SYNTHESIS OF 5-ARYLATED INDOLES VIA PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF 5-INDOLYLBORONIC ACID WITH ARYL AND HETEROARYL HALIDES

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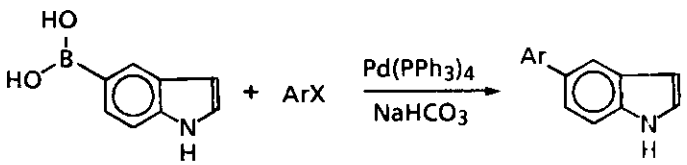
Abstract - Palladium(0)-catalyzed cross-coupling reaction of 5-indolylboronic acid with various aryl and heteroaryl halides results in regioselective formation of 5-arylated indoles in good yields.

5-Arylated indoles are important intermediates in our strategy to synthesize various agonists and antagonists of the central nervous system neurotransmitter serotonin (5-hyroxytryptamine, 5HT), since the 5-arylated indoles can be converted to tryptamines and tetrahydropyridylindoles that are of interest.[1] The classical Fischer indolyzation process provides access to a variety of substituted indoles.[2] However, a mixture of regioisomers can be obtained when unsymmetrical substituted arene precursor or certain forms of aldehyde or ketone are employed.[3] This makes it necessary to either separate the regioisomers or employ the tactic of incorporation and removal of a temporary blocking group. The nickel- and palladium-catalyzed cross-coupling reaction of organometallic reagents with organic electrophiles has been recently employed for the regioselective synthesis of 2-carbon, 3-carbon and 4-carbon arylated indoles. For instance, aryl Grignard reagents and trialkylarylstannanes were successfully used for the synthesis of 2-carbon arylated indoles.[4,5] Dialkylarylborane was also found to be useful for the synthesis of 3-carbon arylated indoles.[6] Somei *et al.*[7,8] reported that 4-arylindoles could be readily obtained by the reaction of trialkylarylstannane or arylboronic acid with (3-formylindol-4-yl)thallium bis-trifluoroacetate, catalyzed by palladium salt. Unfortunately, this tin-thallation or boronation-thallation strategy is not suitable for the

synthesis of other arylated indoles in the benzo ring, since the thallation occurred exclusively at the 4-carbon and/or 3-carbon of the indole ring.[9] Recently, the synthesis of 5-(2-Furyl)-1*H*-indole *via* cross-coupling of 5-indolyl triflate with 2-furylzinc chloride was reported.[10] As a marriage of our combined interest in the cross-coupling reactions of arylboronic acids[11,12] and the synthesis of serotonin analogs,[1] we report that 5-carbon arylated indoles can be regioselectively prepared via the palladium-catalyzed cross-coupling of 5-indolylboronic acid with a variety of aryl and heteroaryl halides (Scheme 1).

Scheme 1



Thus, 5-indolylboronic acid, readily obtained from commercially available 5-bromoindole by an one-pot process,[13] was coupled with a wide variety of aryl and heteroaryl halides in the presence of 3% tetrakis(triphenylphosphine)palladium (0) and aqueous sodium bicarbonate. Although various organic solvents have been used for this coupling reaction, the water soluble ethylene glycol dimethyl ether was found to be particularly suitable for the preparation of 5-arylated indoles. In most cases, the aryl halides employed in this coupling were aryl bromides, but the less active chlorides 2-chloropyrimidine and 2-chloropyrazine still offered reasonable yields of the desired products, despite the report that 3-chloropyridine failed to couple with phenylboronic acid.[14] When 2-bromoxylene and 4-bromo-3,5-dimethylisoxazole were coupled with 5-indolylboronic acid, the yields were markedly lower (6% and 17%) than those obtained with most other halides, suggesting steric hindrance by the *o,o*-dimethyl groups of the aryl halide in the oxidative addition step. Yields, melting points, and elemental analyses for the 5-arylated indoles prepared are given in Table 1.

In summary, the cross-coupling reaction of 5-indolylboronic acid with aryl- and heteroaryl halides provides a general and regioselective methodology for the synthesis of 5-arylated indoles. This method has the advantages of ready accessibility of the reagents, absence of side reactions, good yields, and experimental simplicity.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Jeol FX90Q spectrometer.

The mass spectra were determined on a Hewlett Packard Model 5970 mass spectrometer. Infrared spectra were carried out on a Beckman IR-33 spectrophotometer. Elemental analyses were performed at Desert Analytics, Inc. Tucson, Arizona U.S.A. The nmr, ms and ir spectra were consistent with the structures indicated.

Table I. Analytical and Physical Data for 5-Aryl Indoles

No	5-arylindole	mp (°C)	Yield (%)	Calcd.			Found		
				C	H	N	C	H	N
1	Phenyl	71-73	87	87.01	5.74	7.25	86.97	5.81	7.20
2	4-Fluorophenyl	81-83	75	76.60	4.77	6.63	79.67	4.82	6.57
3	2-Methoxyphenyl	98-100	94	80.69	5.87	6.27	80.93	6.04	6.42
4	4-Methoxyphenyl	118-200	59	80.69	5.87	6.27	80.81	5.99	6.23
5	2-m-Xylyl	a,b	6[a,b]						
6	5-Nitro-2-toluyl	139-141	94	71.41	4.79	11.10	71.59	4.87	11.11
7	2-Pyridyl	121-123	90	80.39	5.19	14.42	80.86	5.21	13.87
8	3-Pyridyl	143-145	72	80.39	5.19	14.42	80.54	5.19	4.43
9	4-Pyridyl	259-260	65	80.39	5.19	14.42	80.16	5.07	14.43
10	2-Pyrimidinyl	155-58	52	73.83	4.65	21.52	73.85	4.55	21.50
11	5-Pyrimidinyl	202-204	73	73.83	4.65	21.52	73.96	4.65	21.40
12	2-Pyrazinyl	154-156	55	73.83	4.65	21.52	74.06	4.66	21.53
13	2-Furyl[c]	100-102	82	78.67	4.95	7.65	78.93	5.00	7.53
14	3-Furyl	95-97	65	78.67	4.95	7.65	78.31	4.95	7.83
15	2-Thienyl[c]	55-56	86	72.33	4.55	7.03	72.58	4.55	6.98
16	3-Thienyl	83-86	78	72.33	4.55	7.03	74.10	4.69	7.02
17	5-Chloro-2-thienyl	92-94	94	61.67	3.45	5.99	62.05	3.44	6.02
18	2-Thiazoyl	119-121	68	65.97	4.27	13.99	66.25	4.08	13.92
19	3,5-Dimethyl-4-isoxazoyl	204-205	17					b	

[a]Not isolated; the yield is by glc.
[b]Identified by gc/ms.
[c]No physical data was reported.[10]

General procedure for the coupling reaction of 5-indolyboronic acids with aryl and heteroaryl halides

A 100 ml two-necked flask equipped with condenser and stirrer was charged with 2.5 m mol of the corresponding halide, 0.075 m mol of tetrakis(triphenylphosphine)palladium(0) and 20 ml ethylene glycol dimethyl ether. After the mixture was stirred for 10 min at room temperature, 2.8 m mol of

5-indolylboronic acid was added, followed by the addition of 7.5 m mol of sodium bicarbonate in 10 ml of water.[11,12] The reaction mixture was refluxed with vigorous stirring under nitrogen atmosphere and analyzed by tlc. After the starting aryl halide was consumed (ca. 4 h) and the organic solvent was removed at reduced pressure, the crude products were purified by chromatography on silica gel 60 with ethyl acetate/hexanes (1/3) for compounds 1, 3, 4, 6, 8, 9, 10, 13, 14, 15, 16, 17 and 18; ethyl acetate/hexanes (15/85) for compound 2; ethyl acetate/hexanes (35/65) for compound 7; and by recrystallization from 95% ethanol for compounds (11 and 12).

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