ELECTROCHEMICAL SYNTHESIS OF SPIROISOXAZOLE
DERIVATIVES AND ITS APPLICATION TO NATURAL PRODUCTS

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Abstract – Efficient synthesis of the trans-spiroisoxazole (1) and its unnatural

cis-isomer (2) was accomplished by employing anodic oxidation of 4, followed

by Zn(BH₄)₂ reduction. This method was applied to an assembly of the carbon

framework of zamamistatin (12).

A family of marine natural products, carrying a dibromophenylpyruvic acid oxime moiety,¹ is of interest,
because of their diverse biological activities, as well as a typical spiroisoxazole framework (1), biogenesis
of which might involve epoxidation of an aromatic ring, followed by intramolecular nucleophilic attack of
an oxime.² In this context, we accomplished the first total synthesis of aerothionins and aerophobin-1³ by
the TTFA (thallium (III) trifluoroacetate) oxidation of phenol (4),⁴ followed by Zn(BH₄)₂ reduction of
spirodienone (3). In particular, reduction of the ketone usually provided unnatural cis-form (2).⁵

Although the thallium oxidation was a reliable method to give the expected spirodienones, the reaction
produced a considerable amount of by-products such as dimers or benzofurans; furthermore, excess
amounts of the oxidant were required to complete the reaction. This reaction feature should be
reconsidered from the viewpoint of recent environmental concerns. Against such background, an
improved synthetic methodology of the spiroisoxazoles (type-3) was elaborated by employing anodic
oxidation of the corresponding phenol derivatives. We disclose herein our research progress involving
synthetic attempts toward zamamistatin (12).⁶
The phenol (4) for the oxidation was synthesized through the Horner-Wadsworth-Emmons reaction (Scheme 1), while our previous investigation included hydrolysis of the azulactone.\textsuperscript{3a,b}

Thus, bromination of 5, followed by benzylation afforded 6, which on coupling with an anion of 7 gave enol ether (8) in a good overall yield. On exposure to hydroxylamine hydrochloride, 8 underwent simultaneous deprotection and oximation. Finally, selective hydrogenolysis produced the expected substrate (4) for electrolysis.

Scheme 1. Reagents: a. i) pyridinium bromide perbromide / Py, 88%; ii) BnBr, K\textsubscript{2}CO\textsubscript{3} / DMF, 90%. b. LHMDS, 7, 96%. c. i) NH\textsubscript{2}OH•HCl / MeOH, 91%; ii) H\textsubscript{2}, 10% Pd-C / AcOH – dioxane, 85%.

Anodic oxidation of 4 was attempted at the following procedure. Procedure: the oxidation was performed under CCE (constant current electrolysis) or CPE (constant potential electrolysis) conditions employing a glassy carbon beaker (200 or 50 mL) as an anode, a platinum wire as a cathode, and
appropriate supporting salts (ca. 0.2 mol / L). As can be seen in Table 1, the MeOH - LiClO₄ combinations (entries 1 - 3) provided by-products (9, 10). Formation of dimer (10) implied that insufficient potential caused one-electron oxidation to give diaryl ether through a radical intermediate (11). Upon using a constant potential at 1.3 V vs. SCE, current was used for other oxidation, resulting in recovery of unreacted 4. The acidic dioxane and acetone were obviously unfit solvents (entries 4, 5), although they contributed to production of oxa-spiro derivatives. Eventually, the best condition was obtained when 4 (1 mmol / L) was oxidized under CPE conditions in MeCN - nBu₄NCIO₄ (entry 7). Successive reduction of 4 with Zn(BH₄)₂ involving a work-up procedure with MgSO₄, afforded corresponding \textit{trans} and \textit{cis} alcohols (1, 2) in 41 and 39% yields, respectively, which were twice higher than those reported previously. In addition, exposure of unnecessary 2 to Et₂NH effected [\textit{\Delta}]-elimination to give 4, which could be repeatedly submitted to the oxidation.

**Table 1. Anodic Oxidation of Dibromophenylpyruvic Acid Oxime (4)**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>supporting salt</th>
<th>potential (V vs. SCE)</th>
<th>current (mA)ᵇ</th>
<th>conc. of 4 (mmol/L)</th>
<th>yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>LiClO₄</td>
<td>0.9-1.3</td>
<td>10</td>
<td>3</td>
<td>11 8 41  -</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>LiClO₄</td>
<td>0.9-1.3</td>
<td>10</td>
<td>1</td>
<td>18 12 14 -</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>LiClO₄</td>
<td>1.3</td>
<td>80-5</td>
<td>3</td>
<td>19 17 14 20</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>LiClO₄</td>
<td>1.5-1.7</td>
<td>50</td>
<td>3</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>acetone</td>
<td>nBu₄NCIO₄</td>
<td>1.6</td>
<td>50-9</td>
<td>3</td>
<td>multi spots</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>nBu₄NCIO₄</td>
<td>1.6</td>
<td>50-5</td>
<td>3</td>
<td>49 - -  7</td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>nBu₄NCIO₄</td>
<td>1.6</td>
<td>20-5</td>
<td>1</td>
<td>68 - - -</td>
</tr>
</tbody>
</table>

a. 10%HClO₄ / dioxane.  b. Equivalent of current: 2 F / mol.
In the next stage, our attention turned to application of this electrochemical methodology to synthesis of natural products. A literature survey of dibromophenylpyruvic acid derivatives of marine origin indicated zamamistatin (12), isolated from the Okinawan sponge *Pseudoceratina purpurea*. The unprecedented bisspiroisoxazole-structure possessed antibacterial activity against *Rhodospirillum salexigens* SCRC 113, which implied 12 would be a candidate of an inhibitor of biofouling.

Scheme 2. Reagents: a. TBSOTf, 2,6-lutidine. b. LiBH₄, 78% in two steps. c. DMSO, SO₂•Py, Et₃N, 90%. d. i) dimethyl phosphate, Et₃N; ii) TBSCI, Imd., 89%. e. LHMDS / THF, then 6, 47%. f. i) TBAF; ii) NH₂OH•HCl, 98% in two steps. g. H₂, Pd black / AcOH - dioxane, 54%. h. CPE, 1.6 V vs SCE, 2 F / mol, nBu₄NClO₄ / MeCN, 35%. i. Zn(BH₄)₂ / CH₂Cl₂, 21a: 26%, 21b: 23%. j. (S)-MTPACl, DMAP, Py, 22: 45%, 23: 43%, 24: 78%.
After protection of an allyl alcohol of 1 as a siloxy ether (13), LiBH₄ reduction provided alcohol (14) in 78% yield from 1 (Scheme 2). Compound (14) was oxidized to give aldehyde (15), which was coupled with dimethyl phosphite under basic conditions, followed by protection of an alcohol generated, leading to the Horner-Wadsworth-Emmons reagent (16). Coupling of an anion of 16 with 6 provided 17 in 47% yield. Successively, 17 was converted through 18⁹ into oxime-phenol (19), which on anodic oxidation provided the bisspiroisoxazoline derivative (20), as a diastereomeric mixture. Zn(BH₄)₂ reduction of 20 gave 21a⁹ and 21b⁹ in 26 and 23% yields, respectively. The stereochemistry of 21a and 21b could be distinguished by conversion into their (S)-MTPA esters: 21a gave a separable mixture of 22 and 23, whereas 21b provided 24 as the sole product. Since zamamistatin (12) has a C₂ symmetry, introduction of an optically active MTPA residue to racemic 21a, would produce a mixture of diastereomers, while meso-compound (21b) gave meso-product (24). Accordingly, 21a should possess the same stereochemistry of the two spiro-centers as zamamistatin (12).¹⁰

In conclusion, we have accomplished an improved synthetic method of the spiroisoxazole derivatives (1, 2) by using anodic oxidation. This method provided access to the assembly of the zamamistatin-framework. Further investigation towards the natural zamamistatin molecule and related natural products carrying dibromophenylpyruvic acid oxime is in progress.

ACKNOWLEDGMENTS

This work was supported by Grant-in-Aid for the 21st Century COE program "KEIO Life Conjugate Chemistry", as well as Scientific Research C (15510181), from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

REFERENCES AND NOTES


8. The TBAF treatment effected a high-yield conversion of the TBS-enol ether into the oxime. Upon a direct use of NH₂OH•HCl as in the case of 8, 18 was obtained in 39% yield.

9. 21a: IR (film) 3434 cm⁻¹; NMR ¹H (CDCl₃) 2.29 (2H, d, J = 8.3 Hz), 3.03 (2H, d, J = 17.6 Hz), 3.76 (6H, s), 4.00 (2H, d, J = 17.6 Hz), 4.44 (2H, d, J = 8.3 Hz), 6.33 (2H, s); ¹C (CDCl₃) 38.6, 60.2, 73.9, 91.0, 112.3, 121.1, 131.0, 148.0, 150.9. HRMS m/z (M⁺OH) Calcd for C₁₈H₁₃N₂O₅₇₉Br₄, 654.7715. Found: 654.7755. 21b: IR (film) 3436 cm⁻¹; NMR ¹H (acetone-d₆) 3.23 (2H, d, J = 17.6 Hz), 3.72 (6H, s), 3.87 (2H, d, J = 17.6 Hz), 4.15 (2H, d, J = 8.3 Hz), 5.44 (2H, d, J = 8.3 Hz), 6.51 (2H, s); ¹C (acetone-d₆) 39.7, 60.2, 75.1, 91.3, 113.7, 122.1, 132.0, 148.6, 151.9. HRMS m/z (M⁺) Calcd for C₁₈H₁₆N₂O₆₇₉Br₄, 671.7682. Found: 671.7712.

10. Unfortunately, efforts to convert into natural product (12) have been unsuccessful up to now, and continuous attempts are still in progress.