Novel Synthesis of Oxathiocine Derivatives by Wittig Olefination and Intramolecular Heck Reaction via an 8-endo-trig Cyclization

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Received 30 July 2008; revised 13 August 2008

Abstract: Syntheses of hitherto unreported heterocycles, such as oxathiocine derivatives, in excellent yields, and a doubly cyclized oxathiocine derivative, through a Wittig olefination and intramolecular Heck reaction sequence via an unusual 8-endo-trig cyclization, are reported.

Key words: Wittig olefination, intramolecular Heck reaction, palladium catalyst, oxathiocine, 8-endo-trig

The importance of medium-sized rings in synthetic organic chemistry is exemplified by their presence as the structural core moiety in a large number of biologically important natural products. Moreover, these units serve as target molecules in numerous synthetic studies. Several excellent articles and monographs have documented such medium-ring syntheses well. Though synthetic protocols for five- and six-membered ring systems are common, seven- and eight-membered ring formations are not abundant. The cyclization strategies for medium-sized rings are often restricted due to entropy factors and transannular interactions. In general, the number of methods available for the synthesis of medium-sized heterocycles are relatively small. Among the various protocols, the palladium-catalyzed intramolecular Heck reaction has become a useful synthetic method due to its excellent functional group tolerance and high stereoselectivity. Recently, we have reported the synthesis of some interesting medium-ring heterocycles by the application of radical cyclization, ring-closing metathesis and the intramolecular Heck reaction. Denieul and Skrydstrup recently showed that during the intramolecular Heck cyclization, the 7-exo-trig mode of cyclization of a compound having a vinyl group attached to an aromatic ring was favored over the 8-endo-trig mode. Subsequently, Guy et al. supported this statement by synthesizing the 8-endo Heck products through a Heck reaction with the activated vinylic systems. The same authors also synthesized eight-membered sulfur heterocycles via the 8-endo-trig mode of cyclization by the same protocol, starting from the highly activated vinylic double bond. These results prompted us to undertake a study on the intramolecular Heck reaction of different Heck precursors with a view to synthesizing eight-membered oxathio-heterocycles fused with diaryl moieties; synthetically, this is a challenge due to the presence of strain within such compounds. Additionally, we were interested in studying the Heck cyclization under ligand-free conditions using aryl bromides in view of a recent finding that ligand-free approaches do not work for the usually preferred aryl bromides. To our knowledge, the synthesis of oxathiocine heterocycles has not yet been reported.

The intramolecular Heck reaction, as stated earlier, can undergo ring-closure by two possible modes, namely exo- and endo-cyclization. Between these two possible modes, small to medium size (5–8) ring-formation is usually favored by an exo-mode, since the endo-mode is sterically very demanding; the endo-mode requires that the olefinic system moves into the loop of the substrate, generating an

![Scheme 1](image-url)

**Scheme 1** Reagents and conditions: (i) anhyd CH2Cl2, Et3N, DMAP, 0 °C→RT, 2–3 h, stirring; (ii) Ph3P, n-BuLi, THF, 0 °C→RT, 1.5 h, stirring.
energetically favorable substituted alkene product. Conversely, large ring (~20) formation with a flexible tether usually favors endo-cyclization. To the best of our knowledge, only a limited number of examples of endo-cyclization for the formation of medium-sized rings have been reported. The required Heck precursors 4a–e were synthesized in 88–95% yields by a Wittig olefination reaction of substrates 3a–e. The Wittig reagent was prepared from Ph3PMeI in anhydrous tetrahydrofuran in the presence of butyllithium, between 0 °C and room temperature, for 30 minutes. The substrates 3a–e were synthesized in 74–90% yield by the reaction of hydroxyaldehydes 1a–e with 2-bromobenzenesulfonyl chloride (2) in anhydrous dichloromethane in the presence of triethylamine and a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP) at between 0 °C and room temperature for 2–3 hours (Scheme 1). Compounds 1a–e were prepared in turn by the Reimer–Tiemann reaction of the corresponding phenolic compounds.

When the intramolecular Heck reaction was carried out with the substrate 4a using the concept of Jeffery's two-phase protocol in the presence of Pd(OAc)2 as catalyst, base, additive and solvent (Table 1). Table 1 Optimization of the Palladium-Catalyzed Intramolecular Heck Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>DMF</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>K2CO3</td>
<td>DMF</td>
<td>81</td>
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<tr>
<td>3</td>
<td>Pd(OAc)2</td>
<td>Et3N</td>
<td>DMF</td>
<td>&lt;5</td>
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<tr>
<td>4</td>
<td>Pd(OAc)2</td>
<td>Ag2CO3</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)2</td>
<td>Cs2CO3</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh3)2Cl2</td>
<td>KOAc</td>
<td>DMF</td>
<td>21</td>
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<tr>
<td>7</td>
<td>PdCl2</td>
<td>KOAc</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>Pd(PPh3)4</td>
<td>KOAc</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>MeCN</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>dioxane</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>toluene</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

a Reactions were carried out at 80 °C, TBAB used as additive.

When the intramolecular Heck reaction was carried out with the substrate 4a using the concept of Jeffery's two-phase protocol in the presence of Pd(OAc)2 as catalyst, base, additive and solvent (Table 1). Table 1 Optimization of the Palladium-Catalyzed Intramolecular Heck Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>DMF</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>K2CO3</td>
<td>DMF</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)2</td>
<td>Et3N</td>
<td>DMF</td>
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<tr>
<td>4</td>
<td>Pd(OAc)2</td>
<td>Ag2CO3</td>
<td>DMF</td>
<td>NR</td>
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<tr>
<td>5</td>
<td>Pd(OAc)2</td>
<td>Cs2CO3</td>
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<td>Pd(OAc)2</td>
<td>KOAc</td>
<td>toluene</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

a Reactions were carried out at 80 °C, TBAB used as additive.

b Catalyst used 5 mol%.
c 2.75 equivalents of base used.
d Isolated yield. NR indicates no reaction.

Optimum conditions for the cyclization were established through a series of experiments whereby various changes were made to the catalyst, base, additive and solvent (Table 1).

During the course of optimization of the reaction, we found that the catalyst, base, additive and solvent all have profound effects on the reaction yield (Table 1). It is important to note that aryl bromides are reported to usually undergo Heck cyclization in the presence of a ligand. However, in the present instance the reaction was achieved under ligand-free conditions. TBAB plays an important role in the Heck cyclization because, in the absence of TBAB, the reaction did not proceed at all. Guy et al. synthesized the endo-Heck product with a sophisticated catalytic combination system [Pd(OAc)2, DMA, Et3NCl, Cy2NMe, 12 h, 100 °C], but our optimized condition are relatively simple [Pd(OAc)2, DMF, KOAc, TBAB, 80 °C] and it takes only 45–70 min for complete conversion while their reaction required 12 hours. To test the generality of the reaction, substrates 4b–e were also treated under the optimized conditions to afford the novel oxathiocine derivatives 5b–e in 79–91% yield. The results are summarized in Table 2.

After achieving the synthesis of the endo-Heck products, we extended the reaction to the readily available, inexpensive starting material 2,7-dihydroxynaphthalene. 2,7-Di-
hydroxynaphthalene-1,8-dicarboxaldehyde (1f) was readily prepared from 2,7-dihydroxynaphthalene by a Reimer–Tiemann reaction. The hydroxyaldehyde 1f, on reaction with 2-bromobenzenesulfonyl chloride (2), gave compound 3f which, on treatment with Ph₃PMeI in the presence of n-BuLi in THF, afforded the corresponding di-Heck precursor 4f (Scheme 3).

The substrate 4f was reacted under the optimized reaction conditions (Table 1, entry 1) for 30 minutes at 120 °C to furnish the 8-endo double Heck product 5f in only 26% yield along with unidentified products. Increasing the reaction time caused considerable decomposition of the doubly cyclized oxathiocine product. When the conditions described in Table 1 (except entry 1) were applied to

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>60</td>
<td>5a</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>55</td>
<td>5b</td>
<td>88</td>
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<td>3</td>
<td>4c</td>
<td>45</td>
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<td>4d</td>
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<tr>
<td>5</td>
<td>4e</td>
<td>70</td>
<td>5e</td>
<td>79</td>
</tr>
</tbody>
</table>

*a All the reactions were performed under optimized reaction conditions [Pd(OAc)₂, DMF, KOAc, TBAB, 45–70 min, 80 °C].

*b Isolated yield.

Scheme 3  Reagents and conditions: (i) CHCl₃, aq NaOH, 70 °C, stirring, 4 h, H₂SO₄; (ii) 2, anhyd CH₂Cl₂, Et₃N, DMAP, 0 °C→r.t., 1 h; (iii) anhyd THF, PPh₃MeI, n-BuLi, stirring, 2 h.
The cyclization of substrates 4 with the sulfonate ester tether may occur via two alternative pathways – either an 8-endo-trig or a 7-exo-trig cyclization. It is interesting to note that we have observed only 8-endo-trig cyclization to afford, exclusively, the eight-membered oxathiocine derivatives.

Denieul and Skrydstrup have reported\(^8\) that the palladium-catalyzed cyclization of a similar substrate with an ester tether to give a mixture of three products: the 7-exo-trig cyclization product (i.e. seven-membered lactone, major product), the 8-endo-trig cyclization product (eight-membered lactone, minor product) and the biaryl coupling product (trace). The authors optimized the 7-exo-trig product with unactivated olefinic systems.\(^8\)\(^a\)

The exclusive formation of benzoxathiocine derivatives 5a-e and 5f via the 8-endo-mode of cyclization is quite unusual. Beletskaya and Cheprakov reported\(^1\) that the endo-Heck cyclization can occur when the Heck precursor possesses a Michael-type olefinic fragment,\(^1\) such as a highly activated double bond, otherwise exclusive exo-cyclization occurs. Subsequently, Guy et al. found that for 8-endo-Heck cyclization to occur, the substrate required an activated vinyl double bond. However, in our present work, the eight-membered oxathiocine derivatives were found to form exclusively via the unusual 8-endo-trig mode of cyclization without such requirements.

In conclusion, we have developed an efficacious, regioselective method for the construction of eight-membered oxathiocine derivatives (and a doubly Heck cyclized endo-Heck product) via an unusual 8-endo-trig cyclization using a Wittig reaction followed by intramolecular Heck cyclization as the key steps. The method represents a simple synthetic protocol for the formation of fused oxathiocine (and doubly cyclized oxathiocine) derivatives.

Preparation of 1a-f by Reimer–Tiemann Reaction; Typical Procedure

2-Naphthol (14 g, 0.1 mol) was added to a round-bottomed flask and a hot solution of NaOH (32 g, 0.8 mol) in H₂O (40 mL) was added. The reaction was heated to ~70 °C in an oil bath and CHCl₃ (16 mL) was added dropwise to it. The reaction mixture was stirred for 1 h at the same temperature and then allowed to cool to r.t. The reaction mixture was transferred to a 500 mL beaker with hot H₂O and subsequently acidified with H₂SO₄ (10 N) and extracted with CH₂Cl₂ (3 × 75 mL), washed with H₂O (2 × 50 mL) and dried (Na₂SO₄). The organic layer was collected and the solvent was distilled off. The crude material was purified by column chromatography over silica gel (PE) to afford the product 1a. Compounds 1b-f were prepared in a similar manner.

Preparation of Compounds 3a–f; Typical Procedure

DMAP (10 mg) and Et₃N (2 mL) were added to a solution of 1a (200 mg, 1.17 mmol) in anhydrous CH₂Cl₂ (20 mL) at 0 °C. 2-Bromobenzensulfonfonyl chloride (2; 300 mg, 1.17 mmol) in anhydrous CH₂Cl₂ (10 mL) was added dropwise and reaction mixture and stirred for 2 h. The reaction mixture was washed with H₂O (3 × 10 mL) and brine (10 mL) and dried (Na₂SO₄). Evaporation of the CH₂Cl₂ gave a crude mass, which was purified by silica gel chromatography (EtOAc–PE, 10%) to afford product 3a. Compounds 3b–f were obtained in a similar manner.

3a

Yield: 83%; solid; mp 115–116 °C.

IR (KBr): 1697, 1371, 1197 cm⁻¹.

³¹P NMR (CDCl₃, 100 MHz): δ = 39.0 [M⁺], 392 [M⁺ + 2].


3b

Yield: 81%; solid; mp 97–98 °C.

IR (KBr): 1693, 1378, 1160 cm⁻¹.

³¹P NMR (CDCl₃, 100 MHz): δ = 7.15 (dd, J = 8.4, 1.2 Hz, 1 H, ArH), 7.37 (t, J = 7.6 Hz, 1 H, ArH), 7.43 (dt, J = 7.6, 1.2 Hz, 1 H, ArH), 7.50–7.54 (m, 2 H, ArH), 7.69 (t, J = 7.6 Hz, 1 H, ArH), 7.84–8.05 (m, 2 H, ArH), 7.90 (d, J = 8.8 Hz, 1 H, ArH), 10.66 (s, 1 H, CHO).

MS: m/z = 340 [M⁺], 342 [M⁺ + 2].


3c

Yield: 90%; solid; mp 90–91 °C.

IR (KBr): 1694, 1372, 1195 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 2.37 (s, 3 H, CH₃), 7.03 (d, J = 8.4 Hz, 1 H, ArH), 7.32 (d, J = 8.4 Hz, 1 H, ArH), 7.45 (t, J = 7.6 Hz, 1 H, ArH), 7.54 (t, J = 7.6 Hz, 1 H, ArH), 7.71 (s, 1 H, ArH), 7.87 (d, J = 8.0 Hz, 1 H, ArH), 7.97 (dd, J = 7.6, 1.2 Hz, 1 H, ArH), 10.26 (s, 1 H, CHO).

MS: m/z = 354 [M⁺], 356 [M⁺ + 2].


3d Yield: 77%; solid; mp 78–79 °C.

IR (KBr): 1691, 1378, 1169 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 3.83 (s, 3 H, OCH₃), 7.04 (d, J = 2.0 Hz, 1 H, ArH), 7.37–7.38 (m, 2 H, ArH), 7.45 (dt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.55 (dt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.88 (dd, J = 8.0, 1.2 Hz, 1 H, ArH), 7.98 (dd, J = 7.6, 1.6 Hz, 1 H, ArH), 10.25 (s, 1 H, CHO).

MS: m/z = 370 [M⁺], 372 [M⁺ + 2].


3b Yield: 89%; solid; mp 69–70 °C.

IR (KBr): 1379, 1193 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 5.24 (dd, J = 11.2, 1.6 Hz, 1 H, =CH₂H₂), 5.67 (dd, J = 17.6, 1.6 Hz, 1 H, =CH₂H₂), 6.79–6.81 (m, 1 H, CH₂=CH₂), 6.92–6.97 (m, 2 H, ArH), 7.13–7.17 (m, 2 H, ArH), 7.40–7.52 (m, 2 H, ArH), 7.85 (dd, J = 6.8, 1.2 Hz, 1 H, ArH), 7.96 (dd, J = 6.4, 1.6 Hz, 1 H, ArH).

MS: m/z = 338 [M⁺], 340 [M⁺ + 2].

Anal. Calcd for C₁₄H₁₃BrO₃S: C, 49.57; H, 3.27. Found: C, 49.37; H, 3.07.

3c Yield: 87%; solid; mp 108–110 °C.

IR (KBr): 1694, 1378, 1169 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 7.15 (d, J = 8.8 Hz, 1 H, ArH), 7.50–7.55 (m, 2 H, ArH), 7.58 (dt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.88–7.89 (m, 2 H, ArH), 8.02 (dt, J = 8.0, 1.6 Hz, 1 H, ArH), 10.23 (s, 1 H, CHO).

MS: m/z = 374 [M⁺], 376 [M⁺ + 2].


3d Yield: 80%; solid; mp 77–78 °C.

IR (KBr): 1362, 1170 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 2.40 (s, 3 H, CH₃), 5.20 (dd, J = 11.2, 1.6 Hz, 1 H, =CH₂H₂), 5.63 (dd, J = 17.6, 1.6 Hz, 1 H, =CH₂H₂), 6.73–6.78 (m, 1 H, CH₂=CH₂), 6.90 (s, 1 H, ArH), 6.93 (d, J = 7.2 Hz, 1 H, ArH), 7.06 (dd, J = 3.0, 1.0 Hz, 1 H, ArH), 7.51 (dt, J = 7.8, 1.7 Hz, 1 H, ArH), 7.58 (dt, J = 7.6, 1.7 Hz, 1 H, ArH), 7.89 (dd, J = 7.7, 1.2 Hz, 1 H, ArH), 7.99 (dd, J = 8.2, 1.2 Hz, 1 H, ArH).

MS: m/z = 352 [M⁺], 354 [M⁺ + 2].


4d Yield: 95%; solid; mp 81–82 °C.

IR (KBr): 1363, 1169 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 3.78 (s, 3 H, OCH₃), 5.23 (dd, J = 11.2, 1.6 Hz, 1 H, =CH₂H₂), 5.61 (dd, J = 17.6, 1.6 Hz, 1 H, =CH₂H₂), 6.67–6.70 (m, 1 H, CH₂=CH₂), 6.85 (s, 1 H, ArH), 6.90 (d, J = 6.8 Hz, 1 H, ArH), 7.02 (d, J = 3.2 Hz, 1 H, ArH), 7.42 (dt, J = 8.0, 1.2 Hz, 1 H, ArH), 7.51 (dt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.83 (dd, J = 7.6, 1.2 Hz, 1 H, ArH), 7.94 (dd, J = 8.0, 1.6 Hz, 1 H, ArH).

MS: m/z = 368 [M⁺], 370 [M⁺ + 2].


4e Yield: 91%; solid; mp 76–77 °C.

IR (KBr): 1365, 1169 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 5.25 (dd, J = 11.2, 1.6 Hz, 1 H, =CH₂H₂), 5.69 (dd, J = 17.6, 1.6 Hz, 1 H, =CH₂H₂), 6.78–6.83 (m, 1 H, CH₂=CH₂), 6.92 (s, 1 H, ArH), 6.96 (d, J = 7.4 Hz, 1 H, ArH), 7.11 (d, J = 2.3 Hz, 1 H, ArH), 7.39–7.56 (m, 2 H, ArH), 7.91 (dd, J = 8.1, 1.0 Hz, 1 H, ArH), 8.01 (dd, J = 7.9, 1.0 Hz, 1 H, ArH).

MS: m/z = 372 [M⁺], 374 [M⁺ + 2].

Yield: 90%; solid; mp 200–201 °C.

IR (KBr): 1353, 1171 cm⁻¹.

MS: m/z = 648, 650, 652.

Yield: 88%; solid; mp 120–121 °C.

IR (KBr): 1334, 1167 cm⁻¹.

MS: m/z = 292 [M⁺].

Yield: 79%; solid; mp 122–123 °C.

IR (KBr): 1334, 1167 cm⁻¹.

MS: m/z = 292 [M⁺].

Yield: 26%; solid; mp 211–212 °C.

IR (KBr): 1352, 1183 cm⁻¹.

MS: m/z = 488 [M⁺].

Yield: 91%; solid; mp 132–133 °C.

IR (KBr): 1354, 1164 cm⁻¹.

Acknowledgment

We thank the DST (New Delhi) for financial assistance. B.C. and B.S. are grateful to the CSIR (New Delhi) for a senior and a junior research fellowship, respectively.

References


