Reactions of macrocyclic rhodium carbenoids: regioselective synthesis of indol-3-yl macrocyclic lactones and cryptands

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Abstract

A wide variety of new macrocyclic diazocarbonyl compounds with various spacers was synthesized. Macrocyclic rhodium(II) carbenoid insertion with various substituted indoles was performed to afford regioselectively, indol-3-yl macrocyclic di- or tetralactones (C3-alkylation). Double carbenoid insertion was also performed to afford indolyl cryptand molecules.

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Keywords: Carbenoids; Cryptands; Diazo ketones; Macrocyclic lactones; Indoles; Rhodium(II) acetate

The reaction of α-diazocarbonyl compounds with rhodium(II) carboxylates is a well described method to generate rhodium carbenoids, which can undergo an array of reactions such as cyclopropanation, C–H or heteroatom–H insertion and ylide formation.1 Carbenoid insertion reactions are important tools for C–C bond formation.2 Generation of carbenoids and their insertion reactions with heterocyclic compounds, either intramolecularly3 or intermolecularly,4 has been described in the literature. However, the intermolecular carbenoid insertion is known to provide a mixture4a–d of products. Recently, the synthesis and the reactions of macrocyclic compounds has received a great deal of attention due to their large number of applications.5 Some macrocyclic diazocarbonyl compounds have been used for the study of molecular mousetraps6 and host–guest complexations.7 In continuation of our research on macrocyclic lactones8 and cryptands,9 herein we report the regioselective intermolecular alkylation/insertion of macrocyclic metallo-carbenoids furnishing a range of indolyl macrocyclic di- or tetralactones and cryptands.

We began our efforts with the synthesis of macrocyclic mono-, bis- or tris-diazocarbonyl compounds. Initially, the reaction of malonyl chloride with tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), hexa(ethylene glycol) or 1,8-octanediol was carried out to furnish5c the respective monomers 1a–e, dimers 2a–h and trimers 3a–e (Scheme 1). Similar methods were followed to synthesize macrocycles 2f–h using ethylene glycol, diethylene glycol

Scheme 1. Synthesis of macrocyclic diazocarbonyl compounds.

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or 1,6-hexanediol, respectively. Further, active methylene compounds 1a, 2a and 3a were treated with 4-acetamidobenzenesulfonyl azide in the presence of DBU to afford the corresponding mono-10, bis-11 and tris-diazocarbonyl compounds 4a, 5a and 6a, respectively (Scheme 1). The mono-diazocarbonyl compounds 4b-d, 3-diazo-1,5-dioxacyclotridecane-2,4-dione 4e and bis-diazocarbonyl compounds 5b-h (Fig. 1) were synthesized successfully using the method described above. These macrocyclic diazocarbonyl compounds 4-6 were fully characterized based on the spectral data.

Next, carbenoid insertion reactions of mono-diazocarbonyl compounds with N-substituted or unsubstituted indoles were performed.12 The macrocyclic diazo compound 4b was reacted with indole using 2 mol % of rhodium(II) acetate as catalyst in dry DCM at reflux to afford the respective indol-3-yl macrocyclic dilactones 7a in 66% yield (Scheme 2 and Table 1). Further, the C-alkylation of indole occurred regioselectively.4c-f Subsequently, the macrocyclic diazo compound 4b was reacted with 5-bromoindole and 5-nitroindole to afford the respective indol-3-yl macrocyclic dilactones 7b and 7c in 80% and 61% yields. This interesting result led us to synthesize libraries of indol-3-yl macrocyclic dilactones. Thus, the diazocarbonyl compounds 4a,b,e were treated with N-methylindole to furnish the corresponding 1-methylindol-3-yl macrocyclic dilactones 7d-f in good yields. The reaction of 4b with N-benzylindole afforded the respective

![Scheme 2. Reaction of macrocyclic carbenoids with substituted indoles.](image)

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazocarbonyl compound</th>
<th>Indol-3-yl macrocyclic dilactone 7</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>66 (7a)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>80 (7b)</td>
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</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>61 (7c)</td>
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<td>4</td>
<td>4a</td>
<td>70 (7d)</td>
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<tr>
<td>5</td>
<td>4b</td>
<td>72 (7e)</td>
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</tr>
<tr>
<td>6</td>
<td>4e</td>
<td>76 (7f)</td>
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</tr>
<tr>
<td>7</td>
<td>4b</td>
<td>74 (7g)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4a</td>
<td>75 (7h)</td>
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</table>

Fig. 1. Synthesized macrocyclic diazocarbonyl compounds.
Table 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazocarbonyl compound</th>
<th>Indol-3-yl macrocyclic dilactone 7</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>4b</td>
<td><img src="image1.png" alt="Image" /></td>
<td>73 (7i)</td>
</tr>
<tr>
<td>10</td>
<td>4b</td>
<td><img src="image2.png" alt="Image" /></td>
<td>78 (7j)</td>
</tr>
<tr>
<td>11</td>
<td>4c</td>
<td><img src="image3.png" alt="Image" /></td>
<td>82 (7k)</td>
</tr>
<tr>
<td>12</td>
<td>4b</td>
<td><img src="image4.png" alt="Image" /></td>
<td>66 (7l)</td>
</tr>
<tr>
<td>13</td>
<td>4b</td>
<td><img src="image5.png" alt="Image" /></td>
<td>60 (7m)</td>
</tr>
</tbody>
</table>

* Yields are unoptimized and refer to isolated pure compound.

1-benzylindol-3-yl macrocyclic dilactone 7g. Reaction of an equimolar quantity of 13-membered macrocyclic diazocarbonyl compound 4a and 1,1'-butane-1,4-diylbis(1H-indole) afforded the corresponding C3-alkylation product 7h in 75% yield. Similar reactions of 4b or 4c with 1,1'-butane-1,4-diylbis(1H-indole), 1,1'-hexane-1,6-diylbis(1H-indole) or 1,1'-[1,2-phenylenebis(methylene)]-bis(1H-indole) furnished the respective indol-3-yl macrocyclic dilactones 7l–1. Further, the tris-indole product 7m was obtained from the reaction of 4b and the corresponding tris-indole. All the products showed a characteristic singlet around δ 5 ppm and the absence of the indole 3-CH proton which confirmed the C3-alkylation reaction of the macrocyclic diazocarbonyl compounds.

Encouraged by the above results, we envisaged the formation of two C–C bonds via a double carbenoid insertion reaction. To this end, 1 equiv of 1,1'-butane-1,4-diylbis(1H-indole) or 1,1'-hexane-1,6-diylbis(1H-indole) was reacted with 2.5 equiv of macrocyclic diazocarbonyl compound 4b in the presence of 2 mol % of Rh2(OAc)4 as catalyst under reflux to furnish the respective bis-crown compounds 8a,b, (Fig. 2) and a minor amount (20–25%) of mono alkylated products 7i,j. The structures of products 8 were confirmed from spectral data.

Next, the double C-alkylation of bis-diazocarbonyl compounds with substituted indoles was investigated. Thus, the reaction of macrocyclic bis-diazocarbonyl compounds with excess N-methylindole or N-benzylindole was performed at reflux to afford the corresponding bis-indol-3-yl macrocyclic tetralactones 9a,b in moderate yields (Scheme 3 and Table 2). The macrocyclic bis-diazocarbonyl compounds 5f,g were reacted with excess N-benzylindole or N-methylindole to afford the bis-indol-3-yl macrocyclic tetralactones 9c–e in moderate yields. Similarly, the bis-diazocarbonyl compounds 5e,h were reacted with excess N-methylindole to afford the corresponding double C3-alkylation products 9f,g.

Finally, we envisaged the synthesis of cryptands based on the above intermolecular carbenoid insertion strategy. Towards this, an equimolar amount of the bis-diazocarbonyl compound 5e and 1,1'-butane-1,4-diylbis(1H-indole) were refluxed in dry benzene and then column chromatographic purification furnished cryptand 10 in 30% yield (Fig. 3) via intermolecular double carbenoid insertion. Similarly, the reaction of the bis-diazocarbonyl compound 5g with 1,1'-[1,2-phenylenebis(methylene)]-bis(1H-indole) afforded the respective cryptand 11 in 32% yield. Mechanistically, all the above reactions might proceed via a zwitterionic intermediate to afford the C3-alkylation product regioselectively.

In conclusion, we have synthesized several mono- and bis-diazo macrocyclic compounds and demonstrated their regioselective intermolecular carbenoid insertion reactions affording a range of indol-3-yl macrocyclic dilactones. Intermolecular double carbenoid insertion was performed with either mono- or bis-diazocarbonyl compounds. The advantage of the intermolecular double alkylation methodology was demonstrated by achieving the synthesis of indolyl cryptands for the first time. A supramolecular study of the above synthesized macrocycles is under progress in our laboratory.

![Image](image6.png)

Fig. 2. Synthesis of bis-crown ethers 8 via double-carbenoid insertion.

![Image](image7.png)

Scheme 3. Reaction of bis-diazocarbonyl compounds with indoles.
Table 2
Synthesis of indol-3-yl macrocyclic tetralactones via Scheme 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazocarbonyl compound</th>
<th>Indol-3-yl macrocyclic dilactone 9</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td><img src="image_url" alt="Image of compound 5a" /></td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td><img src="image_url" alt="Image of compound 5a" /></td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>5f</td>
<td><img src="image_url" alt="Image of compound 5f" /></td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>5f</td>
<td><img src="image_url" alt="Image of compound 5f" /></td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>5g</td>
<td><img src="image_url" alt="Image of compound 5g" /></td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>5e</td>
<td><img src="image_url" alt="Image of compound 5e" /></td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>5h</td>
<td><img src="image_url" alt="Image of compound 5h" /></td>
<td>56</td>
</tr>
</tbody>
</table>

* Yields are unoptimized and refer to isolated pure compound.

Fig. 3. Synthesis of indolyl cryptands via double carbenoid insertion.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.102.

References and notes


11. General procedure for the synthesis of macrocyclic diazocarbonyl compounds 4: To a solution containing macrocyclic diamine 1 (1 mmol) and 4-acetamidobenzenesulfonyl azide (1.2 mmol) in dry dichloromethane (50 mL) was added DBU (1.5 mmol) under an argon atmosphere and the reaction stirred at room temperature overnight. To the reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed. To the above refluxing mixture, macrocyclic tetralactone 8a was added and the mixture refluxed for 4 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective bis[1-H-indol-3-yl] macrocyclic tetracarboxylate 9a. Selected spectral data.

12. General procedure for the synthesis of indol-3-yl macrocyclic dialactones 7: To an oven-dried flask, macrocyclic diazocarbonyl compound 4 (0.5 mmol) and substituted indole (0.6 mmol) in dry benzene or DCM (50 mL) were added under an inert atmosphere. To the above reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed for 4 h. Progress of the reaction was monitored by TLC. On completion, the solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective indol-3-yl macrocyclic dialactones 7. Selected spectral data.}

13. General procedure for the synthesis of bis-indol-3-yl crown compounds 8: To an oven-dried flask, 1,1'-butane-1,4-diylbis(H-indole) or 1,1'-hexane-1,6-diylbis(H-indole) (0.3 mmol) and 2 mol % of rhodium(II) acetate in dry benzene or DCM (100 mL) were charged under an inert atmosphere and refluxed. To the above refluxing mixture, macrocyclic diazocarbonyl compound 4 (0.75 mmol) in dry benzene or DCM was added slowly over 1 h using a syringe pump and the mixture refluxed for 6 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue was purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective bis-C–H insertion products 8. Bis-indol-3-yl macrocyclic dialactones 8a: White solid; mp 128–130 °C, [α] 2005 D 2928, 2879, 1739, 1486, 1335, 1291, 1220, 1140, 754. 1H NMR (CD3OD, 500 MHz) δ 7.25–7.16 (m, 10H, Arom-H). 13C NMR (CD3OD, 125 MHz) δ 130.5 (quat-C), 127.8 (C), 127.1 (quat-C), 121.7 (CH), 119.6 (CH), 119.4 (CH3), 109.4 (CH3), 70.6 (OCH3), 68.7 (OCH3), 64.6 (OCH3), 49.5 (CH), 45.9 (NCH3), 27.5 (CH2). HRMS (ESI+): caledd for C4H2N3O4Na2 (M + 2Na)1+ 813.3395, found 813.3331. Bis-indol-3-yl macrocyclic dialactones 8b: White solid; mp 168–170 °C, [α] 2007 D 3050, 2930, 2876, 1734, 1466, 1274, 1248, 1132, 743. 1H NMR (CDCl3, 200 MHz) δ 7.66–7.61 (m, 2H, Arom-H), 7.58–7.60 (m, 8H, Arom-H), 5.03 (s, 2H, CH2), 4.79–4.76 (m, 12H, OCH2 and NCH3). 13C NMR (CDCl3, 50 MHz) δ 131.2 (quat-C), 128.7 (C), 109.2 (quat-C), 107.5 (quat-C), 70.6 (OCH3), 70.4 (OCH3), 68.7 (OCH3), 64.6 (OCH3), 49.4 (CH), 28.9 (CH2). HRMS (ESI+): calculated for C36H42N2O12Na+ (M + Na)1+ 859.3629, found 859.3588. General procedure for the synthesis of bis-[1-indol-3-yl]- macrocyclic tetracarboxylates 9a: To an oven-dried flask, bis-diazoacarbonyl compound 5 (0.3 mmol) and substituted indole (0.7 mol) in dry benzene or DCM (100 mL) were charged under an inert atmosphere. To the above reaction mixture, 2 mol % of rhodium(II) acetate was added and the mixture refluxed for 6 h. Progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective bis[1-indol-3-yl] macrocyclic tetracarboxylates 9a. 12.25 Bis-[1-[1-methyl-(1H-indol-3-yl)-1,4,7,10,14,17,20,23-octaoxacyclohexacosane-11,13,24,26-tetraene 9a: Brown thick oil; [α] 2000 D (neat) cm−1 3057, 2946, 2874, 1746, 1471, 1333, 1142, 735. 1H NMR (CDCl3, 200 MHz) δ 7.61 (d, 2H, Arom-H, J = 8 Hz), 7.25–7.10 (m, 10H, Arom-H), 5.00 (s, 2H, CH2), 4.28 (m, 8H, OCH2), 3.71–3.62 (m, 16H, OCH2), 3.52 (s, 6H, NCH3), 11C NMR (CDCl3, 50 MHz) δ 169.0 (C=O), 137.3 (quat-C), 129.3 (quat-C), 127.5 (quat-C), 122.4 (CH), 120.1 (CH), 119.7 (CH), 109.9 (quat-C), 70.9 (OCH3), 69.3 (OCH3), 65.3 (OCH3), 49.9 (CH), 33.3 (NCH3). HRMS (ESI+): calculated for C36H42N2O12Na2 (M + 2Na)1+ 717.2635, found 717.2702.
(=CH), 121.9 (=CH), 121.4 (=CH), 120.9 (=CH), 119.6 (=CH),
119.2 (=CH), 118.4 (=CH), 109.4 (=CH), 109.2 (=CH), 106.5 (quat-
C), 65.1 (OCH$_2$), 50.3 (CH), 45.7 (NCH$_3$), 28.5 (CH$_3$), 28.3 (CH$_2$),
27.9 (CH$_2$), 27.6 (CH$_2$), 27.1 (CH$_2$), 25.6 (CH$_2$), 24.9 (CH$_2$), 24.6
(CH$_2$). HRMS (ESI$^+$) calcd for C$_{38}$H$_{44}$N$_2$O$_8$Na (M+Na)$^+$: 679.2995,
found 679.2901. Bis-indol-3-yl cryptand 11: Brown solid; mp 218–
220 °C (decomposition); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3055, 2932, 1734, 1464,
1305, 1282, 1144, 910, 730. $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.67–
6.91 (m, 14H, Arom-H), 5.19 (s, 4H, NCH$_2$), 5.06 (s, 2H, CH$_2$),
4.44–4.12 (m, 8H, OCH$_2$), 3.67–3.46 (m, 8H, OCH$_2$). $^{13}$C NMR
(CDCl$_3$, 50.3 MHz) $\delta$ 168.0, 135.1, 134.7, 129.4, 128.7, 127.8,
127.0, 122.4, 120.2, 118.3, 109.8, 106.9, 68.8, 64.8, 50.5, 48.1. HRMS
(ESI$^+$) calcd for C$_{38}$H$_{36}$N$_2$O$_{10}$Na (M+Na)$^+$: 703.2268, found
703.2283.