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Palladium Catalyzed Cross-Coupling Reaction between 3-Indole Boronic Acids and Tetrahydropyridine Triflates

Qi Zheng, Youhua Yang, and Arnold R. Martin*

Department of Pharmacology and Toxicology
College of Pharmacy, University of Arizona
Tucson, AZ 85721

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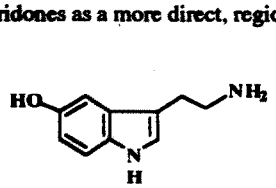
Abstract: The palladium catalyzed cross-coupling reaction between 3-indole boronic acids and vinyl triflates is a good method to introduce vinyl groups into the indole 3-position. The regioselectivity of the enolization of N-substituted-3-piperidones is far greater than previously reported. N-tosyl-3-indole boronic acids can be easily synthesized *via* mercuration-boronation method.

As part of structure-activity studies of the neurotransmitter serotonin (5-Hydroxytryptamine, 5-HT, *1*), we wished to develop a suitable general synthesis of analogs of the 5-HT agonist, RU28253 (*2*). The direct condensation of indoles with N-substituted-3-piperidones (*4*) is nonregioselective[1] and gave extremely low yields (10-30%) of the desired 1,2,5,6-tetrahydropyridyl isomer in our hands. On the other hand, the route that we had devised earlier *via* the corresponding 3-(3-pyridyl)indoles (*3*) prepared by cross-coupling reactions of 3-pyridyltrimethyl stannane and 5-substituted-3-iodoindoles is lengthy[1b]. We therefore decided to investigate the cross-coupling reaction between indole-3-boronic acids and triflates derived from N-substituted 3-piperidones as a more direct, regioselective route.



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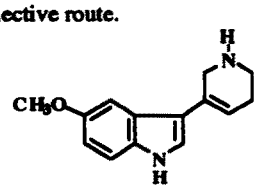

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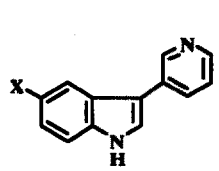

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Palladium(0) catalyzed cross-coupling reactions between aryl boronic acids and vinyl triflates have attracted considerable attention recently[2]. In addition to the unambiguousness of regiochemistry, mild reaction conditions, and usually good to excellent yields, other advantages of this reaction are the ease of preparation of vinyl triflates from a wide variety of enolizable ketones and their comparable reactivities with that of vinyl halides.

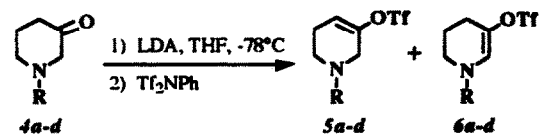
The regiochemistry of enolization of α-amino ketones has been investigated by trapping the enolates as trimethylsilyl ethers[3]. A clear trend emerged based on the nature of the nitrogen substituents. Thus, enolization toward the nitrogen atom predominated when it was substituted with an electron withdrawing group (e.g., CO_2R, SO_2CF_3), and enolization away from the nitrogen atom primarily occurred when it was substituted

with an alkyl group (e.g., ethyl, benzyl). In the case of N-substituted-3-piperidones, the percentage of minor isomers was in the range of 17-23% when lithium diisopropylamide(LDA) was employed as a base[3].

In our effort to synthesize enol triflates from N-substituted-3-piperidones under typical conditions of kinetic control, surprisingly, only one of the two isomers can be detected by GC-MS and high field ^{1}HNMR (Scheme 1). When the N-substituents are electron donating groups (Methyl, Benzyl), only allylamine isomers (***5a*** and ***5b***) were detected. If the substituents are electron withdrawing groups(Cbz, Boc), the enamine isomers (***6c*** and ***6d***) were exclusively observed. These results strongly suggest that the regioselectivity of enolization of 3-piperidones under kinetic condition is far greater than indicated by the trapping of the enolates as trimethylsilyl enol ethers[3] and that some conversion to the minor isomer occurred during or following the latter trapping process.

Although numerous papers describing the chemistry of aryl boronic acids appeared in the last three decades, limited work has been done in indoles wherein halogen-metal exchange methodology was applied[6]. This approach has two major drawbacks. First, many functional groups are sensitive to the organolithium reagents; second, when the method is used to prepare 3-indole boronic acid derivatives, the isomerization of the intermediate 3-indolyllithium to 2-indolyllithium can take place easily[7]. We, therefore, investigated the mercuration-boronation method[8] to synthesize 1-protected 3-indole boronic acids as shown in scheme 2. Compared with the halogen-metal exchange, this method proved a more suitable route since a much wider range of functional groups can be tolerated, no isomerization is observed, the yields are higher, and the reactions are easier to perform. The versatility of aryl boronic acids,

Scheme 1. The Synthesis of Triflates[4]



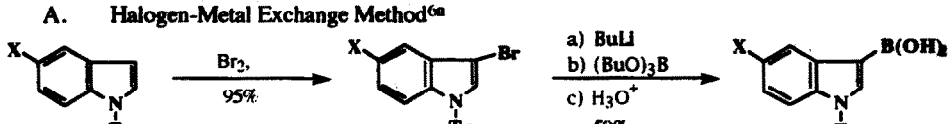
4a-d 5a-d 6a-d

Entry[a]	R	Yield(%)[b]	5	6
a	CH_3	81	>97	c
b	CH_2Ph	86	>97	c
c	Cbz	75	c	>97
d	Boc	73	c	>97

[a] Compounds 4a-d were prepared according to ref 5.
[b] Isolated yields after chromatography on silica gel
[c] Unable to be detected by GC-MS (detection limit is 3%)

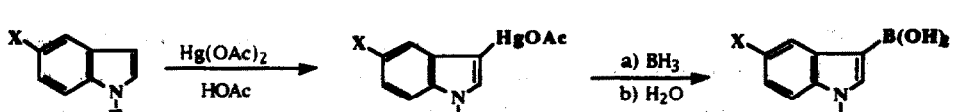
Scheme 2. The Synthesis of 1-Protected 3-Indole Boronic Acids

A. Halogen-Metal Exchange Method[6a]



X = H, CH_3O total yield: ~50%

B. Mercuration-Boronation Method[9]



X = H, CH_3O total yield: ~70%

the structural diversity and broad spectrum of biological properties of indole derivatives give this route potential significance in both medicinal and indole chemistry.

Finally, the N-tosyl-3-indolylboronic acids *7* were cross-coupled with the triflates *5* or *6* in the presence of sodium carbonate, lithium chloride and tetrakis(triphenylphosphine)palladium(0) to give the desired products. As shown in scheme 3 and table 1, high regioselectivity, mild conditions, and good yields prove the cross-coupling reaction between the 3-indole boronic acids and the readily available vinyl triflates to be an excellent method for the introduction of vinyl groups into the indole 3-position.

Scheme 3. Cross-Coupling Reactions[10]

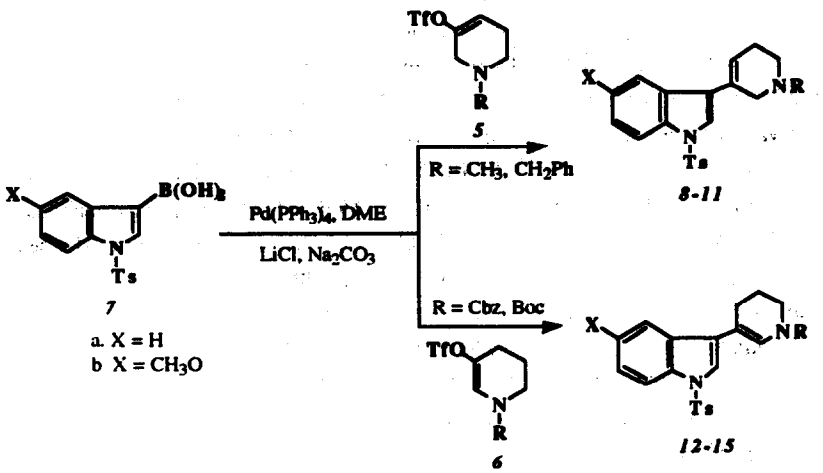


Table 1. N-tosyl-3-(tetrahydropyridine-3-yl)indoles

Compounds*	X	R	m.p. °C	Yields %
8	H	CH_3	**	90
9	H	CH_2Ph	124-126	92
10	CH_3O	CH_3	106-107	86
11	CH_3O	CH_2Ph	127-128	76
12	H	Cbz	125-127	80
13	H	Boc	139-140	89
14	CH_3O	Cbz	112-113	82
15	CH_3O	Boc	154-156	79

* ^{1}HNMR, MS, and elemental analysis were consistent with the structures indicated.

** Unable to get crystal at this point.

ACKNOWLEDGEMENT

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4. *Benzyl 1,2,3,4-Tetrahydro-5-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate 6c* [2c]
   A solution of benzyl 3-oxopiperidine-1-carboxylate ***4c*** (2.33g, 10mmol) in THF(10 mL) was added to a solution of lithium diisopropylamide(LDA, 11 mmol) in THF(10 mL) at -78°C under N_2. After 1 h a solution of N-phenyltrifluoromethanesulfonimide(3.93 g, 11 mmol) in THF(10 mL) was added at -78°C. The slurry was then warmed to 0°C and allowed to stir for 3h. After column chromatography(neutral alumina, CH_2Cl_2; then silica gel, hexanes/AcOEt 9:1),2.74g product was obtained as a colorless oil(75%).
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9. *5-Methoxy-1-tosyl-3-indole boronic acid* [8b]
   The borane solution, 1M in THF (5 mL, 5 mmol) was added to the suspension of 3-acetoxylmercurio-5-methoxy-1-tosylindole (0.28 g, 0.5 mmol) in 14 mL THF at r.t. under N_2. The resulting suspension was allowed to stir for 1h at r.t., then quenched by the careful addition of 2.8 mL water. After removal of elemental mercury and solvent, the white solid was dissolved in 30 mL 10%THF /90%ethyl acetate. The insoluble solid was filtered and the filtrate was washed with water (10 mL X 2), and concentrated. After chromatography of the residue on silica gel (CH_2Cl_2/AcOEt 20:1), 150 mg product was obtained in a 87% yield. M.p. 120-122°C.
10. *5-methoxy-1-tosyl-3-(1'-benzyl-1,2,5,6-tetrahydropyridyl-3-yl)indole 11* [2c]
    A three neck flask which had been purged with N_2 was charged with aq Na_2CO_3(1 mL of a 2M solution), 1,2-dimethoxyethane (DME, 2.5 mL), 5-methoxy-1-tosyl-3-indole boronic acid (345 mg, 1 mmol), LiCl (90 mg, 2.2 mmol), 1-benzyl-3-piperidone triflate (321 mg, 1 mmol) and $Pd(PPh_3)_4$ (41 mg, 0.037 mmol). The mixture was heated to reflux with vigorous stirring. After 2h, the reaction was cooled to r.t. and remove the solvent at 60°C under reduced pressure. The residue is partitioned between CH_2Cl_2(30 mL), aq 2N Na_2CO_3(30 mL) and conc. NH_4OH(2 mL). The aqueous layer was extracted again with CH_2Cl_2 (30 mL X 2) and the combined organic extracts was dried (Na_2SO_4). The solvents were removed under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2:MeOH 60:1) to obtain the product. Yield: 368 mg (76%) M.p. 127-8°C (THF/MeOH).

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