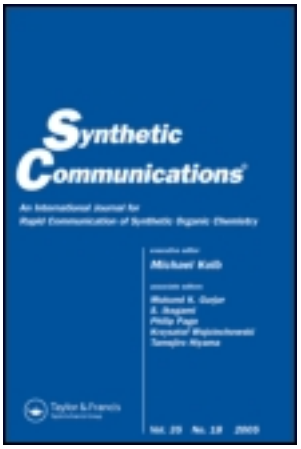

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Ke Wang [a b] & Zhanzhu Liu [a b]
[a] Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Beijing, China
[b] Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
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SYNTHESIS OF ARCYRIARUBIN A AND ARCYRIAFLAVIN A VIA CROSS-COUPLING OF INDOLYLBORONIC ACID WITH DIBROMOMALEIMIDES

Ke Wang and Zhanzhu Liu

Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education and Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Arcyriarubin A was first isolated by Steglich in 1980; it is also the key intermediate in the synthesis of indolocarbazole compounds. A new synthetic approach to the natural products arcyriaflavin A and arcyriarubin A is described. The key step is a Suzuki cross-coupling reaction using indolylboronic acid as the starting material. The preparation of arcyriaflavin A was accomplished in eight steps from indole for a total yield of 21%.

Keywords: Arcyriaflavin A; arcyriarubin A; indolocarbazoles; Suzuki coupling

INTRODUCTION

Since the isolation of staurosporine in 1977,[1] many indolocarbazoles have been isolated from different organisms, including bacteria, fungi, and invertebrates.[2] This family of compounds has attracted the attention of chemists, biologists, and physicians because of the wide range of biological activities that the compounds possess, including antimicrobial, hypotensive, and cell cytotoxic activities as well as inhibition of protein kinase C and platelet aggregation.[3] Several indolocarbazole analogs are currently being tested in the clinic against cancer or other diseases.[4]

Arcyriarubin A[5] is the simplest bisindolylmaleimide, which is also the key intermediate in the synthesis of indolocarbazole compounds. Arcyriaflavin A was isolated by Steglich et al.[5] (Figure 1) in 1980. It exhibits micromolar and submicromolar inhibition against seven protein kinase C isoenzymes, and it inhibits the proliferation of the human lung cancer A549 and P388 murine leukemia cell lines.[6]

Various approaches to the synthesis of this family of natural products have been reported[7]: reaction of indole Grignard reagents with dibromomaleimides, reaction of 3-indolyl lithium with dibromomaleimides, reaction of indolyl-3-glyoxlyl

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Address correspondence to Zhanzhu Liu, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100050, China. E-mail: liuzhanzhu@imm.ac.cn

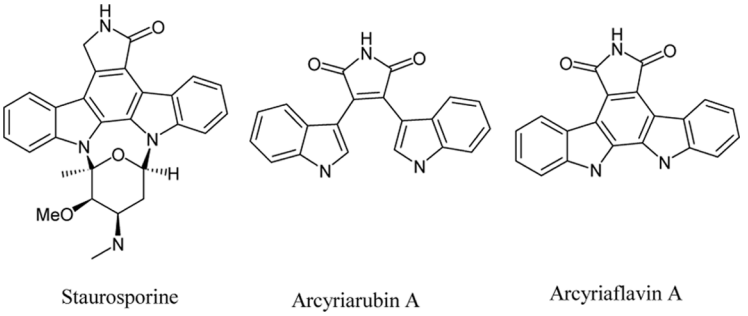


Figure 1. The structures of some bisindole alkaloids.

chlorides with indole-3-acetimidates, and iodine-promoted oxidative coupling of the indole-3-acetic acid trianion and the methylindole-3-acetate dianion. Despite the available synthetic routes to the indolo[2,3-a]pyrrolo[3,4-c]carbazole ring system, a simpler and more efficient one is still needed. We report a novel method for the synthesis of bisindolymaleimide via palladium-catalyzed cross-coupling of indolyl-3-boronic acid with dibromomaleimides.

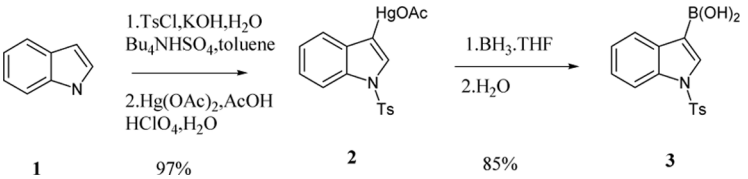
DISCUSSION

Preparation of the indole boronic acid **3** from indole **1** was accomplished through the following steps: protection of the indole NH with p-toluenesulfonyl chloride (TsCl) and then treatment with $Hg(OAc)_2$ to yield compound **2**. Reaction of **2** with BH_3-tetrahydrofuran (THF) followed by hydrolytic workup gave **3** in a total yield of 82%[8] (Scheme 1).

Bisindolylmaleimide **5** was synthesized by the Suzuki cross-coupling of indole boronic acid **3** and dibromomaleimide **4**. Several coupling conditions were tested[9] (Table 1), and the best one was $Pd(PPH_3)_4$-Na_2CO_3-dioxane/CH_3OH, under which compound **5** was obtained in 52% yield (Scheme 2).

With compound **5** in hand, cleavage of both indole nitrogen protective groups was readily accomplished.[10] Basic treatment of **6** led to anhydride **7**. The dimethylformamide (DMF) solution of maleic anhydrides **7** were treated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS)/methanol at room temperature for 16 h to give imide **8** in an excellent yield.[11] Treatment of **8** with 1 equivalent of palladium acetate in acetic acid at reflux for 18 h gave the desired product **9** in 72% yield[12] (Scheme 3).

In conclusion, we have developed a new, efficient approach for the synthesis of bisindolylmaleimides via the Suzuki cross-coupling reaction. The preparation of

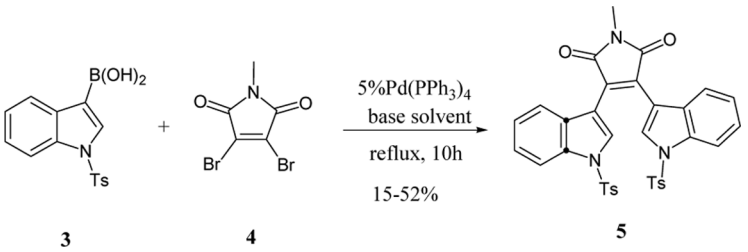


Scheme 1. The synthesis of N-tosyl-3-indolylboronic acid.

Table 1. Conditions and yields for Suzuki cross-coupling reaction between 3 and 4[a]

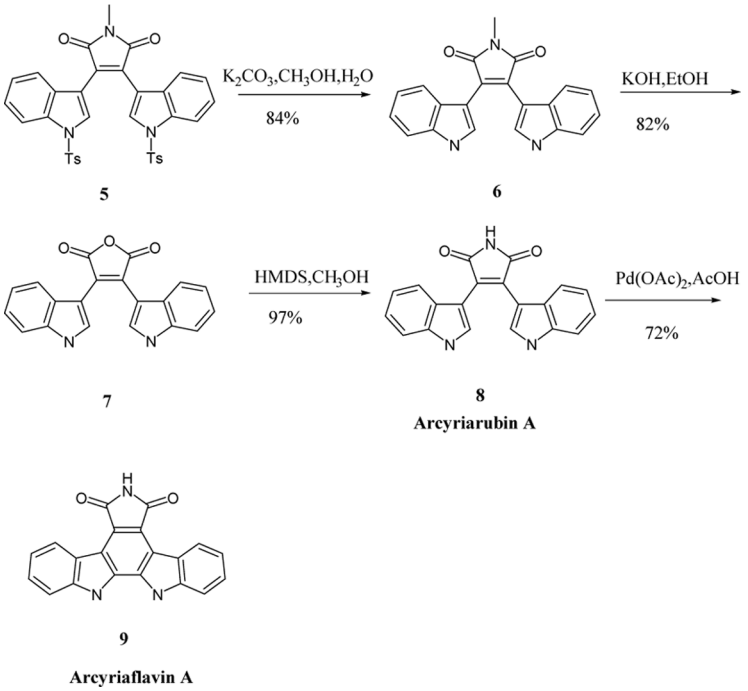
Solvent A	Solvent B	Base	Yield (%)[b]
Benzene	CH_3OH	2 M Na_2CO_3	27
DMF	CH_3OH	2 M Na_2CO_3	15
Dioxane	CH_3OH	2 M Na_2CO_3	52
Toluene	CH_3OH	2 M Cs_2CO_3	46
Toluene	CH_3OH	2 M K_3PO_4	29
Toluene	CH_3OH	2 M Na_2CO_3	45

[a]Reaction conditions: solvent A, 15 ml: solvent B, 3 ml; base 2 ml; catalyst, 10 mol%; refluxing; 10 h.
[b]Isolated yields.



3 4 5

Scheme 2. The synthesis of bisindolylmaleimide skeleton via Suzuki reaction.



5 6 7 8 Arcyriarubin A 9 Arcyriaflavin A

Scheme 3. The synthesis of arcyriarubin A and arcyriaflavin A.

arcyriaflavin A was realized in eight steps from indole in a total yield of 21%. This method is operationally simple, obviating the necessity for anhydrous reaction conditions. Synthesis of indolocarbazole alkaloids and analogs with this method is ongoing in our laboratory.

EXPERIMENTAL

All reagents and solvents were pure analytical-grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. ^{1}H NMR (300 or 400 MHz) spectra were recorded at 24°C unless otherwise stated. The data are reported as chemical shift (ppm), and the interpretation of peak with relevant coupling constants is reported in hertz. Mass spectra (MS) were obtained using an ion trap mass spectrometer equipped with electrospray ionization (ESI) ion source.

3-Acetoxymercurio-N-tosylindole (2)

Tetrabutylammonium hydrogensulfate (1.6 g, 4.8 mmol), potassium hydroxide (KOH; 50% aqueous solution, 88 ml), and a solution of p-toluenesulfonyl chloride (15.6 g, 82 mmol) in toluene (120 ml) were added to a solution of indole (8.0 g, 68.2 mmol) in toluene (60 ml). After stirring for 4 h, H_2O (120 ml) was added and the layers were separated. The organic layer was washed with H_2O (2×50 ml) and brine (1×50 ml),dried over magnesium sulfate, and concentrated under reduced pressure to afford N-tosylindole (18.2 g, 98%) as an off-white powder. ^{1}H NMR (DMSO-d_6): 300 MHz δ 7.94 (m, 1H), 7.87 (m, 2H), 7.79 (d, $J = 3.6$ Hz, 1H), 7.60 (m, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.33 (m, 1H), 7.24 (m, 1H), 6.83 (m, 1H), 2.31 (s, 3H).

Mercuric acetate (4.8 g, 15.0 mmol) was added to a solution of N-tosylindole (4.0 g, 14.8 mmol) in acetic acid (100 ml). After stirring at 23°C for 10 min, perchloric acid (five drops) was added. The mixture was stirred for 24 h, poured into H_2O (150 ml), and then filtered. The resulting white solid was washed with copious amounts of water and dried under vacuum for 12 h to afford organomercurial derivative **2** (7.7 g, 99%) as an unstable white powder that was used immediately without further purification: ^{1}H NMR (DMSO-d_6): 300 MHz δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.49 (s, 1H), 7.39(d, $J = 7.8$ Hz, 2H), 7.32–7.19 (m, 2H), 2.31 (s, 3H), 1.97 (s, 3H).

N-Tosyl-3-indolyboronic Acids (3)

Borane solution (1 M in THF, 32 mL, 32 mmol) was added to a solution of **2** (3.4 g, 6.4 mmol) in THF (100 ml) at 23°C. The resulting solution was stirred for 1 h, and then H_2O (38 ml) was added very slowly. After filtration, the organic solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (2×60 ml). The combined organic layers were washed with brine (1×30 ml) and concentrated under reduced pressure. Trituration of the crude product with hexanes (four times) afforded boronic acid **3** (1.72 g, 85%) as an unstable off-white solid which was used immediately without further purification.

2,3-Bis(1-tosyl-indol-3-yl)-N-methylmaleimide (5)

Aqueous sodium carbonate (2 M, 2 ml) was added to the solution containing dibromo-maleimide **4** (159 mg, 0.6 mmol) and boronic acid **3** (400 mg, 1.3 mmol) in dioxane (15 ml)–methanol (3 ml). The mixture was deoxygenated by bubbling a steam of argon through the reaction mixture for 10 min. Then tetra(triphenylphosphine)palladium (231 mg, 0.2 mmol) was added. The reaction mixture was stirred at refluxing for 10 h and quenched by addition of sodium sulfate (500 mg). Filtration and concentration to dryness under reduced pressure, followed by further purification through flash chromatography (hexane/EtOAc 10:2), afforded compound **5** (200 mg, 52% yield) as a yellow solid: ^{1}H NMR ($CDCl_3$): 300 MHz δ 8.09 (s, 2H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 4H), 7.23 (d, $J = 8.0$ Hz, 4H), 7.11 (t, $J = 7.6$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 2H), 6.55 (t, $J = 7.6$ Hz, 2H), 3.20 (s, 3H), 2.36 (s, 6H). HRMS: calcd. 650.1420 for $C_{35}H_{28}N_3O_6S_2$ $[M+H]^+$; found 650.1443.

2,3-Bis(1H-indol-3-yl)-N-methylmaleimide (6)

A mixture of **5** (119 mg, 0.18 mol), K_2CO_3 (276 mg, 2 mmol), H_2O (5 ml), and MeOH (15 ml) was refluxed under N_2 with magnetic stirring for 5 h. The mixture was allowed to cool to room temperature, and the solvent was removed in vacuo to give a red solid. This was dissolved in EtOAc (20 ml), washed with H_2O (2 × 20 ml) and brine (20 ml), and dried (Na_2SO_4). The solvent was removed in vacuo to give **6** (52.6 mg, 84%) as a red solid. ^{1}H NMR (DMSO-d_6) 300 MHz δ 11.67 (s, 2H), 7.74 (d, $J = 2.7$ Hz, 2H), 7.36 (d, 2H, $J = 7.8$ Hz), 6.97 (t, $J = 16.2$ Hz, 2H), 6.79 (d, $J = 8.1$ Hz, 2H), 6.62 (t, $J = 16.2$ Hz, 2H), 3.04 (s, 3H). HRMS (ESI): calcd. 342.1237 for $C_{21}H_{16}N_3O_2$ $[M+H]^+$; found 342.1224.

2,3-Bis(1H-indol-3-yl)-maleic Anhydride (7)

Compound **6** (300 mg, 0.88 mmol) was refluxed for 1 h in 10% aqueous potassium hydroxide (120 ml), cooled, and acidified with 2 M HCl. The red precipitate was collected to afford **7** as a red solid (236 mg, 82%). ^{1}H NMR (DMSO-d_6) 300 MHz δ 11.89 (d, $J = 1.8$ Hz, 2H), 7.83 (d, $J = 3.0$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.00–7.05 (m, 2H), 6.85 (d, $J = 8.1$ Hz, 2H), 6.67–6.72 (m, 2H). HRMS (ESI): calcd. 329.0921 for $C_{21}H_{16}N_3O_2$ $[M+H]^+$; found 329.0926.

2,3-Bis(1H-indol-3-yl)-maleimide (8) (Arcyriarubin A)

A solution of **7** (110 mg, 0.34 mmol) in DMF (4 ml) was treated with a mixture of 1,1,1,3,3,3-hexamethyldisilazane (542 mg, 3.36 mmol) and methanol (60 mg, 1.87 mmol). After stirring at room temperature for 16 h, the mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed well with water and dried ($MgSO_4$). Removal of solvent under reduced pressure gave 2,3-bis-(1H-indolyl)-maleimide **8** (Arcyriarubin A) as a red solid (106.4 mg, 97%). ^{1}H NMR (CD_3OD) 300 MHz δ 7.61 (d, $J = 1.8$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H),

6.84–6.89 (m, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 6.50 (t, $J = 14.7$ Hz, 2H). HRMS (ESI): calcd. 328.1086 for $C_{20}H_{14}N_3O_2$ $[M+H]^+$; found 328.1080.

Arcyriaflavin A (9)

Palladium acetate (27 mg, 0.12 mmol) was added to a solution of **8** (80 mg, 0.24 mmol) in acetic acid (15 ml), and the reaction mixture was stirred at refluxing for 18 h, then the mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica gel using THF/petroleum ether (PE) (1/2) as eluant afforded **9** (arcyriaflavin A) as a greenish yellow solid (57 mg, 72%). ^{1}H NMR (CD_3COCD_3) 300 MHz δ 11.12 (s, 2H), 9.79 (s, 1H), 9.14 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.53 (t, $J = 15.3$ Hz, 2H), 7.36 (t, $J = 14.7$ Hz, Hz, 2H). HRMS (ESI): calcd. 326.0924 for $C_{20}H_{12}N_3O_2$ $[M+H]^+$; found 326.0917.

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