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IMMOBILIZED INDOLYLBORON AS A KEY INTERMEDIATE FOR SOLID-PHASE SYNTHESIS OF BISINDOLE ALKALOID ANALOGS

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Dedicated to Professor Barry M. Trost on the occasion of his 65th Birthday

Abstract – Immobilized indolylboron was easily prepared from resin-bound iodoindole and the subsequent Suzuki coupling reaction was used for the syntheses of bisindole alkaloid analogs.

Solid-phase synthesis is regarded as a very efficient method for producing combinatorial libraries[1] and combining solid-phase synthesis with high-throughput screening has made a significant contribution for lead discoveries and optimization in pharmaceutical research. Contemporary synthetic reactions that use transition metals, particularly palladium, have been employed as well established methodologies for selective carbon-carbon bond forming reactions for solution-phase synthesis and for solid-phase synthesis.[2]

Indole rings have been found in various biologically active molecules, like a simple arylindole and numerous studies have been done for the efficient construction and functionalization. We recently reported a solid-phase indole synthesis using a palladium catalyzed intramolecular alkenylation or amination.[3]

Suzuki coupling[4] is one of the important palladium catalyzed cross-coupling reactions in medicinal chemistry and is suitable for synthesizing biaryl compounds. This reaction has been already applied to solid phase synthesis.[5~7] Many of the reported works have treated the cross coupling of immobilized aryl halides with arylborons in solution and a limited number of examples were reported for the coupling reactions of immobilized arylmetals with free aryl halides in solution.[6,7] From the viewpoint of coupling partners' availability, the latter seems to be attractive. In this paper, we wish to report the concise preparation of immobilized indolylboron and the subsequent arylation using palladium catalyst. The solid-phase synthesis of bisindole alkaloid analogs using resin-bound indolylboron was accomplished.

The immobilized 3-iodoindole (**1**) was easily prepared from indole *via* iodination followed by immobilization using chlorosulfonylated polystyrene. The preparation of the immobilized indolylboron was investigated using palladium catalyzed borylation.[8] Murata's borylation protocol[9] (pinacolborane, $PdCl_2$(dppf), Et_3N, in dioxane at 80 ºC) was employed to prepare the immobilized indolylboron, which was not easily accessible by other methods.

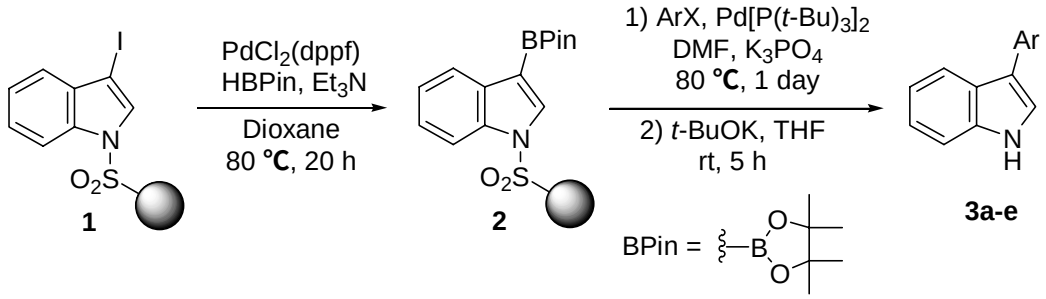
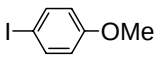
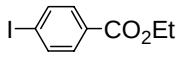
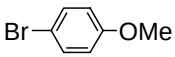
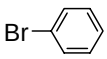
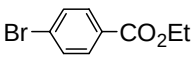


Table 1. Arylation of Immobilized Indolylboron

Entry	ArX	Product	Yield (3 steps)	Entry	ArX	Product	Yield[c](3 steps)
1		**3a**	77%	5		**3c**	74%
2[a]		**3b**	91%	6		**3c**	73%
3		**3a**	74%	7[b]		**3d**	60%
4[a]		**3b**	88%	8[b]		**3e**	82%

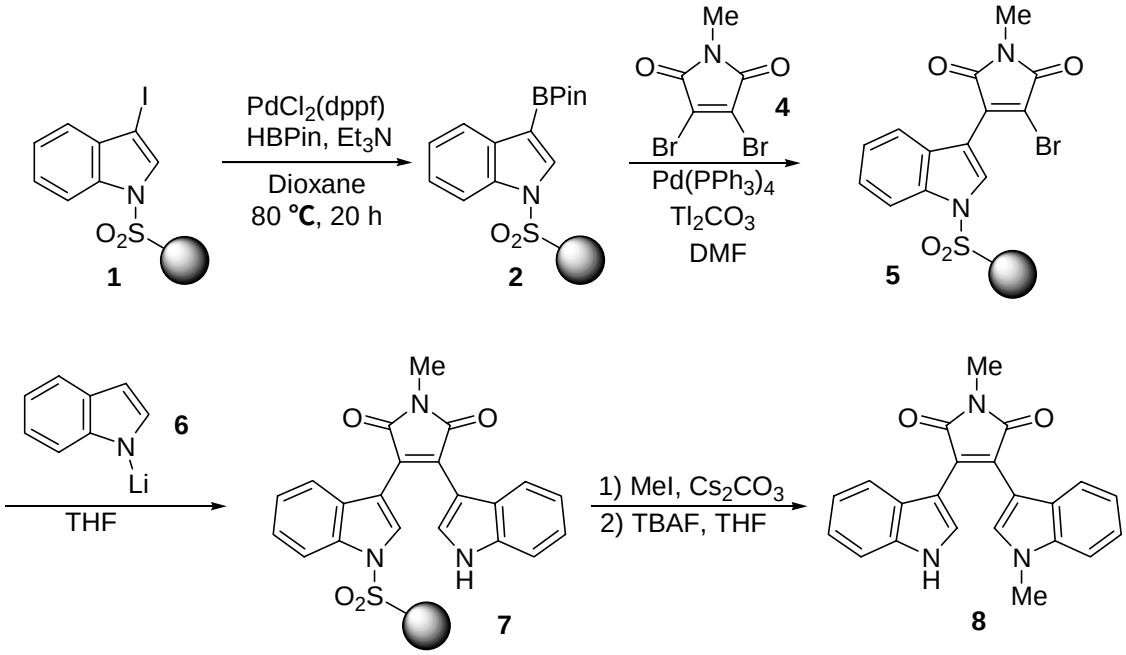
[a]Cleavage condition = TBAF, reflux, 5 h [b]$Pd(PPh_3)_4$ was used in place of Pd[P(*t*-Bu)$_3$]$_2$.
[c]Isolated yields of pure compounds after SiO_2 column chromatography.

The subsequent palladium-catalyzed cross-coupling reactions with aryl halides were examined and Pd[P(t-Bu)$_3$]$_2$[10] was found to be a very active catalyst (Table 1). Since it was difficult to estimate exact loading value (mmol/g) of the immobilized indolylboron, the three-step yield from **1** was used to evaluate the performance of the coupling reaction with various aryl halides. The loading value of **1** was determined as 0.86 mmol/g by cleaving the immobilized 3-iodoindole to isolate 3-iodoindole. Generally, the reaction proceeded smoothly for both of electron rich and poor aryl halides. For the reaction of heteroaryl halides, the better result was obtained by using $Pd(PPh_3)_4$.

3-Arylindoles have been known to be important candidates for serotonin 5-HT_2 antagonist,[11] and some of bisindole alkaloids, which have unique structures that possess a five- or six-membered central ring shared by two indole units and display a high degree of biological activity, have attracted the attention of medicinal chemists. The bisindolylmaleimide subunit is present in numerous biologically active metabolites including staurosporine and rebeccamycin.[12] Bisindolylmaleimides are important

candidates for selectively inhibiting Protein Kinase C (PKC) and recent SAR studies have dramatically improved the potency and selectivity for PKC with structures such as GF 109203X.[13] Since the *N*-alkylated structure showed biological activities, we designed a synthetic route so that monoalkylation could be easily performed. The precursor of the central block for bisindolylmaleimide, dibromomaleimide (**4**), was synthesized according to the reported procedure.[14] For the solid-phase synthesis, the borylation of immobilized 3-iodoindole with pinacolborane in the presence of a palladium catalyst, followed by Suzuki coupling gave the immobilized mono-coupling product (**5**). The bromide (**5**) was then treated with excess *N*-lithioindole to yield the immobilized bisindolylmaleimide (**7**). The bisindolylmaleimide (**7**) was treated with excess MeI in the presence of Cs_2CO_3 to give the monomethylated compound. Finally the immobilized bisindole was cleaved by TBAF and mono-methylated bisindolylmaleimide (**8**) was synthesized in 38% yield from the immobilized iodoindole in 5 steps (Scheme 1).

Scheme 1. Solid-Phase Synthesis of Bisindolylmaleimide Derivative



In summary, 3-aryl- and heteroaryl- indoles were synthesized using an immobilized indolylboron as a key intermediate. The methodology was also extended for the solid-phase synthesis of bisindolylmaleimide.

ACKNOWLEDGMENT

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15. **Procedure for the Preparation of Immobilized 3-Iodoindole (1):** A mixture of indole (1.75 g, 15.0 mmol) and KOH (3.20 g, 57 mmol) in DMF (20 mL) was stirred for 10 min. Then iodine (4.10 g, 16.1 mmol) was added, and the mixture was stirred for 30 min. The mixture was poured into the solution (H_2O 200 mL, 25% NH_3aq 4 mL, $Na_2S_2O_5$ 200 mg), and the precipitation was separated by filtration. The precipitation was dissolved in DMF, and 60% NaH (610 mg, 15.3 mmol) was added at 0 ºC. The mixture was stirred for 30 min at rt and polystyrene sulfonyl chloride (1.97 mmol/g, 2.61 g, 5.14 mmol) was added at 0 ºC. The mixture was stirred slowly at room temperature for 16 h. Saturated aqueous NH_4Cl was added, and the resin was separated by filtration and washed with THF (three times), H_2O (three times), MeOH (three times), Et_2O (two times). The resin was dried *in vacuo* to afford 2.72 g of **1**. The loading (mmol/g) of **1** was derived from 3-iodoindole generated from cleavage of **1**. A mixture of resin **1** (240.6 mg) and *t*-BuOK (532.5 mg, 4.7 mmol) in THF (5 mL) under an argon atmosphere was stirred at rt for 3 h. Saturated aqueous NH_4Cl (10 mL)was added, and the resin was separated by filtration and washed with THF (three times), H_2O (three times), AcOEt (three times). The aqueous phase was extracted with AcOEt, and organic phase was dried over $MgSO_4$. The evaporation of the organic phase gave the crude product, and the crude product was purified by chromatography on silica gel using hexane/AcOEt (9:1) to afford 50.3 mg of 3-iodoindole. The loading of **1** was estimated as 0.860 mmol/g.
16. **Procedure for the preparation of immobilized indolylboron (2):** In a sealed tube, Et_3N (0.115 mL, 0.810 mmol) and pinacolborane (0.095 mL, 0.635 mmol) were added into a mixture of resin (**1**) (171.3 mg, 0.1473mmol), $PdCl_2$dppf complex with dichloromethane (1:1) (12.6 mg 0.01543 mmol), and dioxane (1.5 mL), and the mixture was heated at 80 ºC for 20 h under an argon atmosphere. The resin was separated by filtration and washed with THF (three times), MeOH (three times), $CHCl_3$ (three times), Et_2O (two times). The resin was dried *in vacuo* to afford the immobilized indolylboron (**2**).
17. **General procedure of solid-phase Suzuki coupling using resin (2) (Table 1):** In a sealed tube, the mixture of resin (**2**), K_3PO_4 (100.6 mg, 0.4739 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (8.5 mg, 0.01663 mmol), 4-iodoanisole (Entry 5, 176.4 mg, 0.7537 mmol), and DMF (2.5 mL) was heated at 80 ºC for 1 day under an argon atmosphere. The resin was separated by filtration and washed with THF (three times), H_2O (three times), MeOH (three times), $CHCl_3$ (three times), Et_2O (two times). The resin was dried *in vacuo* to afford the immobilized arylindole. The resin of the immobilized arylindole and *t*-BuOK (177.7 mg, 1.583 mmol) in THF (5 mL) was stirred at rt for 6 h under an argon atmosphere. Saturated aqueous NH_4Cl was added into the mixture. The resin was separated by filtration, and washed with THF (three times), H_2O (three times), AcOEt (three times). The

aqueous phase was extracted with AcOEt, and organic phase was washed with brine and dried over $MgSO_4$. The evaporation of the organic phase gave the crude product, and the crude product was purified by chromatography on silica gel using hexane/AcOEt (92:8)-(85:15) to afford 24.2 mg (Entry 5, 74% from **1**) of 3-(4-methoxyphenyl)-1*H*-indole.

18. **3-Phenyl-1*H*-indole (Table 1, Entries 1, 3):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17-7.30 (m, 3H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.67 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.18 (br s, 1H); MS (EI) *m/z*: (rel intensity): 193 (M^+, 100%), 165 (25); HRMS (EI) Calcd for $C_{14}H_{11}N$: 193.0891. Found: 193.0907.

4-(1*H*-Indol-3-yl)benzoic acid ethyl ester (Table 1, Entries 2, 4): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (t, *J* = 6.8 Hz, 3H), 4.40 (q, *J* = 6.8 Hz, 2H), 7.22 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.27 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.2, Hz, 2H), 8.41 (br s, 1H); MS (EI) *m/z* (rel intensity): 265 (M^+, 100%), 237 (32), 220 (32), 165 (14), 149 (14); HRMS (EI) Calcd for $C_{17}H_{15}NO_2$: 265.1103. Found: 265.1084.

3-(4-Methoxyphenyl)-1*H*-indole (Table 1, Entries 5, 6): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.86 (s, 3H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 8.17 (1H, br s); MS (EI) *m/z* (rel intensity): 223 (M^+, 100%), 208 (69), 180 (12), 152 (10), 111 (13); HRMS (EI) Calcd for $C_{15}H_{13}NO$: 223.0997. Found: 265.0987.

3-Thiophen-2-yl-1*H*-indole (Table 1, Entry 7): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.07-7.08 (m, 1H), 7.18-7.25 (m, 6H), 7.88 (br s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H); MS (EI) *m/z* (rel intensity): 199 (M^+, 100%), 171 (14); HRMS (EI) Calcd for $C_{12}H_9NS$: 199.0456. Found 199.0428.

3-Pyridin-2-yl-1*H*-indole (Table 1, Entry 8): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.08-7.11 (m, 1H), 7.20-7.24 (m, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.63-7.64 (m, 1H), 7.67-7.68 (m, 2H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.65 (d, *J* = 4.8 Hz, 1H), 9.43 (br s, 1H); MS (EI) *m/z* (rel intensity): 194 (M^+, 100%), 166 (18), 149 (13), 83 (21); HRMS (EI) Calcd for $C_{13}H_{10}N_2$: 194.0844. Found: 199.0830.