SUBSTITUTED BENZIMIDAZOLES. PART 2.\(^1\)
SYNTHESIS AND PROPERTIES OF 2-ARYL-1-HYDROXY-5-(2-THENOYL)BENZIMIDAZOLE 3-OXIDES

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Abstract — A selected set of 2-aryl- and 2-hetaryl-1-hydroxy-5-(2-thienoyl)benzimidazole 3-oxides (10a-m) was prepared for bioassay via condensation of the corresponding aldehydes with 4-(2-thienoyl)-1,2-benzoquinone dioxime (8) as catalyzed by perchloric acid. The dioxime (8) was obtained by facile reduction of 5-(2-thienoyl)benzofuroxan (7a) with 1,2-diphenylhydrazine. The furoxans (7a, b) are accessible by pyrolysis of the respective o-nitrophenyl azides (6a,b). Compounds (10a-g) showed a comparable range of in vitro activity against *Escherichia coli* and *Candida albicans* (MIC 62.5 - 125 \(\mu\)g/mL).

Introduction

Active research on the synthesis and chemistry of benzimidazoles led to a number of commercially available pharmaceuticals and veterinary medical products.\(^2,3\) Structural modifications of substituents in 2- and 5-positions of the benzimidazole nucleus provided the most active drugs. Thus, thiabendazole [2-(4-thiazolyl)benzimidazole] (1) is an
anthelmentic agent with a remarkable broad spectrum of activity against nematode species,\textsuperscript{4,5} while 2-(2-thienyl)benzimidazole (2) was reported to possess germicidal and antibacterial activity.\textsuperscript{6} Nocodazole (3), a synthetic benzimidazole derivative having a 2-thenoyl group at the 5(6)-position, is a potentially useful antitumor drug with a noteworthy specificity directed toward malignant cells.\textsuperscript{7,8} 1-Hydroxybenzimidazole 3-oxides are also of potential biological interest, and some derivatives were reported to exhibit antibacterial and germicidal activity.\textsuperscript{9}

We envisaged that incorporation of the 2-thenoyl moiety into benzimidazole N-oxides might enhance and/or modify their bioactivity. In particular, some 2-aryl-1-hydroxy-5-(2-thenoyl)benzimidazole 3-oxides (10) (Scheme 3) were prepared for bioassay. Herein their synthesis and some properties are described.

Synthesis
The synthetic versatility of the title benzimidazole N-oxides (10) entails the following steps: (i) Preparation of 5-(2-thenoyl)benzofuroxan (7a), (ii) reduction of 7a to the corresponding 4-(2-thenoyl)-1,2-benzoquinone dioxime (8), and (iii) reaction of the latter dioxime with an appropriate aromatic or heteroaromatic aldehyde. These procedures are illustrated in Schemes 1, 2 and 3, respectively.

The benzofuroxan (7a), hitherto unknown, was readily accessible in good yields by pyrolysis of 4-azido-3-nitro-2-thenoylbenzene (6a) in boiling toluene. The azide (6a) was obtained by treatment of 4-chloro-3-nitro-2-thenoylbenzene (5a) with sodium azide in
dimethyl sulfoxide at room temperature. Compound (5a) in turn, was prepared by Friedel-Crafts aroylation of thiophene with 4-chloro-3-nitrobenzoyl chloride (4) in dichloromethane in the presence of anhydrous aluminum chloride, following a reported procedure\textsuperscript{10,11} (Scheme 1). The generality of the above method, namely pyrolysis of o-nitrophenyl azides for preparing benzofuroxans, has been documented.\textsuperscript{12} It is noteworthy that a number of substituted o-chloronitrobenzenes were converted directly to the corresponding benzofuroxans upon heating with sodium azide in dimethyl sulfoxide without isolation of the intermediate o-nitrophenyl azide.\textsuperscript{13} In the present work, heating of compound (5a) with sodium azide in dimethyl sulfoxide at 100 °C for 0.5 h gave, however, a mixture of intractable products.

![Scheme 1](image-url)

(a : R = H ,  b : R = \( \text{Lewis acid} \))

Scheme 1
In an analogous manner, 5(6)-(2,2'-bithienyl-5-carbonyl)benzofuroxan (7b) was prepared by pyrolysis of the intermediate azide (6b) which, in turn, was obtained by the reaction of sodium azide with 4-chloro-3-nitro-5-(2,2'-bithienyl-5-carbonyl)benzene (5b). The latter compound was accessible by aroylation of 2,2-bithiophene with 4-chloro-3-nitrobenzoyl chloride (4) in refluxing benzene in the presence of stannic chloride (Scheme 1).

The key synthon, 4-thenoyl-1,2-benzoquinone dioxime (8), was prepared by reduction of the corresponding benzofuroxan (7a) with 1,2-diphenylhydrazine in chloroform at ambient temperature. The latter reagent has previously been successfully applied for the reduction of related benzofuroxans to the corresponding o-benzoquinone dioximes. Dehydration of 4-thenoyl-1,2-benzoquinone dioxime (8) to 4-thenoylbenzofurazan (9) proceeded smoothly in aqueous potassium hydroxide solution under reflux (Scheme 2). A conversion reaction of related o-benzoquinone dioximes into benzofurazans (in alkaline media) was described in the literature.

A modified convenient route for the synthesis of 2-aryl-1-hydroxybenzimidazole 3-oxides involves direct interaction of o-benzoquinone dioxime with the particular aldehyde in ethanol in the presence of perchloric acid as a catalyst. In this way the target heterocycles,
2-aryl- and 2-hetaryl-1-hydroxy-5-(2-thenoyl)benzimidazole 3-oxides (10a-m), were prepared in moderate to good yields by the reaction of 4-thenoyl-1,2-benzoquinone dioxime (8) with the appropriate aldehyde (Scheme 3). The reaction conditions are essentially similar to those recently reported.\textsuperscript{17}

\[
\begin{align*}
8 & \xrightarrow{\text{Ar-CH}=O} \xrightarrow{\left(\text{C}_2\text{H}_5\text{OH}, \text{HClO}_4\right)} 10 \text{a-m} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
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<td>[\text{C}_5\text{H}_4]</td>
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<tr>
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<td>3-FC\text{H}_4</td>
<td>4-Cl\text{C}_6\text{H}_4</td>
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</table>

Scheme 3

On the other hand, the reaction of benzofuroxan with primary nitroalkanes was described as a convenient method for preparing 2-alkyl-1-hydroxybenzimidazole 3-oxides.\textsuperscript{18,19} For a
comparative study 1-hydroxy-2-methyl-5-(2-thenoyl)benzimidazole 3-oxide (11) was prepared via this route wherein 5-(2-thenoyl)benzofuroxan (7a) was allowed to react with nitroethane at room temperature in THF in the presence of triethylamine (Scheme 4). The physical and analytical data for compounds (5-11) are given in Table 1.

![Scheme 4](image)

**Mass spectra**

The molecular ions and the major fragment ions, observed in the MS spectra of the compounds (10a-m) are shown in Scheme 5. The spectra display the correct molecular ions [M]+, albeit of low relative abundance. Prominent fragment ions [M-16]+ (base peak in a number of cases) arise via the elimination of an N-oxide oxygen from the respective molecular ions [M]+. This behaviour is characteristic for related 1-hydroxybenzimidazole 3-oxides.[17,20,21] Consecutive loss of another oxygen atom produces the corresponding non-oxygenated benzimidazole ion as an intense peak [M-32]+. Other significant fragmentation modes involve α-cleavage at the carbonyl moiety, resulting in the formation of the thenoyl cation [A] at m/z 111 [Scheme 5, path (a)], and the hetaroyl cation [B] in path (b). The latter ion ejects carbon monoxide to form ion [C]. Similarly, the thenoyl cation (base peak in a number of cases) extrudes CO to form the thienyl cation [D] at m/z 83. This fragmentation pathway is analogous to that observed for acylthiophenes[22] under electron impact. It is worth mentioning that such an α-cleavage process does not occur to any appreciable extent prior to loss of one or both N-oxide oxygen atoms from [M]+.
Table 1. Physical and Analytical Data for Compounds (5b, 7-11)

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<th>Compd No</th>
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<th>Yield (%)</th>
<th>Mol. Formula</th>
<th>[M]⁺ Analysis % (Calcd / Found)</th>
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<th>H</th>
<th>N</th>
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An intense peak corresponding to the fragment ion [ArCO]+ was also observed in all spectra. This ion is formed through a rearrangement process involving an intermediate oxaziridine system [E], produced in a typical N-oxide → oxaziridine transformation under electron impact (Scheme 5). The occurrence of [ArCO]+ as the base peak in the mass spectra of related 2-arylbenzimidazole N-oxides was previously reported.23 Subsequent elimination of CO from [ArCO]+ produces [Ar]+, a process [F] → [G] for which metastable ions were detected.

The MS spectra of the benzofuroxans (7a, b) showed the correct molecular ions [M]+, as suggested by their molecular formulas. The fragment ions at m/z M-16 arise through elimination of the N-oxide oxygen atom from [M]+, a mode which is diagnostic of heterocyclic N-oxides. The base peak at m/z = 111 corresponds to the 2-thenoyl cation.

Table 1 (continued)

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<th>M / M+</th>
<th>%</th>
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</table>
Scheme 5

[M]⁺⁺

[M-O]⁺⁺

[M-2O]⁺⁺

[E]

[C] (m/z = 83)

[D] (m/z = 111)

[A] (m/z = 111)

[B]

[C] (m/z = 83)

[D] (m/z = 111)

[Ar]^+
EXPERIMENTAL

The starting compounds are commercially available, except 2,2'-bithiophene-5-carbaldehyde, which was prepared according to a literature procedure.\textsuperscript{24} Melting points were measured on an electrothermal Mel-Temp. apparatus, and are uncorrected. Electron impact (EI) MS spectra were obtained with a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by M. H. W. Laboratories at Phoenix, Arizona, U.S.A. Due to the poor solubility in conventional solvents we did not get NMR spectra of 10a-m.

4-Chloro-3-nitro-1-(2-thenoyl)benzene (5a).
Thiophene (8.4 g, 100 mmol) was added dropwise within 30 min to a stirred solution of 4-chloro-3-nitrobenzoyl chloride (4) (22 g, 100 mmol) and anhydrous aluminum chloride (13.5 g, 100 mmol) in dichloromethane (100 mL). The reaction mixture was stirred for 4 h, then poured onto ice-cooled aqueous HCl (5 %, 500 mL). The organic layer was separated, washed with 5 % sodium bicarbonate (150 mL), and water (150 mL). The solvent was evaporated in vacuo, and the residual solid was recrystallized from ethanol. Yield 23.0 g (85 %), mp 105-106 °C (lit.,\textsuperscript{11} mp 107-108 °C).

4-Azido-3-nitro-1-(2-thenoyl)benzene (6a).
4-Chloro-3-nitro-1-(2-thenoyl)benzene (5a) (26.8 g, 100 mmol) was stirred with sodium azide (7.0 g, 110 mmol) in dimethyl sulfoxide (100 mL) for 30 min at rt. The reaction mixture was poured onto water (500 mL), the precipitated solid was filtered, dried and recrystallized from chloroform / pet. ether (bp 40-60 °C). Yield 22 g (80 %), mp 81-82 °C (decomp). (Caution: This compound explodes violently upon melting).

5(6)-(2-Thenoyl)benzofuroxan (7a).
4-Azido-3-nitro-1-(2-thenoyl)benzene (6a) (27.4 g, 100 mmol) was refluxed in toluene (250 mL) for 30 min. The solvent was then evaporated under reduced pressure, and the residual solid was recrystallized from hot ethanol. Yield 23 g (94 %), mp 116-117 °C.
4-Chloro-3-nitro-5-(2,2'-bithienyl-5-carbonyl)benzene (5b).
To a solution of 4-chloro-3-nitrobenzoyl chloride (4) (2.2 g, 10 mmol) in benzene (20 mL) containing stannic chloride (2.3 g, 10 mmol) was added a solution of 2,2'-bithiophene (1.66 g, 10 mmol) in benzene (10 mL) during 15 min with vigorous stirring. The resulting mixture was then heated at 75 °C for 2 h, cooled and cautiously poured onto a cold solution of aqueous HCl (5 %, 100 mL). The organic layer was separated, washed with aqueous sodium bicarbonate (5 %, 3 x 50 mL), and then with water (2 x 25 mL). The organic phase was concentrated to half of its original volume under reduced pressure, the precipitated solid was collected and recrystallized from hot ethanol to give yellow needles. Yield 1.3 g (56 %), mp 162-163 °C.

4-Azido-3-nitro-5-(2,2'-bithienyl-5-carbonyl)benzene (6b).
A solution of 4-chloro-3-nitro-5'-(2,2'-bithienyl-5-carbonyl)benzene (5b) (1.75 g, 5 mmol) and sodium azide (0.65 g, 10 mmol) in dimethyl sulfoxide (10 mL) was stirred for 30 min at rt. The mixture was then poured into water (25 mL) and the precipitated solid was collected, dried and recrystallized from chloroform / pet. ether (bp 40-60 °C). Yield 1.5 g (84 %), mp 120-121 °C (decomp).

5-(2,2'-Bithienyl-5-carbonyl)benzofuroxan (7b).
4-Azido-3-nitro-5-(2,2'-bithienyl-5-carbonyl)benzene (6b) (1.8 g, 5 mmol) was refluxed for 30 min in toluene (15 mL). The solvent was then evaporated and the residual solid was recrystallized from ethanol to give tiny orange plates. Yield 1.5 g (90 %), mp 196-197 °C.

4-(2-Thenoyl)-1,2-benzoquinone Dioxime (8).
A filtered solution of 5(6)-2'-thenoyl)benzofuroxan (7a) (4.9 g, 20 mmol) and 1,2-diphenylhydrazine (6.0 g, 330 mmol) in chloroform (50 mL) was kept at rt under nitrogen atmosphere for 24 h. The reaction mixture was then extracted with aqueous sodium hydroxide (5 %, 2 x 50 mL). Acidification of the combined alkaline extracts with acetic acid
yielded an orange precipitate which was collected, dried, and recrystallized from ethanol. Yield 2.5 g (50 %), mp 148-149 °C (decomp).

5-(2-Thenoyl)benzofurazan (9).

4-(2'-Thenoyl)-1,2-benzoquinone dioxime (8) (2.5 g, 10 mmol) was refluxed for 30 min in aqueous potassium hydroxide (5 %, 30 mL). The solid which separated upon cooling was collected, washed successively with water and cold methanol, dried, and recrystallized from chloroform/pet. ether (bp 40 - 60 °C). Yield 2.0 g (87 %), mp 105-106 °C.

Preparation of 2-aryl- and 2-hetaryl-1-hydroxy-6-(2-thenoyl)benzimidazole 3-Oxides (10a-m).

General procedure. Perchloric acid (70 %, 2 mL, 20 mmol) was added to a solution of 4-(2-thenoyl)-1,2-benzoquinone dioxime (8) (1.24 g, 5.0 mmol) and the appropriate aldehyde (5.0 mmol) in ethanol (15 mL). The reaction mixture was then heated under reflux for 2 h with continuous stirring. The product began to crystallize after 30 min. At the end of the reaction, the precipitate was collected, washed with cold ethanol and dried. In the case of compounds (10a, d, e, m) water was added to the cold reaction mixture to complete the precipitation of the product.

The title products were purified by dissolving in aqueous sodium hydroxide solution, filtration, and reprecipitation with acetic acid. The precipitated product was collected, washed successively with methanol, chloroform and diethyl ether. Yields were in the range 50 - 78 % (Table 1). Most of the title compounds melt with decomposition > 200 °C.

1-Hydroxy-2-methyl-5-(2-thenoyl)benzimidazole 3-Oxide (11).

To a solution of 5(6)-(2'-thenoyl)benzofuroxan (7a) (2.46 g, 10 mmol) and nitroethane (0.9 g, 12.0 mmol) in THF (100 mL) was dropwise added triethylamine (1.2 g, 12.0 mmol) over a period of 30 min at rt. An instantaneous exothermic reaction was observed and the product started to crystallize within 1 h. The reaction mixture was allowed to stand
overnight at rt, and the product was collected, washed with methanol, dried, and recrystallized from propanol. Yield 0.77 g (60 %), mp 223-224 °C.

Bioassay

Compounds (7a, b, 9 and 10a-m) were tested in vitro against E. coli and C. albicans. The MICs were determined by conventional agar dilution procedures at pH 7.4. Aqueous stock solutions of the test compounds were prepared with 0.1N NaOH. Serial dilutions were then made to obtain concentrations ranging from 125 – 1.25μg/ mL. The agar plates were inoculated with approximately 10^4 CFU per spot. The agar plates were then incubated at 37 °C for 18 h. The test compounds exhibited comparable, rather low activity against E. coli and C. albicans (MIC 62.5 – 125 μg/ mL).

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REFERENCES


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