme I). To our knowledge, this is the first reported approach to 2-aryltryptamines that features coupling of unprotected 2-haloindoles with arylboronic acids.[4]



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Several commercially available tryptamines (from Aldrich or Sigma) have been used to demonstrate the scope of our methodology. Protection of the amino group with N-carbethoxyphthalimide(**3**)[5a-c] in refluxing THF for 1 - 2 days afforded pure phthalimide **4** in high yield after trituration with hexane / CH_2Cl_2 (3 : 1). The phthalimide **4** was selectively brominated at the 2-position with pyridine hydrobromide perbromide **5** [6a,b] to form the key intermediate **6**. Among several modifications of the Suzuki reaction[7] that we have tried, the combination of Na_2CO_3, LiCl, and $Pd(PPh_3)_4$ in refluxing toluene / EtOH most effectively cross-coupled **6** with a wide variety of arylboronic acids **7** in moderate to high yields.[8] Table 1 shows the

tryptamines that have been used and the respective yields of the cross-couplings with different arylboronic acids, available commercially or prepared from the corresponding aryl bromides.[9a,b] The reaction proceeded smoothly with arylboronic acids containing electron-donating or electron-withdrawing substituents (**8a** - **8d**). In addition, the reaction tolerated a single *ortho*-substituent (**8i**), although a significantly lower yield was obtained when both *ortho*-positions were occupied (**8k**).

Scheme I

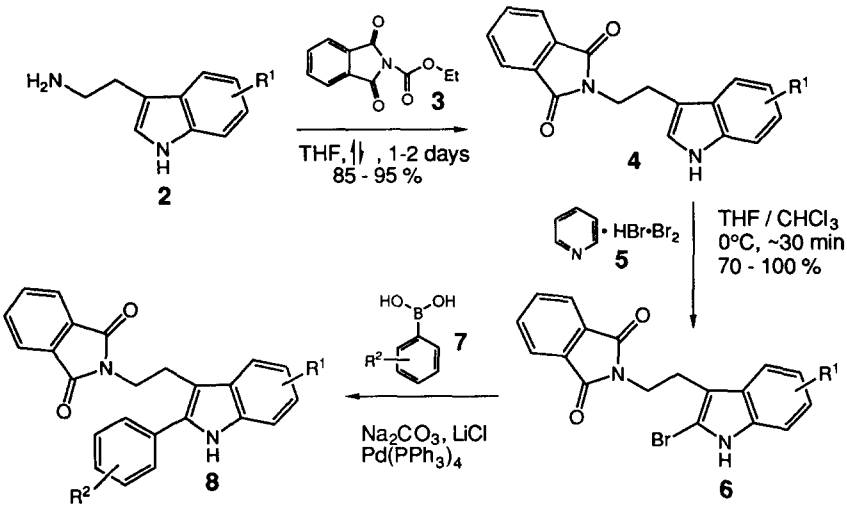
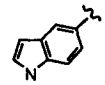
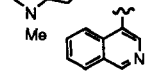


Table 1

6, R^1=	**7**, R^2-Ph =	**8**, isolated yield	**6**, R^1=	**7**, R^2-Ph =	**8**, isolated yield
H	3,5-bis-CF_3-phenyl	**8a**, 88 %	H	3-nitrophenyl	**8m**, 67 %
H	3,5-dichlorophenyl	**8b**, 70 %	H	3-methylphenyl	**8n**, 89 %
H	3,5-dimethylphenyl	**8c**, 85 %	H	3-methoxyphenyl	**8o**, 60 %
H	3,5-dimethoxyphenyl	**8d**, 86 %	H	4-fluorophenyl	**8p**, 86 %
H	1-naphthyl	**8e**, 91 %	H	4-methylphenyl	**8q**, 74 %
H	2-naphthyl	**8f**, 80 %	H	4-chlorophenyl	**8r**, 79 %
			H	phenyl	**8s**, 79 %
H		**8g**, 74 %	5-OBn	1-naphthyl	**8t**, 80 %
			5-OBn	3,5-dimethylphenyl	**8u**, 83 %
H		**8h**, 86 %	5-OMe	3,5-dimethylphenyl	**8v**, 89 %
H	2-methylphenyl	**8i**, 74 %	5-Cl	3,5-dimethylphenyl	**8w**, 59 %
H	2,4-dichlorophenyl	**8j**, 70 %	5-Me	3,5-dimethylphenyl	**8x**, 77 %
H	2,6-dimethylphenyl	**8k**, 12 %	6-F	1-naphthyl	**8y**, 84 %
H	3-Cl-4-F-phenyl	**8l**, 70 %	7-Me	3,5-dimethylphenyl	**8z**, 70 %

Although the function of the added lithium chloride has not been extensively investigated, we did notice a consistent decrease in yield when lithium chloride was absent (Table 2). It is possible that LiCl accelerated the rate of the desired reaction and/or decreased the rate of side reactions. Stille[10] has noted that in the Pd-catalyzed coupling of vinyl triflates with organostannanes, LiCl accelerated product formation to a greater extent than did LiBr. In each case, the halides facilitated the formation of the initial palladium-olefin σ-complex by displacing the triflate ligand. Product formation from this complex may be more productive with chloride than bromide because with the latter ligand, a significant degree of catalyst decomposition was observed. In the present case, facile exchange of added chloride with the bromide ligand may produce a relatively more stable catalytic species, maximizing product formation.[11]

Table 2

6, R^1=	**7**, R^2-Ph =	LiCl, equiv.	Rxn Time	**8**, isolated yield
H	3,5-dimethylphenyl	3.0	4 hr	85 %
H	"	0	4 hr	50 %
H	3-nitrophenyl	3.0	2.5 hr	67 %
H	"	0	2.5 hr	42 %
H	2,4-dichlorophenyl	3.0	5 hr	70 %
H	"	0	5 hr	7 %

In conclusion, we have demonstrated a versatile methodology for the preparation of a wide selection of 2-aryltryptamines applying a modification of the Suzuki reaction on various boronic acids with an unprotected indole.

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2. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

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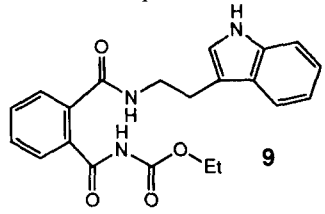
4. There has been one recent account on syntheses of 6- and 7-arylindole via Pd-catalyzed coupling of unprotected 6- and 7-bromoindole: Carrera, G. M.; Sheppard, G. S. *Synlett* **1994**, 93.

5. a) McArthur, C.; Worster, P.; Jiang, J-L.; Leznoff, C. *Can. J. Chem.* **1982**, *60*, 1836. However, it is worth noting that when the conditions reported in the aforementioned reference were employed on our substrate **2** (R^1 = H), only the intermediate **9** was formed. Prolonged heating for 1 - 2 days was essential in order to drive the reaction to completion.



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b) One equivalent of triethylamine was added in the reaction when a hydrochloride salt of the starting tryptamine(**2**) was used. c) When a Boc group was used to protect the tryptamine, a complex mixture resulted in the subsequent bromination step, possibly due to bromination on the carbamate NH, which then led to undesired side products.

6. a) Grieco, P.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630. b) When there was a strong electron-donating substituent present on the indole (eg. 5-OBn, 5-OMe), undesired bromination on the 6-position of the indole was observed as a competing side-reaction.

7. Miyaura, N.; Suginome, H.; Suzuki, A. *Synth. Commun.* **1981** *11*, 513

8. In a typical experiment, the bromide **6** (0.67 mmol, 1 equiv.) and boronic acid **7** (1.0 mmol, 1.5 equiv.) were dissolved in 8 mL of toluene and 8 mL of absolute ethanol. Na_2CO_3 (1.0 M solution in H_2O, 2.5 equiv.), LiCl (anhydrous, 3 equiv.), and tetrakis(triphenylphosphine) palladium (purchased from Aldrich, 5 mol %) were added sequentially. The resulting heterogeneous system was then brought up to refluxing condition for 3 - 5 hours under a nitrogen atmosphere. The end point of the reaction was usually accompanied by a change in color of the reaction mixture from yellow to dark orange/brown. When the completion of reaction was confirmed by TLC, the reaction mixture was concentrated directly *in vacuo* and azeotroped 2 - 3 times with toluene. The organics were dissolved in a mixture of hexane/methylene chloride/ethyl acetate, and flash chromatographed on silica with appropriate mixtures of hexane/ethyl acetate.

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