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Nicholas Reactions in the Synthesis of Dicobalt Dibenzocyclooctyne Complexes

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ABSTRACT

Hexacarbonyldicobalt complexes of biaryl-substituted 4-methoxybutynones and 4-methoxy-2-butynes undergo intramolecular Nicholas reactions to form dibenzocyclooctyne–\(\text{Co}_2\text{(CO)}_6\) complexes in good yields. Reductive decomplexation of the cyclization products is possible, and the method has been applied to a formal synthesis of isoschizandrin.

Cyclooctyne is well-known as the smallest of the simple cycloalkynes with sufficient stability to be capable of isolation in the conventional sense.\(^1\) This does not apply to all cyclooctyne derivatives, as increasing unsaturation in the eight-membered ring renders the compounds more marginally stable or incapable of isolation.\(^2\) In contrast, the hexacarbonyldicobalt complexes of cyclooctynes appear to have excellent stability. While direct preparation from cyclooctyne itself is known,\(^4\) this is synthetically limited. Several scattered reports of de novo construction of cyclooctyne–\(\text{Co}_2\text{(CO)}_6\) complexes have been published,\(^5\) including those resulting from Nicholas reaction chemistry,\(^5\) ring-closing metathesis,\(^6\) aldol and Michael reaction chemistry,\(^7\) Diels–Alder reactions,\(^8\) and epoxide ring-openings.\(^9\) In addition, cyclic ether and amine complexes have been prepared.\(^10\) Despite the viability of systems of this class, there has been no attempt to prepare dibenzocyclooctynedicobalt complexes (\(1\), Figure 1) or to explore their applicability toward dibenzocyclooctane-containing compounds.

The dibenzocyclooctane lignans are a large group of natural products occurring widely, particularly in the Schizandraceae family.\(^11\) Their structural features and


wide-ranging biological activities have made them recent attractive synthetic targets. Synthesis of the eight-membered rings of these systems is overwhelmingly attractive synthetic targets. Synthesis of the eight-membered rings of these systems is overwhelmingly advantageous.

Our group had recent success with the use of intramolecular Nicholas reaction chemistry in the preparation of dibenzocycloheptynes—CO₂(aryl), complexes, and have found the method useful in allocolchicine synthesis in conjunction with reductive decomplexation reactions. As a result of these developments, we have chosen to explore a novel method of complexation by Co₂(CO)₈ to afford the corresponding ketones (9a—d) of functionalized dibenzocyclooctane lignans in addition to their C₈-hydroxy-substituted and nonoxygen-substituted counterparts, we considered it important to include both γ-carbonyl cation (4—5) and normal (6—7) versions of these Nicholas reactions.

Table 1. Preparation of 4

| 9a, R⁴ = OMe, Ar = 2,3,4-(-MeO)₃C₆H₄ | 10a (86%) | 8a (96%) | 4a (93%) |
| 9b, R⁴ = R⁵ = OMe, Ar = 2,3,4-(-MeO)₃C₆H₄ | 10b (97%) | 8b (78%) | 4b (90%) |
| 9c, R⁵ = OMe, Ar = 3-thiényl | 10c (94%) | 8c (79%) | 4c (87%) |
| 9d, R⁴ = R⁵ = R⁶ = OMe, Ar = 2,3,4-(-MeO)₃C₆H₄ | 10d (98%) | 8d (92%) | 4d (93%) |

* MnoO₂, CH₂Cl₂, rt; † Swern conditions.

The precursors for γ-carbonyl cation complexes were selected to be 4-alkoxy-2-butylnoyl-substituted biaryls (8) (Table 1), which were prepared from the biarylcaboxaldehydes (9) in straightforward fashion.

Reaction of the aldehydes with the lithium acetylde derived from 3-methoxy-1-propane (propargyl methyl ether) gave the benzylic/propargylic alcohols (8) in good to excellent yield (Table 1); subsequent oxidation with MnoO₂ or using Swern conditions when MnO₂ performed sluggishly, gave the corresponding ketones (8). Complexation of the alkyl functions of these alkynes with CO₂(CO)₈ then afforded 4 readily.

The biaryls bearing 4-methoxy-2-butylnoyl functions (11) were also prepared from the biarylcaboxaldehydes (9) in three steps (Table 2). Reduction of the aldehyde function to the benzylic alcohols (12) occurred cleanly and in excellent yields. Substitution of bromide for the alcohol function (13) was accomplished with PB₃. For tetramethoxy-substituted 13f, reaction of the benzyl bromide with the lithium acetylide derived from propargyl methyl ether afforded 11f in acceptable yield. In other cases, this protocol gave poor yields; conversely, use of this lithium acetylide in the presence of InCl₃ and catalytic amounts of Pd(dppf)Cl₂ gave 11c—e successfully. Once again, the alkyn functions underwent complexation by CO₂(CO)₈ to afford 6 readily.

Cyclization reactions of the aryl alkynone complexes were investigated first. While previous experience has...
shown that Nicholas reaction based γ-carbonyl cations are more reliably generated using Bu3BOTf as Lewis acid,19 BF3·OEt2 (3 equiv, 0 °C) gave good rates of reaction in the case of 4 (Table 3). Reactions were conducted at 4 × 10−3 M; doubling the concentration reduced yield modestly (entry 4 versus entry 5). The addition of i-Pr2NEt (1.5 equiv, 0 °C to rt, CH2Cl2 (4 M)).

Table 2. Preparation of 6

<table>
<thead>
<tr>
<th>9</th>
<th>12</th>
<th>13</th>
<th>11</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>9e, R1 = OMe, Ar = 3-thienyl</td>
<td>12e (89%)</td>
<td>13e (73%)</td>
<td>11c (61%)</td>
<td>6c (86%)</td>
</tr>
<tr>
<td>9d, R1 = R2 = R3 = OMe, Ar = 2,3,4-(MeO)3C6H2</td>
<td>12d (93%)</td>
<td>13d (99%)</td>
<td>11d (69%)</td>
<td>6d (99%)</td>
</tr>
<tr>
<td>9e, R1 = OMe, Ar = 3,5-Me2C6H3</td>
<td>12e (92%)</td>
<td>13e (63%)</td>
<td>11e (66%)</td>
<td>6e (86%)</td>
</tr>
<tr>
<td>9f, R1 = OMe, Ar = 3,4,5-(MeO)3C6H2</td>
<td>12f (99%)</td>
<td>13f (80%)</td>
<td>11f (61%)</td>
<td>6f (78%)</td>
</tr>
</tbody>
</table>

*InCl3 and Pd(dppf)Cl2 omitted.

In the event, the Co2(CO)6 unit with predominant overreduction of the alkene function to give cyclooctanone 6 could be obtained as the predominant product (44% yield, 51% based on recovered starting material) by employing 2 equiv of NaH2PO2 in 2-methoxyethanol;21 this was accompanied by 13% of cyclooctenone 8 and 14% of unreacted 5d. The use of the conventionally employed 5 equiv of hypophosphite gave greater amounts of cyclooctanone 14 (29%), at the expense of 15 (36%).22

Decomplexation reactions of the cyclooctynones were studied using 5d as a model compound (Scheme 1). Use of Bu3SnH20 resulted in the successful removal of the Co2(CO)6 unit with predominant overreduction of the alkene function to give cyclooctanone 14 (82% yield), along with a small amount of cyclooctenone 15 (9% yield). The cyclooctenone 15 could be obtained as the predominant product (44% yield, 51% based on recovered starting material) by employing 2 equiv of NaH2PO2 in 2-methoxyethanol;21 this was accompanied by 13% of cyclooctanone 14 and 14% of unreacted 5d. The use of the conventionally employed 5 equiv of hypophosphite gave greater amounts of cyclooctanone 14 (29%), at the expense of 15 (36%).22

Table 3. Intramolecular Nicholas Reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>conditionsa</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>A</td>
<td>5</td>
<td>5a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>B</td>
<td>6</td>
<td>5b</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>B</td>
<td>8</td>
<td>5c</td>
<td>68b</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>A</td>
<td>8</td>
<td>5d</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>A’</td>
<td>8</td>
<td>5d</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>6c</td>
<td>A</td>
<td>1</td>
<td>7c</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>6d</td>
<td>A</td>
<td>2</td>
<td>7d</td>
<td>93</td>
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<tr>
<td>8</td>
<td>6e</td>
<td>A</td>
<td>2</td>
<td>7e</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>6f</td>
<td>A</td>
<td>1</td>
<td>7f</td>
<td>91</td>
</tr>
</tbody>
</table>

*a: BF3·OEt2 (3 equiv), 0 °C to rt, CH2Cl2 (4 × 10−3 M); B: BF3·OEt2 (4 equiv), Pr2NEt (1.5 equiv) 0 °C to rt, CH2Cl2 (4 × 10−3 M). 2c-5c 14:1. 36 × 10−3 M.


In the case of dibenzocyclooctyne complex 7d, the reductive decomplexation was much more straightforward. Employing our hydrosilylation/protodesilylation modification of the Isobe protocol, $^{16,23}$ 7d afforded 16 cleanly (95% yield).

Alkene 16 is well suited for use in the synthesis of isoschizandrin. Epoxidation of the alkene function occurred readily with dimethyldioxirane (DMDO), giving 17 in 87% yield (Scheme 2). Lewis acid mediated cuprate attack of the epoxide gave alcohol 18 with complete diastereoselectivity (92% yield). Swern oxidation of the alcohol then afforded 19 in 95% yield. The Meyers group has previously converted enantioenriched 19 into (−)-isoschizandrin (79% yield, along with 9% (−)-schizandrin) by methyllithium addition, $^{17a}$ consequently, this constitutes a formal synthesis of racemic isoschizandrin.

In summary, we have found that intramolecular Nicholas reactions of both biaryl-4-methoxybutynonedicobalt complexes and biaryl-4-methoxy-2-butynedicobalt complexes afford the corresponding dibenzocyclooctyne–CO$_2$(CO)$_6$ complexes in good yields. Reductive decomplexation of these cyclization products is possible, and the process may be applied to the formal synthesis of isoschizandrin.

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**Supporting Information Available.** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.