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Palladium Mediated Intramolecular Multiple C-X/C-H Cross Coupling & C-H Activation: Synthesis of Carbazole Alkaloids Calothrixin B & Murrayaquinone A

Srinivasan. A Kaliyaperumal, Shyamapada Banerjee, Syam Kumar. U. K.*

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Abstract: A straightforward palladium mediated synthesis of calothrixin B and murrayaquinone A are described. Regioselective palladium mediated intramolecular multiple C-X/C-H cross coupling reaction on N-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-N-(2-iodophenyl)acetamide followed by CAN oxidation afforded calothrixin B in excellent yield in two steps. A linear synthesis has also been developed for calothrixin B. Utilizing C-H functionalization as well as palladium mediated intramolecular C-X/C-H cross coupling reaction, murrayaquinone A synthesis was achieved. Overall, these synthetic methodologies provide an expedient entry to the biologically active alkaloids in short reaction sequence.

INTRODUCTION

The pentacyclic carbazole alkaloids calothrixin A (1) and B (2) were isolated by Rickards et al. from Calothrix cyanobacteria in 1999. Calothrixins possess unprecedented indolo[3,2-j]phenanthridine framework with a striking assemblage of quinoline, quinone and indole pharmacophores. Calothrixin A (1) and B (2) exhibited antimalarial activity as well as inhibitory effects on chloroquine resistant strain of the malarial parasite Plasmodium falciparum. Both 1 and 2 inhibit the growth of human HeLa cancer cells and act as inhibitors of bacterial-RNA polymerase. Kelly et al. reported the first total synthesis of calothrixins in 2000 utilizing ortho-lithiation strategy. Further several elegant total syntheses of 1 and 2 were illustrated in literature utilizing hetero Diels-Alder protocol, Friedel Crafts reaction, palladium mediated tandem cyclization-cross coupling reaction C-H activation, FeCl3 mediated domino reaction and radical assisted cyclization as well as biomimetic approach. Murrayaquinone A (3) is an indole alkaloid isolated by Furukawa et al. from Murraya euchrestifolia. The plant genus Murraya has been used as a folk medicine for analgesia and local anaesthesia and also for the treatment of eczema, rheumatism and dropsy (Fig 1).

RESULTS & DISCUSSION

Multiple Heck reaction of polyhaloarenes provides the opportunity for building several C-C bonds in a single synthetic operation, however multiple intramolecular C-X/C-H cross coupling reactions are rarely explored. Herein we report the total synthesis of calothrixin B (2) via multiple as well as stepwise palladium mediated intramolecular multiple C-X/C-H cross coupling reactions and murrayaquinone A (3) synthesis by C-H activation and also by C-X/C-H cross coupling reaction from its basic starting materials.

The disconnection strategy for the synthesis of calothrixin B (2) is depicted in Scheme 1. Calothrixin B (2) could be obtained by the oxidative demethylation, dehydrogenative oxidation and...
deacylation of 13. The most salient features of our strategy are the creation of C7a-C7b and C13a-C13b bonds under palladium mediated intramolecular multiple C-X/C-H cross coupling reaction in a single synthetic operation from 4. The substitution pattern on A and C rings of 4 would allow the regioselective C-X/C-H cross couplings. The dihaloarene 4 could be accessed via the reductive amination of biarylaminoaldehyde 5 with aniline 10. The iodoaldehyde 6 could be used as a synthetic precursor for palladium mediated Buchwald aryl amination reaction with 8 to access the biarylaminoaldehyde 5.

Scheme 2 Buchwald–Hartwig amination. Reagents and conditions: (i) 
AgNO3, MeOH, r.t., 12 h, 95%; (ii) Pd(dppf)Cl2·CH2Cl2, (±)-BINAP, Cs2CO3, 8a or 8b, MeCN, 70 °C, 12 h, (X = Br, 85%; X = H, 90%)

The synthesis of key intermediates, 2,5-dimethoxy-4-(phenylamino)benzaldehyde 5a and 2,5-dimethoxy-4-(2-bromophenylamino)benzaldehyde 5b required for the preparation of calothrixin B (2) is outlined in Scheme 2. The synthesis of 5a and 5b were initiated with commercially accessible aldehyde 7. The iodination of aldehyde 7 with stoichiometric amount of iodine in presence of silver nitrate afforded the iodo aldehyde 6 in 95% yield.13 The Buchwald–Hartwig coupling reaction of amine 8b with iodoaldehyde 6 was carried out with Pd(dppf)Cl2·CH2Cl2, rac-BINAP and Cs2CO3 combination in acetonitrile at 60–70 °C for 10–12 hours, and produced 5b in excellent yield. Though the Buchwald aryl amination on 6 with aryl halo amines are not well exemplified in the literature,14 our attempted aryl amination reaction went very well, notably with less background reaction.

Other phosphine ligands such as PPh3, P(o-tolyl), P(o-tolyl), P(o-tolyl) have been employed in Buchwald amination, and gave either low conversion or poor product/reduced substrate ratios. To check the possibility of carbazole synthesis via C-H functionalization, 5a was synthesized by Buchwald–aryl amination protocol. Owing to the moderate conditions employed in the synthesis of 5b via Buchwald amination reaction, no C-C bond formation and dehalogenation were observed.

Initially the synthesis of carbazole 9 was attempted under intramolecular C-X/C-H cross coupling reaction conditions from 5b (Scheme 3). To identify the appropriate conditions for palladium mediated intramolecular C-X/C-H cross coupling reaction, Pd(OAc)2 have been chosen as the catalyst and the reaction was attempted with various solvent/base combinations in the presence of phosphine ligands. The results of these studies are summarized in Table 1.

1,4-dimethoxy-9H-carbazole-3-carbaldehyde (9) was obtained in good yield when the reaction was carried out with 5 mol% of Pd(OAc)2, 20 mol% PCy3 and 10 mol% JohnPhos in the presence of K2CO3 base in acetonitrile. The reaction was complete after 12 hours at 100 °C (entry 6) and afforded 9H-carbazole-3-carbaldehyde 9 in 90% yield along with a small percentage (7%) of 5a.

Scheme 3 Synthesis of carbazole derivatives. Reagents and conditions:
(i) X = H, Pd(OAc)2(2 equiv.), AcOH, 130 °C, 6 h, 91%; X = Br, Pd(OAc)2, K2CO3, 10 mol% JohnPhos, 20 mol% PCy3, MeCN, 100 °C, 12 h, 90%;

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Ligand</th>
<th>Time</th>
<th>Yield (%) 5a</th>
<th>Yield (%) 9</th>
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<tbody>
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<td>5 mol% Pd(OAc)2</td>
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<tr>
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<tr>
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<td>MeCN</td>
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<td>30</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
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<td>MeCN</td>
<td>20 mol% PCy3 &amp; 10 mol% JohnPhos</td>
<td>12</td>
<td>7</td>
<td>90</td>
</tr>
</tbody>
</table>

We also extensively studied the C-H activation methodology for the construction of 9 (Table 2) from 5a (Scheme 3). More importantly, the synthesis of carbazole by C-H activation was carried out in the absence of an oxidizing agent.

Table 2 Synthesis of carbazole 9 from 5a by C-X/C-H cross coupling reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Ligand</th>
<th>Time</th>
<th>X</th>
<th>Yield (%) 9</th>
</tr>
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<tbody>
<tr>
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<td>Toluene</td>
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<td>2</td>
<td>5 mol% Pd(OAc)2</td>
<td>DMF</td>
<td>20 mol% PPh3</td>
<td>24</td>
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<tr>
<td>3</td>
<td>10 mol% PdCl2</td>
<td>DMF</td>
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<td>24</td>
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<tr>
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<td>5</td>
<td>5 mol% Pd(OAc)2</td>
<td>MeCN</td>
<td>AcOH</td>
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<td>6</td>
<td>H</td>
<td>91*</td>
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</tbody>
</table>

*a Reaction was conducted in absence of ligand and oxidizing agent*
when the C-H activation reactions were performed with stoichiometric amount or excess of palladium acetate. Using 2 equiv. of Pd(OAc)$_2$, the complete consumption of 5a, along with substantially higher yields of the desired product 9 (more than 90%) was obtained within 6 hour when the C-H activation reaction was conducted in acetic acid as solvent.

The direct reductive amination on 9 with 2-iodoaniline (10) was then carried out with sodium triacetoxyborohydrate in the presence of TFA in isopropyl acetate solvent$^{[12]}$ and afforded 11 in 95% yield (Scheme 4).

The palladium mediated intramolecular C-X/C-H cross coupling reaction on 11 under various conditions failed to yield to the calothrixin framework probably due to the electronic effect. To reduce the electron density and to afford effective coordination with Pd(II), N-acylation on 11 was carried out with acetyl chloride in the presence of triethylamine in dichloromethane to afford 12. Subsequently 12 was subjected to the intramolecular reaction using 5 mol% of Pd(OAc)$_2$, 20 mol% PCy$_3$ and powdered K$_2$CO$_3$ in DMF. The C-X/C-H cross coupling reaction proceeded as expected and 13 was isolated in 90% yield after purifications.$^{[14]}$ The CAN was found to be a very effective reagent for the oxidation of phenanthridine 13 to afford the corresponding quinone. However, during the oxidative demethylation of 13, concomitant aromatization as well deacylation was observed and the natural alkaloid, calothrixin B (2) was obtained in 85% yield.

After the successful completion of the calothrixins B (2) synthesis via iterative process, we focussed our attention towards the synthesis of 2 under double intramolecular C-X/C-H cross coupling reaction conditions (Scheme 5). Though, the use of C-H activation methodology was initially planned for the construction of C7a-C7b bond, owing to the high Pd(II) loading required for the reactions, instead of C-H activation methodology, intramolecular multiple C-X/C-H cross coupling reaction was utilized for the synthesis of 2.

**Scheme 4** Iterative synthesis of calothrixin B (2). Reagents and conditions: (i) 2-iodoaniline (10), TFA, NaBH(OAc)$_2$, i-ProOAc, rt., 10 min, 99%; (ii) NEt$_3$, AcCl, CH$_2$Cl$_2$, 5 °C to rt., 2 h, 94%; (iii) Pd(OAc)$_2$, K$_2$CO$_3$, 20 mol% PCy$_3$, DMF, 110 °C, 10 h, 90%; (iv) CAN, MeCN/Water, rt., 2 h, 85%.

The reductive amination of 4-((2-bromophenyl)amino)-2,5-dimethoxy benzaldehyde (5b) with 2-iodoaniline (10) was then carried out with sodium triacetoxyborohydrate in the presence of TFA in isopropyl acetate solvent afforded 14 in 95% yield. The intermediate 14 has all the structural requisite for carrying out the multifold C-X/C-H cross coupling reaction to construct the alkaloid 2 framework. The acylation of 14 with acetyl chloride in the presence of triethylamine exclusively afforded 4 and no trace of diacetyl product were observed in this reaction. The double intramolecular C-X/C-H cross coupling reaction was then attempted on 4 under several conditions and the best yield was obtained when the reaction was carried out with 5 mol% of Pd(OAc)$_2$ in the presence of 30 mol% of PCy$_3$ and 10 mol% of JohnPhos. The reaction went smoothly when performed with 4 equiv. of powdered K$_2$CO$_3$ in DMF at 110 °C. The progress of the reaction was monitored by LCMS method, which clearly confirmed the early formation C13a-C1a bond leading to the phenanthridine framework, followed by the C7a-C7b bond construction. This probably due to the lower activation energy required for the insertion of transition metal at C13 position, because of the presence of adjacent N-acetyl group. The oxidative demethylation, deacetylation and further aromatization on 13 were carried out with CAN in a single pot reaction and produced the natural alkaloid 2 in good yield.

As a part of these studies, we also synthesized the Murrayaquinone A (3) (Scheme 6). The carbazole-3-carbaldehyde 9 obtained by C-H activation of 5a was subjected to reduction with TMSI/TES to yield 3-methyl-9H-carbazole 15. Owing to the decomposition of 15 under CAN oxidation conditions,$^{[19]}$ the demethylationative of 15 was attempted with boron tribromide under aerial oxidation conditions as reported by Moody et al.$^{[20]}$ and the alkaloid 3 was isolated in 74% yield.
In an alternate attempt for the synthesis of murrayaquinone \( 3 \) (Scheme 7), 4-((2-bromophenyl) amino)-2,5-dimethoxybenzaldehyde (5b) was reduced with TES/TMSCl afforded the natural alkaloid murrayaquinone A (3) in 88% yield.

**Conclusion:**

In conclusion, two efficient protocols for the synthesis of calothrixin B (2) have been developed in overall excellent yields. These syntheses were achieved through the development of efficient mono and double C-X/C-H cross coupling reactions through the exploration of various palladium catalysts and ligands. Utilizing C-H activation as well as intramolecular C-X/C-H reaction protocols, murrayaquinone A (3) has also been synthesized. Studies are underway to expand the scope of these methodologies for the synthesis of more complex bisindole alkaloids.

**EXPERIMENTAL SECTION**

**General.** All reactions were carried out in the oven dried glassware under an atmosphere of \( \text{N}_2 \), with magnetic stirring and the reactions were monitored by TLC, using Merck aluminum-backed plates pre-coated with silica (0.25 mm, 60, F254). The TLC plates were visualized under UV light (254 nm) or developed using a sol. of \( \text{KMnO}_4 \) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier Transform spectrometer. NMR spectra were measured in \( \text{CDCl}_3, \text{CD}_2\text{OD} \) or DMSO-\( \text{d}_6 \) (all with TMS as an internal standard) on Varian Gemini 400 MHz FT magnetic resonance spectrometers. Chemical shifts are reported in ppm, and coupling constants \( (J) \) are in Hz. The following abbreviations were used to explain the multiplicities: \( s = \text{singlet}, d = \text{doublet}, t = \text{triplet}, q = \text{quartet}, m = \text{multiplet} \).

**Procedure for the Preparation of 2,5-dimethoxybenzaldehyde (5b)**

A mixture of 2,5-dimethoxybenzaldehyde 7 (10.2 g, 61.4 mmol), silver nitrate (10.4 g, 61.4 mmol), and iodine (16.2 g, 64 mmol) in 250 mL of methanol was stirred under nitrogen for overnight. The yellow precipitate was filtered and washed with methanol. The remaining iodine was reduced with saturated sodium bisulfite solution and the solvent was removed on a rotary evaporator and recrystallized from 95% ethanol to yield off white coloured title compound 6 (17.08 g, 95%).

Blockquote

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55

45

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25

15

pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.5:10) which gave the title compound 5b as a pale yellow colored solid (0.449 g, 91%).

From 4-[(2-bromophenyl)amino]-2,5-dimethoxybenzaldehyde (5b)

A mixture of 4-[(2-bromophenyl)amino]-2,5-dimethoxybenzaldehyde (5b) (1 g, 2.9 mmol), powdered K2CO3 (0.823 g, 5.9 mmol), palladium (II) acetate (0.033 g, 0.1 mmol), tricyclohexylphosphine (0.167 g, 0.6 mmol) and 10 mol% of (2-Biphenyl)di-tert-butylphosphine (JohnPhos) (0.089 g, 0.3 mmol) in acetonitrile (20 mL) was heated at 100 °C for 12 hours with gentle stirring under argon atmosphere. After completion of the reaction, the mixture was filtered over celite bed and washed with EtOAc. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2:5) which gave the title compound 9 as a pale yellow colored solid (0.679 g, 90%).

mp: 173-175 °C. IR (ν\textsubscript{max} cm\textsuperscript{-1}) 3349, 2851, 1657, 1622, 1586, 1456, 1217.

1H, J = 7.4 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H) and 8.32 (s, 1H, δC (DMSO-d\textsubscript{6}, 100 MHz) 23.0, 44.7, 54.9, 56.0, 100.4, 108.3, 110.8, 119.5, 119.8, 121.9, 122.6 (2C), 125.4 (2C), 129.2, 130.2, 138.6, 139.6, 142.1, 146.8 and 147.4. LRMS (ESI): m/z = 457 (M+H)+. 240 (M–iodoaniline). HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{12}I\textsubscript{3}NO\textsubscript{2} (M+H)+: 501.0675, Found: 501.0696.

Preparation of N-(2-bromophenyl)-4-(((2-iodophenyl)amino)methyl)-2,5-dimethoxyaniline (14)

To a round bottom flask charged 2-iodoaniline (10) (0.358 g, 1.5 mmol) and 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (5b) (0.5 g, 1.5 mmol) followed by i-PrOAc (10 mL) and trifluoroacetic acid (0.339 g, 3 mmol). Sodium triacetoxylborohydride (0.630 g, 3 mmol) was added as a solid over 2 min (exothermicity was observed up to ~ 40 °C). After 10 min agitation TLC showed the completion of the reaction. The reaction mixture was diluted with ethyl acetate (30 mL). A solution of 2 wt% of aqueous NaOH was added into the reaction mixture until pH 8-9. The layer was separated and the organic layer was washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4}. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2:5) which gave the title compound 14 as a dark brown coloured gummy liquid (0.764 g, 95%).

IR (ν\textsubscript{max} cm\textsuperscript{-1}) 3584, 3393, 3019, 2918, 1588, 1456, 1217. δ\textsubscript{H} (DMSO-d\textsubscript{6}, 400 MHz) 3.69 (s, 3H), 3.77 (s, 3H), 4.31 (d, J = 5.9 Hz, 2H), 5.20 (t, J = 5.9 Hz, 1H), 6.39 (t, J = 7.8 Hz, 1H), 6.63 (t,
Preparation of \( N \)-((2-bromophenylamino)-2,5-dimethoxybenzyl)-N-(2-iodophenyl)acetamide (4)

To a round bottom flask charged with 2-(bromophenylamino)methyl)-2,5-dimethoxyaniline (14) (0.5 g, 0.92 mmol) and triethylamine (0.141 g, 0.14 mmol) in degassed dry DMF (6 mL), PCy \(_3\) (0.025 g, 0.08 mmol), anhydrous powdered K \(_2\)CO \(_3\) (0.683 g, 5.8 mmol) and trimethylsilyl chloride (0.532 g, 4.9 mmol) in acetonitrile (5 mL) and water (5 mL), ceric ammonium nitrate (4.29 mmol) in degassed dry DMF (6 mL), PCy \(_3\) (0.025 g, 0.08 mmol), anhydrous powdered K \(_2\)CO \(_3\) (0.683 g, 5.8 mmol) and trimethylsilyl chloride (0.532 g, 4.9 mmol) in acetonitrile (5 mL) and water (5 mL), ceric ammonium nitrate (4.29 mmol) were added. The reaction mixture was stirred at 110 °C under argon atmosphere for 10 hours (The reaction was monitored by TLC). The reaction mixture was cooled to room temperature and filtered over celite bed and washed with EtOAc (10 ml). The combined organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 2.5:5) which gave the desired compound as a brown solid 13 (0.280 g, 88%).

Preparation of Calothrixin B (2)

To a stirred solution of compound 13 (0.2 g, 0.54 mmol) in acetonitrile (5 mL) and water (5 mL), ceric ammonium nitrate (CAN) (0.740 g, 1.35 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, water (20 mL) was added into the reaction mixture and extracted with EtOAc (3*20 mL). The organic layer was washed with brine and dried over Na\(_2\)SO\(_4\). The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0.5:10) to give the title compound 8 (0.137 g, 85%) as a brown coloured amorphous solid. HRMS (ESI) calcd for C\(_{23}\)H\(_{32}\)NO\(_3\)Br (M+H): \(373.1552\) Found: \(373.1548\)
Preparation of 1,4-dimethoxy-3-methyl-9H-carbazole (15) (0.3 g, 1.2 mmol) in dichloromethane (5 ml) was cooled to -78 °C and the mixture was stirred for 2 hours. Boron tribromide in dichloromethane (1 M; 2.5 ml, 2.4 mmol) was added at -78 °C and the mixture was stirred for 2 hours at room temperature under air. The reaction mixture was then poured into ice water (10 ml) and the product was extracted into EtOAc (3*20 ml). The organic layer was separated and dried over Na$_2$SO$_4$. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0:2) which afforded red colored title compound (0.559 g, 88%).

Preparation of Murrayaquinone A (3)

To a solution of 1,4-dimethoxy-3-methyl-9H-carbazole (15) (0.3 g, 1.2 mmol) in dichloromethane (5 ml) was cooled to -78 °C and the mixture was stirred for 2 hours. Boron tribromide in dichloromethane (1 M; 2.5 ml, 2.4 mmol) was added at -78 °C and the mixture was stirred for 2 hours at room temperature under air. The reaction mixture was then poured into ice water (10 ml) and the product was extracted into EtOAc (3*20 ml). The organic layer was separated and dried over Na$_2$SO$_4$. The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc: petroleum ether = 0:2) which afforded red colored title compound (0.559 g, 88%).


