Molecular Iodine Assisted Electrocyclisation Approach towards the Synthesis of Arcyriaflavin A and Staurosporinone.

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Keywords: Indolocarbazole / Electrocyclisation / Iodine / Aromatisation / Wittig reaction / Graphite

A new and efficient method for the synthesis of arcyriaflavin A and staurosporinone has been described. The synthetic strategy employs a graphite catalysed alkenation, one-pot oxidation-Wittig reaction, iodine catalysed electrocyclisation and nitrene insertion as the key steps.

Introduction

Indolocarbazole (ICZ) alkaloids constitute an important class of natural products known for more than 30 years. These alkaloids have been isolated from various natural sources such as soil organisms, slime moulds and marine invertibrates,[1] and almost all of the isolated ICZs contain the indolo[2,3-a]pyrrolo[3,4-c]carbazole ring structure. They exhibit a wide spectrum of biological activities[2,3] which include antibacterial, antifungal, antiviral, hypotensive, antitumour, inhibition of kinases like PKC, D1/CDK4, JAK3, platelet aggregation and cell cytotoxicity. The interesting structural features of these compounds and their significant biological relevance has gained them a considerable attention from various disciplines of research.

Figure 1. Arcyriaflavin A and Staurosporinone

Arcyriaflavin A 1 and staurosporinone or K252c 2 (Fig. 1) are two important members of the ICZ family. Arcyriaflavin A was isolated in 1980 from the fungi Arcyria denudata and Arcyria nutans.[4] A few years later in 1986, another ICZ alkaloid, staurosporinone was isolated from the slime moulds of Nocardiopsis sp.[5] and was found to be an aglycone of the highly potent staurosporine. Both these alkaloids were later found in the marine ascidian Eudistoma sp. collected off the coast of West Africa.[6] Ever since then, these compounds have been the attractive targets for many synthetic and medicinal chemists, predominantly due to the high therapeutic significance associated with them.[7] A plethora of reviews covering the aspects related to isolation, biological activities, and synthesis of ICZs are well documented in the literature. Various synthetic strategies describing the total synthesis of 1 and 2, and their structural analogues have been reported in recent years. While many of these syntheses employ biindoles or bisindolyl maleimides or anhydrides as precursors,[8] other approaches involving a Diels-Alder reaction[9,10] or Fischer indolisation[10] have also been successfully used. A recent report by Orito and co-workers[11] makes use of gramine methiodide and 3-(N-benzyl)indolyl acetonitrile for the synthesis of 2. Mohanakrishnan and Rajeshwaran[12] have also synthesised 2 employing an interesting thermal electrocyclisation approach.

Continuing our interest in indole motifs,[13] we report herein a new and efficient synthesis of arcyriaflavin A and staurosporinone starting from 3-vinyl indole-2-methanol 7. The envisioned synthesis is based on the retrosynthetic pathway presented in Scheme 1.

Scheme 1. Retrosynthesis of Arcyriaflavin A and Staurosporinone

Anhydride 3, a known precursor of 1 and 2, could be prepared from the corresponding diester 4. Assembly of 4 was envisaged from the alcohol 7 by a tandem oxidation–Wittig reaction[14] sequence to form 6 which in the same vessel at elevated temperatures would get electrocyclised and aromatised to form 5, and in presence of a reductive agent could further get converted to 4 via a nitrene insertion reaction. The postulated sequence of reactions was attractive as it would provide the pentacyclic framework of indolocarbazole in a single step.
Results and Discussion

Synthesis of the required 3-vinyl indole-2-methanol 7(ii+ii) was accomplished by a graphite catalysed alkenation procedure developed in our laboratory. The isomeric alcohols were obtained in 90% yield in 88:12 (E:Z) ratio. Since both these isomers were expected to give the same product after electrocyclisation, the mixture was subjected to reaction with MnO2, ω-nitrobenzyltriphenylphosphonium bromide, triethyl amine and triphenyl phosphine and 10% Pd/C in refluxing diphenyl ether. In this one pot experiment, was obtained. In the next attempt, aldehyde 10 was isolated in 78% yield after MnO2 oxidation, and then subjected to a domino Wittig reaction and electrocyclisation with ω-nitrobenzyltriphenylphosphonium bromide, triethyl amine, in refluxing diphenyl ether. No success was gained in this case also.

Difficulties in achieving multiple reactions in a single step prompted us to adopt an alternate route wherein the oxidation and Wittig reaction would be carried out in a tandem manner. Thus, 7 was treated with excess of MnO2, ω-nitrobenzyltriphenylphosphonium bromide, and triethyl amine in chloroform at room temperature. In this case the expected product 6 was obtained in low yield along with large amount of unreacted aldehyde. The yield of 6 was increased to satisfactory level (60%) when three fold excess of Wittig salt was used. Hence, we followed a sequential procedure wherein base was added after the oxidation reaction was complete (monitored by TLC). This furnished the Wittig product 6 in 75% yield as a mixture of four isomers viz.; E:E; E:Z; Z:E and Z:Z of which the E:Z isomer appeared to be the major component (from 1H NMR).

Electrocyclisation of the triene 6 to form the nitro intermediate 5 however proved to be an arduous task. Several reaction conditions had to be screened for the achievement of this, results of which are summarised in Table 1. Initial attempts using 10% Pd/C in refluxing xylene (entry 1) or toluene in sealed tube (entry 2) failed to give us the desired product, though similar reaction had been earlier reported by Mohanakrishnan et al.12 The reason for the failure in our system could be attributed to the presence of an extra electron withdrawing group on the triene. Another important factor playing a decisive role in electrocyclisation could be the geometry of the substrate which was not very favorable in our case. Reaction with DDQ was also not successful (entry 3). Next, the reaction was carried out in refluxing diphenyl ether, during which 5 was formed in 20% yield (entry 4). Having succeeded in obtaining 5, we next focused our efforts on improvement in its yield.

Recently, molecular iodine has been extensively used in various organic transformations mainly due to its broad catalytic potential, high tolerance to air and moisture, cheap availability and environmental safety associated with it.15 Use of iodine in our electrocyclisation reaction in refluxing diphenyl ether also showed a slight increase in the yield and a considerable decrease in the reaction time (entry 4). To further optimise these conditions, we carried out the reaction in nitromethane using equivalent amount of iodine (entry 5) during which an increase in yield upto 33% was observed. Decreasing the concentration of iodine showed an increase in the yield of the product (entry 6 and 7). Best results were obtained when the catalyst loading was 30 mol%. A further decrease in concentration of iodine decreased the formation of product, while some of the starting remained unreacted even after 48 hours. This reaction was also tried under photochemical conditions using 30 mol% of iodine without any success.

Table 1. Optimization of reaction condition for electrocyclisation and aromatisation step

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield of 10% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xylene, 10% Pd/C, reflux, 12 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene, 10% Pd/C, sealed tube, 150-180°C, 12h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>DDQ, dioxane, 12h</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd2O, reflux, 3h</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>Pd2O, I2 (0.1 eq.), reflux, 1h</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Toluene, I2 (0.1 eq.), sealed tube, 150-180°C, 8h</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Nitromethane, I2 (1 eq.), 95°C, 24h</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>Nitromethane, I2 (0.5 eq.), 95°C, 24h</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Nitromethane, I2 (0.3 eq.), 95°C, 24h</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>Nitromethane, I2 (0.1 eq.), 95°C, 48h</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>I2 (0.3 eq.), h, benzene, 72h</td>
<td>0</td>
</tr>
</tbody>
</table>

The nitro intermediate 5 thus formed was then refluxed in triethyl phosphate at 160 °C to afford 4 in 34% yield. An improvement in the yield upto 55% was observed when triphenyl phosphate was used for the nitrene insertion reaction. Alternatively, a domino electrocyclisation-aromatisation- nitrene insertion reaction sequence was also attempted on 4 by refluxing it in presence of PPh3 in diphenyl ether or o-dichlorobenzene which successfully gave 4 however in poor yields (8-10%).

The diester 4 was then subjected to hydrolysis with KOH in methanol. Acidic workup of this reaction to our delight afforded directly the anhydride 3 in 85% yield which on heating with ammonium acetate furnished arcryialflavin A in 72% yield. Further conversion of 1 to staurosporinone is reported in the literature.7e Hence this strategy also constitutes a formal synthesis of 2.
Conclusions

In conclusion, we have developed an efficient synthesis of the ICZ alkaloids arcyriaflavin A and staurosporinone, using one pot oxidation-Wittig reaction, electrolysis and nitrene insertion approach.

Experimental Section

Commercial reagents were used without further purification. Solvents were distilled prior to use. Column chromatography was performed on silica gel (60-120 mesh). Flash Chromatography was done using silica gel (230-400 mesh). Infrared spectra were recorded on FT-IR spectrophotometer. 1H NMR (400 MHz) and 13C NMR (100 MHz) were recorded using CDCl3 & DMSO-d6 as solvents and TMS as an internal standard. HRMS were recorded on ES-QTOF. Melting points were recorded using Thieles apparatus and are uncorrected.

Synthesis of 3-vinyl indole-2-methanol 7: To a magnetically stirred suspension of indole-2-methanol (2.0 g, 13.6 mmol) and graphite (0.2 g, 16.7 mmol) in a 1:1 mixture of ethanol and water (20 mL) was added dimethylethylidine dicarboxylate (2.8 g, 20.4 mmol) dropwise and stirred at room temperature for 48 hours. Reaction mass was filtered and washed with ethanol (5 mL). The filtrate was concentrated to remove ethanol and extracted in chloroform (3x10 mL). The combined organic extracts were separated using column chromatography (chloroform : methanol, 95:5 v/v). 

E/Z isomer 7i: Bright yellow oily liquid, IR (KBr): δ 3307.92, 1712.79, 1710.86, 1519.91, 1340.43 cm⁻¹. 1H NMR (400 MHz, CDCl3): δ = 3.60 (s, 3H, OCH3), 3.85 (s, 3H, OCH3), 7.20 (t, 1H, Ar-H), 7.44 (m, 4H, 3 x Ar-H, 1 x H-CαC), 9.22 (br, s, 1H, NH), 9.78 (s, 1H, CHO) ppm. 13C NMR (100 MHz, CDCl3): δ =52.2 (CH3), 53.3 (CH2), 112.7 (CH), 118.6 (Cq), 121.4 (CH), 121.6 (CH), 126.9 (Cq), 127.2 (CH), 132.1 (CH), 132.7 (Cq), 135.4 (Cq), 136.8 (Cq), 165.0 (CO), 166.3 (CO), 181.5 (CO) ppm. HRMS (ESI): [M + Na]+ Calcd for C16H16N2O6Na: 429.1063; Found 429.1065.

Z-isomer 7ii: Yellow solid, m.p. 169-170 °C, IR (KBr): = 3323-3381.21 br., 1712.7 cm⁻¹. 1H NMR (400 MHz, DMSO): δ = 3.70 (s, 3H, OCH3), 3.84 (s, 3H, OCH3), 4.67 (d, J = 5.2Hz, 2H, CH2), 5.74 (t, J =5.2Hz, 1H, OH), 6.15 (s, 1H, H=CαC), 7.10 (t, J = 5.2 Hz, 1H, Ar-H), 7.16 (t, J = 7.2Hz, 1H, Ar-H), 7.46 (d, J = 8.4 Hz, 2H, Ar-H), 11.30 (s, 1H, NH) ppm. 13C NMR (100 MHz, DMSO): δ = 51.9 (CH3), 52.7 (CH3), 56.2 (CH3), 105.7 (Cq), 112.6 (CH), 113.4 (CH), 118.9 (CH), 121.2 (CH), 122.5 (CH), 126.2 (CH), 135.7 (Cq), 142.9 (Cq), 143.9 (Cq), 166.0 (CO), 169.1 (CO) ppm. HRMS (ESI): [M + Na]+ Calcd for C16H16N2O6Na: 312.0848; Found 312.0850.

Synthesis of 3-vinylindole-2-methanol 7: A mixture of 3-vinylindole-2-methanol (1.0 g, 3.5 mmol) and MnO2 (1.8 g, 20.8 mmol) in chloroform (10 mL) at room temperature was stirred overnight. After completion of the reaction, the reaction mixture was filtered under suction and concentrated. The crude reaction mixture was purified using flash chromatography in ethyl acetate and hexanes (30:70). Thick orange liquid (mixture of four isomers as seen from the 1HNMR spectrum) was obtained in 78% yield (0.77g).

Synthesis of indolocarbazole diester 4: A mixture of 3-vinylindole-2-methanol 7(•+•) (1.0 g, 3.44 mmol) and o-nitrobenzyl triphenylphosphonium bromide (4.94 g, 10.3 mmol) in chloroform (20 mL) containing freshly prepared MnO2 (1.5 g, 17.2 mmol) was stirred at room temperature for 12 hours. After complete conversion of the alcohol to aldehyde (monitored by TLC) triethyl amine (1.45 mL, 10.3 mmol) was added and reaction continued for further 12 hours. Reaction mass was filtered and washed with ethanol (5 mL). The filtrate was concentrated to remove ethanol and extracted in chloroform (3x10 mL). The combined organic extracts were separated using column chromatography (chloroform : methanol, 95:5 v/v). The E/Z ratio after isolation was found to be 88:12.

Synthesis of 2,3-divinyl indole 6: A mixture of 3-vinylindole-2-methanol 7(•+•) (1.0 g, 3.44 mmol) and o-nitrobenzyl triphenylphosphonium bromide (4.94 g, 10.3 mmol) in chloroform (20 mL) containing freshly prepared MnO2 (1.5 g, 17.2 mmol) was stirred at room temperature for 12 hours. After complete conversion of the alcohol to aldehyde (monitored by TLC) triethyl amine (1.45 mL, 10.3 mmol) was added and reaction continued for further 12 hours. Reaction mass was filtered and washed with ethanol (5 mL). The filtrate was concentrated to remove ethanol and extracted in chloroform (3x10 mL). The combined organic extracts were separated using column chromatography (chloroform : methanol, 95:5 v/v). The E/Z ratio after isolation was found to be 88:12.

Synthesis of 2-nitrophenyl carbazole 5: To a solution of 2,3-divinyl indole 6 (0.2 g, 0.5 mmol) in nitromethane (30 mL) was added 30 mol % I2 and heated at 95 °C for 24 hours. Reaction mass was filtered and washed with ethanol (5 mL). The filtrate was concentrated to remove ethanol and extracted in chloroform (3x10 mL). The combined organic extracts were separated using column chromatography (chloroform : methanol, 95:5 v/v). The E/Z ratio after isolation was found to be 88:12.

Synthesis of indolocarbazole diester 4: To a solution of 2-nitrophenyl carbazole 5 (0.15 g, 0.37 mmol) was refluxed in diphenyl ether (5 mL) along with triphenylphosphine (0.24 g, 0.93 mmol) for 1.5 hours. Reaction mass was then subjected to column chromatography during which diphenyl ether was eluted using hexanes. Further elution using ethyl acetate and hexanes (55:45 v/v) furnished pale yellow crystals of indolocarbazole diester in 55% yield (0.076g).
Indolocarbazole diester 4 (0.1 g, 0.27 mmol) was refluxed with KOH (0.1 g, 0.61 mmol) for 2.5 hours in methanol for 12 hours. Methanol was then distilled off and the reaction mass was extracted in ethyl acetate. Product was then transferred in water (4 x 10 mL) and the combined aqueous layers were acidified using conc. HCl. Brown solid precipitated out which was extracted in ethyl acetate, washed with water, dried and concentrated. The product after several washings with ether was obtained as a brown solid in 85% yield (0.075 g).

m.p. >300 °C. IR (KBr): $\nu =3390.86$, 1818.87, 1730.15 cm$^{-1}$. $^1$H NMR (400 MHz, $[D_6]$DMSO): $\delta =7.35$ (t, $J =7.6$Hz, 2H, Ar-H), 7.56 (t, $J =7.2$ Hz, 2H, Ar-H), 7.50 (d, $J =8.0$ Hz, 2H, Ar-H), 8.97 (d, $J =8.0$ Hz, 2H, Ar-H), 11.00 (s, 1H, NH-imide), 11.78 (s, 2H, NH-indole) ppm.

Supporting Information (see footnote on the first page of this article): Copies of $^1$H NMR, $^{13}$C NMR and DEPT spectra of all intermediates and products.

Acknowledgments

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A synthesis of indolocarbazole alkaloids-Arcyriaflavin A and Staurosporinone has been achieved from indol-2-ylmethanol. The key steps involved are one-pot oxidation-Wittig reaction followed by an iodine catalysed electrocyclisation and nitrene insertion reaction.

Keywords: Indolocarbazole / Electrocyclisation / Iodine / Aromatisation / Wittig reaction / Graphite
Supporting Information

Molecular Iodine Assisted Electrocyclisation Approach towards the Synthesis Of Arcyriaflavin A and Staurosporinone

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$^1$H NMR spectrum of 7i

$^{13}$C NMR spectrum of 7i
DEPT spectrum of 7i

\[ \begin{align*}
\text{MeOOC} & \equiv \text{COOMe} \\
\text{H} & \quad \text{CH}_2\text{OH}
\end{align*} \]

$^1$H NMR spectrum of 7ii

\[ \begin{align*}
\text{MeOOC} & \equiv \text{COOMe} \\
\text{H} & \quad \text{CH}_2\text{OH}
\end{align*} \]
$^{13}$C NMR spectrum of 7ii

DEPT spectrum of 7ii
$^1$H NMR spectrum of 10

$^{13}$C NMR spectrum of 10
DEPT spectrum of 10

\[ \text{Ratio of 6a-d} = (8:4:1.2:1) \]

\[ \text{1H NMR spectrum of 6(a-d)} \]
\[ \text{Ratio of 6a-d} = (8:4:1.2:1) \]
$^{13}$C NMR spectrum of 6

DEPT spectrum of 6
$^{1}H$ NMR spectrum of 5

$^{13}C$ NMR spectrum of 5
DEPT spectrum of 5

1H NMR spectrum of 4
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DEPT spectrum of 4
$^1$H NMR spectrum of 3

$^{13}$C NMR spectrum of 3
DEPT spectrum of 3

$^{1}H$ NMR spectrum of 1
$^1$H NMR spectrum of 1 in D$_2$O