Synthesis of 2-(2-, 3-, and 4-Pyridyl)benzoxazoles by the Reaction of Phenolic Schiff Bases with Thianthrene Cation Radical

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2-(2-, 3-, and 4-Pyridyl)benzoxazole derivatives were prepared in excellent yields by the oxidative cyclization of phenolic Schiff bases with thianthrene cation radical perchlorate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine.

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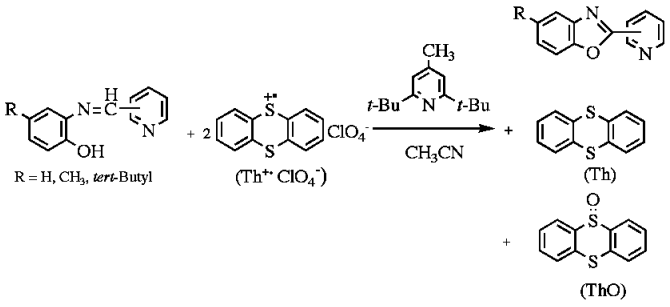
Benzoxazole derivatives, especially 2-(pyridyl)benzoxazoles, have attracted particular interests for their biological and analytical significance [1]. For an example, 5-substituted 2-(3-pyridyl)benzoxazoles were reported to show significant activity against microorganisms [2]. Due to their applications in industry and argriculture, a variety of methods have been developed for the synthesis of benzoxazoles using benign oxidizing agents [3]. Generally, 2-(2-pyridyl)benzoxazoles are made by the condensation of a pyridinecarboxylic acids with *o*-aminophenols [4]. Also, 2-(3-pyridyl)benzoxazoles were obtained from 3-pyridinecarbaldehyde (nicotinaldehyde) and *o*-aminophenols in the presence of iodobenzene diacetate [5]. Recently, we have also prepared various benzoxazole derivatives [6] from phenolic Schiff bases and thianthrene cation radical ($Th^{+\cdot}ClO_4^-$). In the present study, we report the preparation and mechanism of 2-(2-, 3-, and 4-pyridyl)benzoxazoles as shown in Scheme 1 and 2 respectively.

Scheme 1



The reaction of phenolic Schiff base with 2 equivalents of thianthrene cation radical perchlorate at room temperature in acetonitrile containing 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded 2-(2-, 3-, and 4-pyridyl)benzoxazoles in excellent yields as shown in Tables 1-3.

In this reaction, Schiff bases treated with thianthrene cation radical participated in oxidative cyclization at room temperature. Among the nine products shown in Tables 1-3, 5-*tert*-butyl-2-(2-, 3-, and 4-pyridyl)benzoxazoles (**2c**, **4c**, and **6c**) are new compounds. In all of the reactions, formation of thianthrene oxide is not related to the main reaction but stems from the hydrolysis of thianthrene cation radical due to either adventitious water or water added in the work-up procedure.

Scheme 2

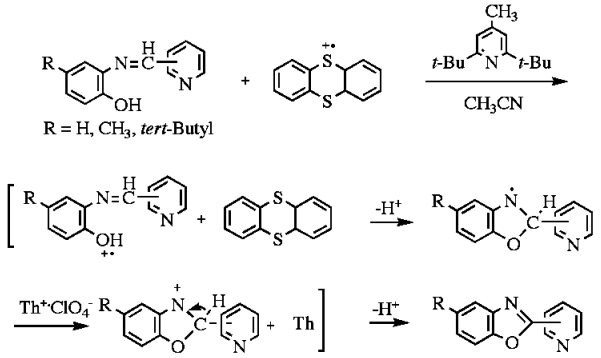
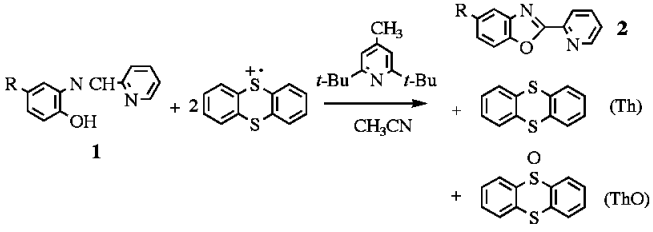


Table 1
2-(2-Pyridinyl)benzoxazoles

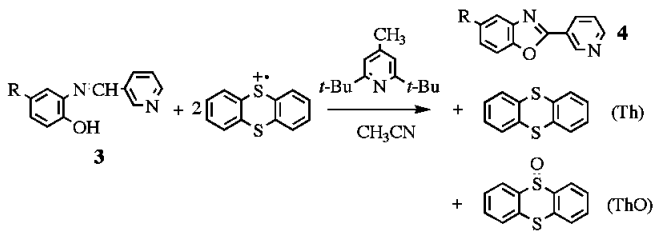


Entry	R	Schiff base (**1**) (%)	**2** [a] (%)	Th (%)	DTBMP (%)	ThO (%)
1a	H	2	83	91	87	2
1b	CH_3	0	96	99	86	1
1c	*t*-Butyl	0	99	97	88	3

[a] conversion yield

In conclusion, oxidative cyclization of phenolic Schiff bases to 2-(2-, 3-, and 4-pyridyl)benzoxazoles was achieved in excellent yields by thianthrene cation radical under mild conditions. It was also observed that Schiff bases with electron donating group were cyclized to give products in higher yields.

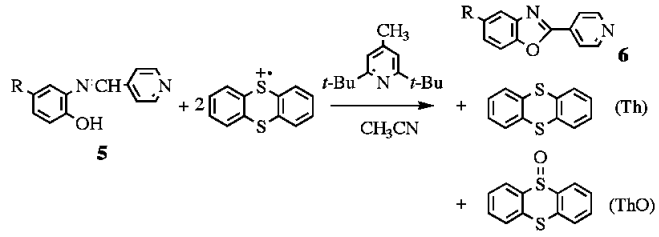
Table 2
2-(3-Pyridyl)benzoxazoles



Entry	R	Schiff base (**3**) (%)	**4** [a] (%)	Th (%)	DTBMP (%)	ThO (%)
3a	H	7	90	98	90	1
3b	CH_3	4	92	98	90	1
3c	t-Butyl	1	94	98	87	1

[a] conversion yield

Table 3
2-(4-Pyridyl)benzoxazoles



Entry	R	Schiff base (**5**) (%)	**6** [a] (%)	Th (%)	DTBMP (%)	ThO (%)
5a	H	2	78	96	91	3
5b	CH_3	7	87	97	89	1
5c	*t*-Butyl	3	96	97	83	1

[a] conversion yield

EXPERIMENTAL

Acetonitrile was purified by distillation over phosphorus pentoxide under argon prior to use. Thianthrene (Aldrich) was recrystallized twice from acetone. Aldehydes and aminophenols were used without further purification. Thianthrene cation radical perchlorate and Schiff bases were prepared according to the known procedure [5,7].

General Procedure.

The phenolic Schiff base, thianthrene cation radical perchlorate, and 2,6-di-*tert*-butyl-4-methylpyridine were placed in a septum-capped flask, which was evacuated and then filled with argon. Acetonitrile (20 mL) was added to the flask with a syringe. The reaction mixture was stirred at room temperature, during which time the cation radical color disappeared completely within 5-10 minutes. After stirring was continued overnight, water (10 mL) was added and the reaction mixture was neutralized with dilute aqueous sodium bicarbonate. The resultant mixture was extracted with methylene chloride (5x30 mL) and the combined organic layers were dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated at room temperature. The solid residue was dissolved in methylene chloride (50 mL) and used for identification of products by GC and GC-MS and for quantitative analysis by GC. The products were identified by GC, GC-MS and by comparison with authentic samples [8]. Yields of the products were determined by GC with biphenyl, as an internal standard, and predetermined response factors. The benzoxazoles were purified by chromatography on silica gel (methylene chloride:methanol = 15:1) and identified by ^{1}H NMR, GC-MS and elemental analysis. Each reaction was carried out twice.

Preparation of Thianthrene Cation Radical Perchlorate.

To a solution of perchloric acid (70%, 0.60 mL) in acetic anhydride (33 mL) was added a solution of thianthrene (1.0 g, 4.6 mmoles) in carbon tetrachloride (66 mL). The reaction mixture was then allowed to stand for 24 hours in the dark at room temperature. Dark purple colored crystals were formed and were collected by filtration and washed with carbon tetrachloride until the filtrate was colorless. The crystals were then dried in a flask under vacuum. The product (1.2 g, 3.9 mmoles, 84%) was dried under vacuum for short periods before use.

4-*tert*-Butyl-2-[(2-pyridylmethylene)amino]phenol (**1c**).

To a stirred solution of 2-amino-4-*tert*-butylphenol (3.34 g, 20 mmoles) in ethanol (20 mL) was added dropwise a solution of 2-pyridinecarbaldehyde (2 mL, 21 mmoles) in ethanol (20 mL) at room temperature. After stirring for 2 hours, the solvent was evaporated and the residue was crystallized from ethanol to give yellow crystals (3.04 g, 60%), mp 134-136°; ^{1}H nmr (300 MHz, deuterioacetone): δ 8.84 (s. 1H, methylene), 8.70 (dt, 1H, C6'-H, *J*=4.8), 8.41 (dt, 1H, C3'-H, *J*=7.9), 8.04 (s. 1H, OH), 7.92 (td, 1H, C4'-H, *J*=7.7, 1.7), 7.51-7.44 (m, 2H, C3-H, C5'-H), 7.28 (dd, 1H, C6-H, *J*=8.5, 2.3), 6.88 (d, 1H, C5-H, *J*=8.5), 1.30 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.08; N, 11.02. Found: C, 75.53; H, 7.20; N, 11.13.

4-*tert*-Butyl-2-[(3-pyridylmethylene)amino]phenol (**3c**).

Compound **3c** was prepared from 2-amino-4-*tert*-butylphenol and 3-pyridinecarbaldehyde by the above procedure and the residue was crystallized from ethanol to give yellow crystals (4.16 g, 82%), mp 100-102°; ^{1}H nmr (300 MHz, deuterioacetone): δ 9.15 (s, 1H, C2'-H), 8.98 (s. 1H, methylene), 8.67 (dd, 1H, C6'-H, *J*=4.8, 1.6), 8.46 (dt, 1H, C4'-H, *J*=7.9, 2.0), 8.01 (s. 1H, OH), 7.50 (td, s, 2H, C5'-H, *J*=6.9, C3-H), 7.25 (dd, 1H, C6-H, *J*=8.5, 2.3), 6.87 (d, 1H, C5-H, *J*=8.5), 1.32 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.08; N, 11.02. Found: C, 75.81; H, 7.37; N, 10.92.

4-*tert*-Butyl-2-[(4-pyridylmethylene)amino]phenol (**5c**).

Compound **5c** was prepared from 2-amino-4-*tert*-butylphenol and 4-pyridinecarbaldehyde by the above procedure and the residue was crystallized from ethanol to give yellow crystals (4.77 g, 94%), mp 150-152°; ^{1}H nmr (300 MHz, deuterioacetone): δ 8.95 (s. 1H, methylene), 8.71 (dd, 2H, C2'-H, *J*=4.4, 1.6), 8.06 (s. 1H, OH), 7.96 (dd, 2H, C3'-H, *J*=4.4, 1.6), 7.50 (d, 1H, C3-H, *J*=2.3), 7.28 (dd, 1H, C6-H, *J*=8.5, 2.3), 6.90 (d, 1H, C5-H, *J*=8.5), 1.31 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.08; N, 11.02. Found: C, 75.40; H, 7.20; N, 10.95.

5-*tert*-Butyl-2-(2-pyridyl)benzoxazole (**2c**).

The reaction was carried out with thianthrene cation radical perchlorate (315 mg, 1.0 mmol), **1c** (127 mg, 0.5 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (308 mg, 1.50 mmol) in acetonitrile to yield compound **2c** (125 mg, 99%), mp 116-117°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.75 (dq, 1H, C6'-H, *J*=4.8), 8.30 (dt, 1H, C3'-H, *J*=7.9, 0.9), 7.85-7.79 (m, 2H, C4'-H, C4-H), 7.53 (d, 1H, C7-H, *J*=8.6), 7.44-7.36 (m, 2H, C6-H, C5'-H), 1.35 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.41; H, 6.66; N, 11.10.

5-*tert*-Butyl-2-(3-pyridyl)benzoxazole (**4c**).

The reaction was carried out with thianthrene cation radical perchlorate(315 mg, 1.0 mmol), **3c** (127 mg, 0.5 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (308 mg, 1.50 mmol) in acetonitrile to yield compound **4c** (118 mg, 93%), mp 109-111°; ^{1}H nmr (300 MHz, deuterioacetone): δ 9.37 (dd, 1H, C2'-H, *J*=2.1, 0.7), 8.76 (dd, 1H, C6'-H, *J*=4.8, 1.6), 8.50 (dt, 1H, C4'-H, *J*=7.9, 2.0), 7.77 (s, 1H, C4-H), 7.61-7.50 (m, 3H, C6-H, C7-H, C5'-H), 1.38 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.22; H, 6.48; N, 11.24.

5-*tert*-Butyl-2-(4-pyridyl)benzoxazole (**6c**).

The reaction was carried out with thianthrene cation radical perchlorate (315 mg, 1.0 mmol), **5c** (127 mg, 0.5 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (308 mg, 1.50 mmol) in acetonitrile to yield compound **6c** (117 mg, 93%), mp 120-122°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 8.76 (dd, 2H, C2'-H, *J*=4.4, 1.6), 8.01 (dd, 2H, C3'-H, *J*=4.4, 1.6), 7.92 (s, 1H, C4-H), 7.50-7.42 (m, 2H, C6-H, C7-H), 1.36 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.17; H, 6.45; N, 11.26.

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