

A New Approach for the Synthesis of some 1,4-Benzoxathiin 4,4-Dioxide Derivatives

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A series of 1,4-benzoxathiin 4,4-dioxide derivatives have been prepared by a new synthetic route. The reactions of 2-chloro-4-nitrobenzenethiol **1** with 1-aryl-2-chloroethanones **2** in the presence of sodium hydroxide give 1-aryl-2-(2-chloro-4-nitrophenylthio)ethanones **3** which on oxidation with 30% aqueous hydrogen peroxide afford 1-aryl-2-(2-chloro-4-nitrophenylsulfonyl)ethanones **4**. By the reactions of compounds **4** with 2-[3 or 4-(bromomethyl)phenyl]benzoxazole in the potassium carbonate, triethylbenzylammonium chloride and dimethylformamide system, 2-aryl-3-arylmethyl-7-nitro-1,4-benzoxathiin 4,4-dioxides **5** or **6** are obtained *via* a tandem alkylation-cyclization process.

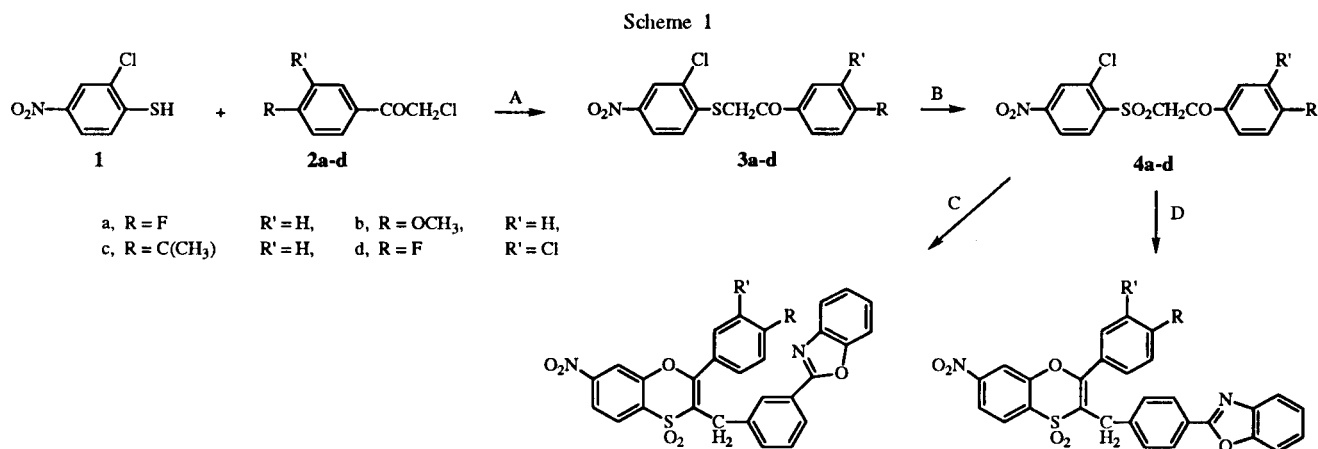
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The sulfonyl group-containing heterocyclic compounds have been extensively studied because they have great importance in biological and medicinal chemistry [1-3]. We have considerable interest in this field, and have focused our attention on the synthesis and reactions of 1,4-benzoxathiin 4,4-dioxide derivatives because of their biological activity, *e.g.* lipoxigenase inhibitors [4]. After 1,4-benzoxathiin 4,4-dioxide was synthesized by Parham and Jones [5] in 1954, a few synthetic methods of 1,4-benzoxathiin 4,4-dioxide derivatives were reported [6-8]. In this paper, a new process for synthesis of some 1,4-benzoxathiin 4,4-dioxide derivatives **5** and **6** is described.

The new synthetic approach which was achieved in a 3-step procedure is outlined in Scheme 1. First, treatment of 2-chloro-4-nitrobenzenethiol **1** with 1-aryl-2-chloroethanones **2a-d** in the presence of sodium hydroxide and triethylbenzylammonium chloride as a phase transfer catalyst afforded 1-aryl-2-(2-chloro-4-nitrophenylthio)ethanones **3a-d**. The intermediates **3** were obtained in

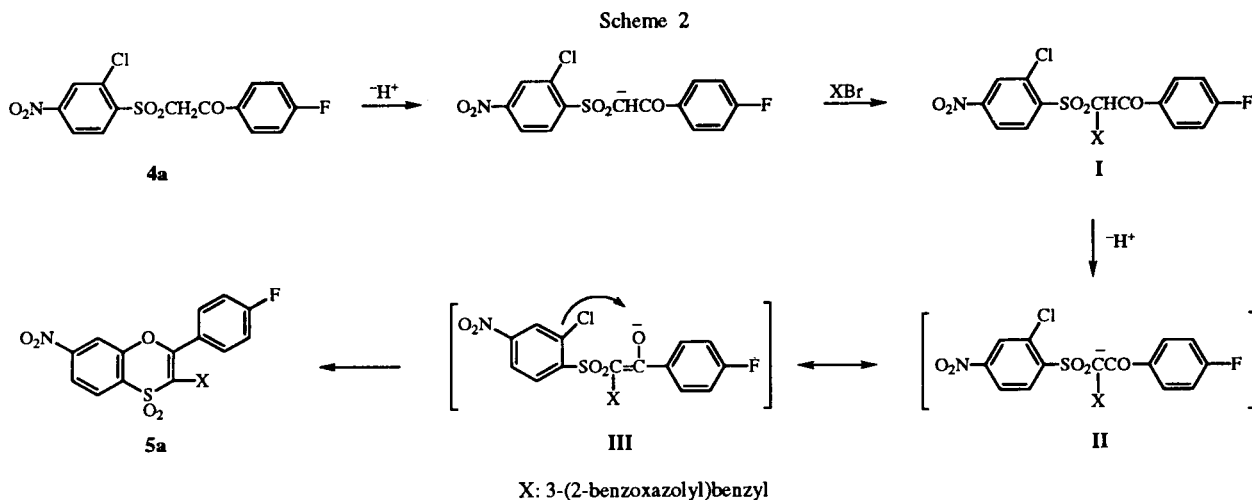
excellent yields, exceeding 80%. Then 1-aryl-2-(2-chloro-4-nitrophenylsulfonyl)ethanones **4a-d** were obtained on oxidation of **3a-d** with 30% aqueous hydrogen peroxide at 55° in acetic acid. The 30% aqueous hydrogen peroxide was chosen as an oxidizing agent because it is inexpensive and easy to handle. We obtained the key intermediates **4** in satisfactory yields of 54%-78%. Finally, in the presence of potassium carbonate as a base, triethylbenzylammonium chloride as a phase transfer catalyst and dimethylformamide as a solvent, compounds **4a-d** reacted with 2-[3-(bromomethyl)phenyl]benzoxazole and 2-[4-(bromomethyl)phenyl]benzoxazole at 60° to give 2-aryl-3-arylmethyl-7-nitro-1,4-benzoxathiin 4,4-dioxides **5a-d** and **6a-d**, respectively.

In the third step, the formation of **5** and **6** was *via* a tandem alkylation-cyclization process illustrated in Scheme 2. We demonstrated this process by the preparation of 3-[3-(2-benzoxazolyl)benzyl]-2-(4-fluorophenyl)-7-nitro-1,4-benzoxathiin 4,4-dioxide **5a**. Under the reaction conditions,



[A] Sodium hydroxide, triethylbenzylammonium chloride, room temperature. [B] 30% aqueous hydrogen peroxide, acetic acid, 55°. [C] 2-[3-(Bromomethyl)phenyl]benzoxazole, potassium carbonate, triethylbenzylammonium chloride, dimethylformamide, 60°. [D] 2-[4-(Bromomethyl)phenyl]benzoxazole, potassium carbonate, triethylbenzylammonium chloride, dimethylformamide, 60°.

compound **4a** was alkylated with 2-[3-(bromomethyl)phenyl]benzoxazole to afford **I** which existed as the transition states **II** and **III** in the basic system. In the transition state **III**, negative oxygen substituted active chloride *via* an intermolecular nucleophilic substitution to give the alkylation-cyclization compound **5a**. The fact that no monoalkylated or C,O-alkylated product was detected in the reaction confirmed the validity of this process.



EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage apparatus and are uncorrected. The IR spectra were recorded in potassium bromide on a NICOLET 170 SX FT-IR spectrometer. The ^1H NMR spectra were recorded on a JEOL PMX 60 SI apparatus. Chemical shifts were reported in δ (ppm) units relative to the internal standard, tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer with EI (70 eV) and FAB (ionization by Ar, accelerating voltage 8 kV). Elemental analyses were performed on a FOSS HERAEUS CHA-O-RAPID analyzer.

2-Chloro-4-nitrobenzenethiol **1** was prepared by the method of Takikawa and Takizawa [9]. 2-[3-(Bromomethyl)phenyl]benzoxazole was prepared by the method of Rose [10]. The preparation of 2-[4-(bromomethyl)phenyl]benzoxazole was by literature method [11]. The preparation of 1-aryl-2-chloroethanones **2a-c** is that reported [12-14]

2-Chloro-1-(3-chloro-4-fluorophenyl)ethanone **2d**.

This compound was prepared as described [15], yield 62%, mp 25-27° (from ether); ^1H NMR (deuteriochloroform): δ 4.60 (s, 2H, ClCH_2CO), 7.26-7.68 (m, 3H, phenyl protons).

General Procedure for the Preparation of 1-Aryl-2-(2-chloro-4-nitrophenylthio)ethanones **3a-d**.

A mixture of 2-chloro-4-nitrobenzenethiol **1** (11.4 g, 60 mmol), sodium hydroxide (2.4 g, 60 mmol) and water (150 ml) was stirred under nitrogen and heated until a deep red solution developed. After cooling, to this solution triethylbenzylammonium chloride (0.9 g, 4 mmol) was added and then a solution of compound **2** (60 mmol) and acetone (50 ml) was added dropwise during 1 hour at room temperature. After stirring for an additional

hour, the precipitate was filtered, washed with water and recrystallized from a suitable solvent to afford compounds **3**.

2-(2-Chloro-4-nitrophenylthio)-1-(4-fluorophenyl)ethanone **3a**.

This compound was obtained in 90% yield, mp 179-180° (from ethyl acetate); ^1H NMR (deuteriochloroform): δ 4.30 (s, 2H, SCH_2CO), 7.25-8.30 (m, 7H, phenyl protons).

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{ClFNO}_3\text{S}$: C, 51.62; H, 2.79; N, 4.30. Found: C, 51.88; H, 3.18; N, 3.94.

2-(2-Chloro-4-nitrophenylthio)-1-(4-methoxyphenyl)ethanone **3b**.

This compound was obtained in 85% yield and not identified by analytical and spectral data. It was directly utilized in the next reaction.

2-(2-Chloro-4-nitrophenylthio)-1-(4-*tert*-butylphenyl)ethanone **3c**.

This compound was obtained in 89% yield, mp 130-131° (from ethyl acetate); ^1H NMR (deuteriochloroform): δ 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$), 4.37 (s, 2H, SCH_2CO), 7.18-7.70 (m, 4H, phenyl protons), 7.82-8.19 (m, 3H, phenyl protons).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{ClNO}_3\text{S}$: C, 59.41; H, 4.99; N, 3.85. Found: C, 59.67; H, 5.06; N, 3.79.

1-(3-Chloro-4-fluorophenyl)-2-(2-chloro-4-nitrophenylthio)ethanone **3d**.

This compound was obtained in 82% yield, mp 156-157° (from chloroform); ^1H NMR (deuteriochloroform): δ 4.36 (s, 2H, SCH_2CO), 7.20-7.71 (m, 3H, phenyl protons), 7.81-8.16 (m, 3H, phenyl protons).

Anal. Calcd. for $\text{C}_{14}\text{H}_8\text{Cl}_2\text{FNO}_3\text{S}$: C, 46.68; H, 2.24; N, 3.89. Found: C, 46.83; H, 2.34; N, 3.92.

General Procedure for the Preparation of 1-Aryl-2-(2-chloro-4-nitrophenylsulfonyl)ethanones **4a-d**.

Compound **3** (50 mmol) was dissolved in acetic acid (50 ml). Aqueous hydrogen peroxide (30%, 10 ml) was added to the solution with stirring at 55°. After the reaction was complete, the solvent was distilled under reduced pressure. The residue was poured into ice water to give a pale yellow precipitate which was filtered, washed with water and recrystallized from ethanol to afford compounds **4**.

2-(2-Chloro-4-nitrophenylsulfonyl)-1-(4-fluorophenyl)ethanone 4a.

The reaction time was 4.5 hours, yield 69%, mp 122-123°; ir: ν 1673 (CO), 1525 and 1333 (NO₂), 1286 and 1157 (SO₂) cm⁻¹; ¹H nmr (DMSO-d₆): δ 5.00 (s, 2H, SO₂CH₂CO), 6.90-7.30 (m, 2H, phenyl protons), 7.70-8.00 (m, 2H, phenyl protons), 8.10-8.36 (m, 3H, phenyl protons).

Anal. Calcd. for C₁₄H₉ClFNO₅S: C, 47.00; H, 2.54; N, 3.92. Found: C, 47.17; H, 2.56; N, 3.96.

2-(2-Chloro-4-nitrophenylsulfonyl)-1-(4-methoxyphenyl)ethanone 4b.

The reaction time was 5 hours, yield 54%, mp 105-106°; ir: ν 1678 (CO), 1533 and 1330 (NO₂), 1290 and 1152 (SO₂) cm⁻¹; ¹H nmr (DMSO-d₆): δ 4.10 (s, 3H, OCH₃), 5.18 (s, 2H, SO₂CH₂CO), 7.04-8.29 (m, 7H, phenyl protons).

Anal. Calcd. for C₁₅H₁₂ClNO₆S: C, 48.72; H, 3.27; N, 3.79. Found: C, 48.95; H, 3.47; N, 3.68.

2-(2-Chloro-4-nitrophenylsulfonyl)-1-(4-*tert*-butylphenyl)ethanone 4c.

The reaction time was 5 hours, yield 78%, mp 141-142°; ir: ν 1679 (CO), 1532 and 1320 (NO₂), 1285 and 1152 (SO₂) cm⁻¹; ¹H nmr (DMSO-d₆): δ 1.30 (s, 9H, C(CH₃)₃), 5.01 (s, 2H, SO₂CH₂CO), 7.16-8.36 (m, 7H, phenyl protons).

Anal. Calcd. for C₁₈H₁₈ClNO₅S: C, 54.61; H, 4.58; N, 3.54. Found: C, 54.83; H, 4.77; N, 3.32.

1-(3-Chloro-4-fluorophenyl)-2-(2-chloro-4-nitrophenylsulfonyl)ethanone 4d.

The reaction time was 8 hours, yield 58%, mp 140-142°; ir: ν 1682 (CO), 1530 and 1327 (NO₂), 1297 and 1153 (SO₂) cm⁻¹; ¹H nmr (DMSO-d₆): δ 5.20 (s, 2H, SO₂CH₂CO), 7.18-8.04 (m, 3H, phenyl protons), 8.36-8.47 (m, 3H, phenyl protons).

Anal. Calcd. for C₁₄H₈Cl₂FNO₅S: C, 42.87; H, 2.06; N, 3.57. Found: C, 42.99; H, 2.40; N, 3.60.

General Procedure for Preparation of 2-Aryl-3-arylmethyl-7-nitro-1,4-benzoxathiin 4,4-Dioxides 5a-d and 6a-d.

A mixture of 4 (3 mmoles), 2-[3-(bromomethyl)phenyl]benzoxazole or 2-[4-(bromomethyl)phenyl]benzoxazole (0.86 g, 3 mmoles), potassium carbonate (1.6 g, 12 mmoles), triethylbenzylammonium chloride (0.15 g, 0.6 mmole) and dimethylformamide (25 ml) was stirred at 60°. After the reaction was complete, the mixture was diluted with water (25 ml) and acidified with 3 *M* hydrochloric acid. The precipitate was collected by filtration, thoroughly washed with water and purified by column chromatography to afford the corresponding compounds 5 or 6.

3-[3-(2-Benzoxazolyl)benzyl]-2-(4-fluorophenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 5a.

The reaction time was 9 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 5:1), yield 63%, mp 206°; ir: ν 1532 and 1355 (NO₂), 1300 and 1156 (SO₂), 1620 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 4.05 (s, 2H, CH₂), 6.92-8.18 (m, 15H, phenyl protons); ms: *m/z* (%) 528 (M⁺, 100.0).

Anal. Calcd. for C₂₈H₁₇FN₂O₆S: C, 63.63; H, 3.24; N, 5.30. Found: C, 63.73; H, 3.32; N, 5.44.

3-[3-(2-Benzoxazolyl)benzyl]-2-(4-methoxyphenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 5b.

The reaction time was 10 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 3:1), yield 65%, mp 173-174°; ir: ν 1534 and 1351 (NO₂), 1301 and 1157 (SO₂), 1606 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.90 (s, 3H, OCH₃), 4.22 (s, 2H, CH₂), 7.05-8.30 (m, 15H, phenyl protons); ms: *m/z* (%) 541 (M⁺+1, 0.4) (FAB method).

Anal. Calcd. for C₂₉H₂₀N₂O₇S: C, 64.43; H, 3.73; N, 5.18. Found: C, 64.70; H, 3.48; N, 5.20.

3-[3-(2-Benzoxazolyl)benzyl]-2-(4-*tert*-butylphenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 5c.

The reaction time was 8 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 3:1), yield 78%, mp 210-211°; ir: ν 1531 and 1350 (NO₂), 1299 and 1156 (SO₂), 1623 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.15 (s, 9H, C(CH₃)₃), 4.16 (s, 2H, CH₂), 7.15-8.26 (m, 15H, phenyl protons); ms: *m/z* (%) 567 (M⁺+1, 13.8) (FAB method).

Anal. Calcd. for C₃₂H₂₆N₂O₆S: C, 67.83; H, 4.62; N, 4.94. Found: C, 67.75; H, 4.72; N, 5.05.

3-[3-(2-Benzoxazolyl)benzyl]-2-(3-chloro-4-fluorophenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 5d.

The reaction time was 10 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1), yield 68%, mp 214-216°; ir: ν 1539 and 1355 (NO₂), 1300 and 1157 (SO₂), 1620 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 4.20 (s, 2H, CH₂), 7.30-8.44 (m, 14H, phenyl protons); ms: *m/z* (%) 564 (M⁺+2, 0.5), 562 (M⁺, 1.5), 154 (100.0).

Anal. Calcd. for C₂₈H₁₆ClFN₂O₆S: C, 59.74; H, 2.86; N, 4.98. Found: C, 59.37; H, 2.68; N, 5.12.

3-[4-(2-Benzoxazolyl)benzyl]-2-(4-fluorophenyl)-7-nitro-1,4-benzoxathiin 4,4-dioxide 6a.

The reaction time was 9 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1), yield 59%, mp 198-200°; ir: ν 1534 and 1353 (NO₂), 1291 and 1154 (SO₂), 1620 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 4.16 (s, 2H, CH₂), 7.22-8.50 (m, 15H, phenyl protons); ms: *m/z* (%) 529 (M⁺+1, 0.6) (FAB method).

Anal. Calcd. for C₂₈H₁₇FN₂O₆S: C, 63.63; H, 3.24; N, 5.30. Found: C, 63.77; H, 3.61; N, 5.25.

3-[4-(2-Benzoxazolyl)benzyl]-2-(4-methoxyphenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 6b.

The reaction time was 7 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1), yield 72%, mp 182-183°; ir: ν 1536 and 1351 (NO₂), 1302 and 1153 (SO₂), 1608 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.90 (s, 3H, OCH₃), 4.13 (s, 2H, CH₂), 6.98-8.20 (m, 15H, phenyl protons); ms: *m/z* (%) 540 (M⁺, 69.5), 135 (100.0).

Anal. Calcd. for C₂₉H₂₀N₂O₇S: C, 64.43; H, 3.73; N, 5.18. Found: C, 64.67; H, 4.14; N, 5.50.

3-[4-(2-Benzoxazolyl)benzyl]-2-(4-*tert*-butylphenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide 6c.

The reaction time was 10 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 5:1), yield 64%, mp 213°; ir: ν 1534 and 1346 (NO₂), 1301 and 1159 (SO₂), 1620 (C=C) cm⁻¹; ¹H nmr

(deuteriochloroform): δ 1.07 (s, 9H, C(CH₃)₃), 4.17 (s, 2H, CH₂), 7.15 8.25 (m, 15H, phenyl protons); ms: m/z (%) 566 (M⁺, 68.8), 161 (100.0).

Anal. Calcd. for C₃₂H₂₆N₂O₆S: C, 67.83; H, 4.62; N, 4.94. Found: C, 67.86; H, 4.31; N, 5.20.

3-[4-(2-Benzoxazolyl)benzyl]-2-(3-chloro-4-fluorophenyl)-7-nitro-1,4-benzoxathiin 4,4-Dioxide **6d**.

The reaction time was 10 hours. This compound was obtained and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1), yield 57%, mp 234-236°: ir: ν 1540 and 1359 (NO₂), 1295 and 1159 (SO₂), 1622 (C=C) cm⁻¹; ¹H nmr (deuteriochloroform): δ 4.16 (s, 2H, CH₂), 7.20-8.36 (m, 14H, phenyl protons); ms: m/z (%) 563 (M⁺+1, 0.7) (FAB method).

Anal. Calcd. for C₂₈H₁₆ClFN₂O₆S: C, 59.74; H, 2.86; N, 4.98. Found: C, 59.99; H, 3.12; N, 5.10.

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