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A new sulfonyl group-containing heterocyclic compound 2-(2-chloro-4-nitrophenylsulfonyl)-1-(2-thienyl)ethanone **2** was prepared from the corresponding sulfide 2-(2-chloro-4-nitrophenylthio)-1-(2-thienyl)ethanone **1**. Two different cyclization reactions of the compound **2** were discussed. In contrast to the tandem alkylation-cyclization process [1], another cyclic procedure was described. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene as a base and dimethylformamide as a solvent, compound **2** was treated with ethyl acrylate or methyl methacrylate at 50-55° to give the 1,4-benzoxathiin 4,4-dioxide **5** or **6** respectively *via* a tandem Michael conjugate addition-cyclization process.

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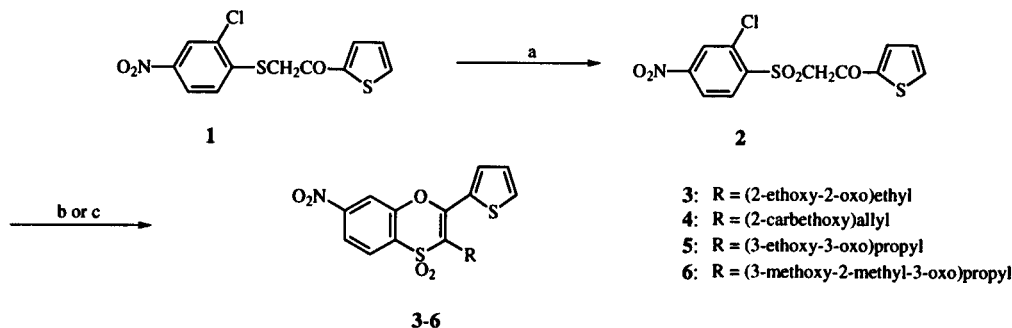
In our former paper [1] we have reported a tandem alkylation-cyclization process for the synthesis of 1,4-benzoxathiin 4,4-dioxide derivatives. These compounds were potentially useful in pharmacy for their bioactivities [2,3]. In this paper, we report the syntheses of four new 1,4-benzoxathiin 4,4-dioxides by two different cyclization processes. Based on the previous work [1,4], we placed a heterocyclic group into the key intermediate 1-aryl-2-(2-chloro-4-nitrophenylsulfonyl)ethanone. Fortunately, by an analogous synthetic method [1] we successfully prepared 2-(2-chloro-4-nitrophenylsulfonyl)-1-(2-thienyl)ethanone **2**. We consider that these heterocyclic intermediates such as compound **2** are more valuable in organic syntheses and reactions [5].

We studied first the alkylation-cyclization reactions of compound **2**. In the presence of potassium carbonate as a base, triethylbenzylammonium chloride as a phase transfer catalyst and dimethylformamide as a solvent, compound **2** was treated with ethyl bromoacetate or ethyl bromomethacrylate at 50-55° to give cyclic product **3** or **4** respectively, which is illustrated in Scheme 1. In the

course of our studies, product **4** was obtained in a good yield (75%) and in the reaction, a Michael conjugate addition product did not separate. Thus under the given reaction conditions, the described tandem alkylation-cyclization process is a very practical and feasible method to obtain the 1,4-benzoxathiin 4,4-dioxides.

To serve as a better donor of Michael conjugate addition reactions, compound **2** must be active in these reactions. We used 1,8-diazabicyclo[5.4.0]undec-7-ene as a base for more efficient basic conditions and dimethylformamide as a solvent to treat compound **2** with ethyl acrylate or methyl methacrylate at 50-55°. Finally, we obtained products **5** and **6** noted in the Scheme 1. Products **5** and **6** are 1,4-benzoxathiin 4,4-dioxide derivatives. In contrast to the tandem alkylation-cyclization process, the preparation of **5** and **6** was *via* a tandem Michael conjugate addition-cyclization process, whose possible mechanism is suggested in Scheme 2. We illustrated this process with the reaction of compound **2** and ethyl acrylate under the reaction conditions given. In transition state **II**, the chloride was a good leaving group because of the

Scheme 1



[a] Aqueous 30% hydrogen peroxide, acetic acid, 55°; [b] Ethyl bromoacetate or ethyl bromomethacrylate, potassium carbonate, triethylbenzylammonium chloride, dimethylformamide, 50-55°; [c] Ethyl acrylate or methyl methacrylate, 1,8-diazabicyclo[5.4.0]undec-7-ene, dimethylformamide, 50-55°.

strong electron-withdrawing effect of the nitro and sulfonyl groups. The negative oxygen could easily attack the active chloride by an intermolecular nucleophilic substitution reaction to give cyclic product **5**.

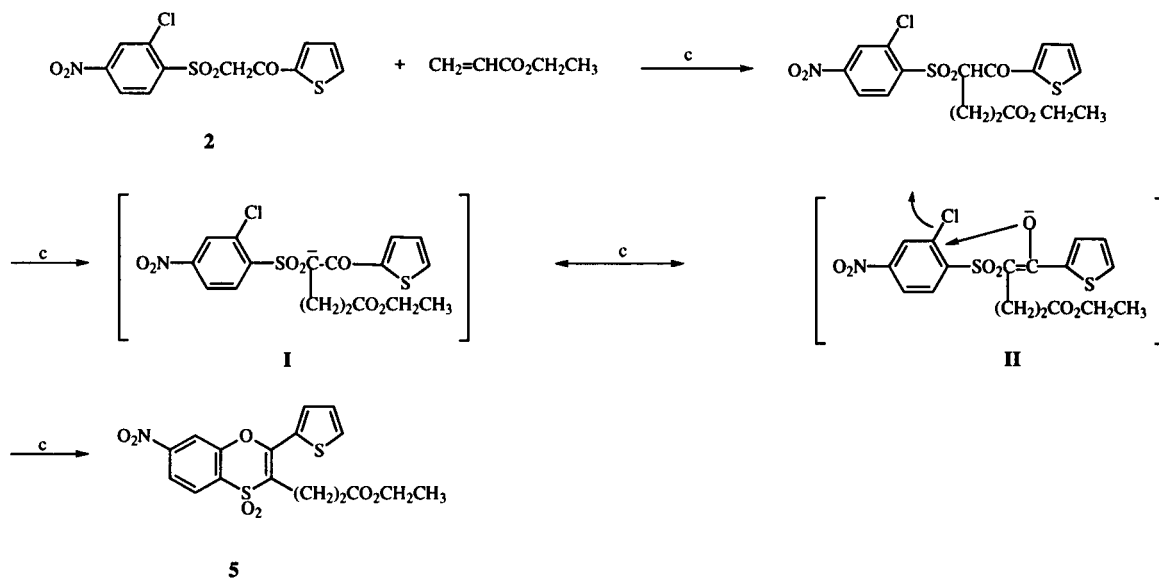
In the tandem Michael conjugate addition-cyclization reaction process, no Michael monoconjugate addition product separated and compounds **5** and **6** were obtained in good yields (74%, 68%). In view of the easily available starting materials, good yields and the mild reaction conditions, the present procedure provides another useful method for the preparation of 1,4-benzoxathiin 4,4-dioxide derivatives. We are currently investigating additional details of this process. Additionally, in our work we found that 2-(2-chloro-4-nitrophenylsulfonyl)-1-(2-thienyl)ethanone **2** would be decomposed at a higher reaction temperature under the given reaction conditions to provide the main decomposition product, 2-chloro-1-methylsulfonyl-4-nitrobenzene [6]. The relatively low reaction temperature should be noted in the reaction systems described in this paper.

FAB (ionization by Argon, accelerating voltage 8 kV). Elemental analyses were performed on a Foss Hereaus CHN-O-Rapid analyzer. The preparation of ethyl bromomethacrylate was based on the method of Villieras and Rambaud [7]. Other materials were commercially available.

General Procedure for the Preparation of **1** and **2**.

A mixture of 2-chloro-4-nitrobenzenethiol (11.4 g, 60 mmoles), sodium hydroxide (2.4 g, 60 mmoles) and water (150 ml) was heated and stirred under nitrogen to a deep red solution. After cooling, to this solution triethylbenzylammonium chloride (0.8 g) was added, then a solution of 2-chloroacetylthiophene (9.6 g, 60 mmoles) followed by acetone (50 ml) dropwise during one hour at room temperature. After stirring for an additional one hour, the precipitate was filtered, washed with water and recrystallized from ethyl acetate to afford compound **1**. Then compound **1** was dissolved in acetic acid (50 ml) and oxidized with 30% aqueous hydrogen peroxide (10 ml) at 55° for 24 hours. 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 give compound **2**.

Scheme 2



c: 1,8-Diazabicyclo[5.4.0]undec-7-ene, dimethylformamide, 50-55°.

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 spectrophotometer. The ^1H nmr spectra were recorded on a JEOL PMX 60 SI apparatus. Chemical shifts were reported in ppm relative to the internal standard, tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer with EI (70 eV) and

2-(2-Chloro-4-nitrophenylthio)-1-(2-thienyl)ethanone **1**.

This compound was obtained as yellow needles in 92% yield, mp 152-153°; ^1H nmr (deuteriochloroform): δ 4.45 (s, 2H, SCH_2CO), 7.25-8.30 (m, 6H, phenyl protons).

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{ClNO}_3\text{S}_2$: C, 45.93; H, 2.57; N, 4.46. Found: C, 45.86; H, 2.60; N, 4.48.

2-(2-Chloro-4-nitrophenylsulfonyl)-1-(2-thienyl)ethanone **2**.

This compound was obtained as pale yellow crystals in 52% yield, mp 142-143°; ir: 1689 (CO), 1533 and 1340 (NO_2), 1290

and 1159 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.32 (s, 2H, $\text{SO}_2\text{CH}_2\text{CO}$), 7.45-8.55 (m, 6H, phenyl protons).

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{ClNO}_5\text{S}_2$: C, 41.68; H, 2.33; N, 4.05. Found: C, 41.78; H, 2.60; N, 4.34.

General Procedure for the Preparation of 3 and 4.

A mixture of compound 2 (1.04 g, 3 mmoles), ethyl bromoacetate or ethyl bromomethacrylate (3 mmoles), potassium carbonate (1.6 g, 12 mmoles), triethylbenzylammonium chloride (0.15 g) and dimethylformamide (20 ml) was stirred at 50-55° for 10 hours. After the reaction was complete, the mixture was diluted with water (20 ml) and acidified with 3 M hydrochloric acid. The precipitate was collected by filtration, thoroughly washed with water and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1) to give compound 3 or 4 respectively.

3-(2-Ethoxy-2-oxo)ethyl-7-nitro-2-(2-thienyl)-1,4-benzoxathiin 4,4-Dioxide 3.

This compound was obtained as white needles in 78% yield, mp 138-139°; ir: 1742 (CO), 1621 (C=C), 1545 and 1357 (NO_2), 1291 and 1159 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_3 , $J = 6.5$ Hz), 3.90 (s, 2H, CH_2), 4.33 (q, 2H, OCH_2 , $J = 6.5$ Hz), 7.30-8.45 (m, 6H, phenyl protons); ms: m/z 396 ($\text{M}^+ + 1$, 1.4%) (FAB method).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_7\text{S}_2$: C, 48.60; H, 3.31; N, 3.54. Found: C, 48.77; H, 3.44; N, 3.56.

3-(2-Carboxy)allyl-7-nitro-2-(2-thienyl)-1,4-benzoxathiin 4,4-Dioxide 4.

This compound was obtained as white needles in 75% yield, mp 144°; ir: 1711 (CO), 1622 (C=C), 1523 and 1353 (NO_2), 1306 and 1155 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_3 , $J = 6.5$ Hz), 4.30 (q, 2H, OCH_2 , $J = 6.5$ Hz), 4.60 (s, 2H, CH_2), 6.00 (br, 2H, $=\text{CH}_2$), 7.00-8.20 (m, 6H, phenyl protons); ms: m/z 422 ($\text{M}^+ + 1$, 2.7%) (FAB method).

Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{NO}_7\text{S}_2$: C, 51.29; H, 3.59; N, 3.32. Found: C, 50.94; H, 3.92; N, 3.34.

General Procedure for the Preparation of 5 and 6.

A mixture of 2 (1.04 g, 3 mmoles), ethyl acrylate or methyl methacrylate (3 mmoles), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.86 g, 6 mmoles) and dimethylformamide (20 ml) was stirred at 50-55° for 10 hours. The mixture was diluted with water

(20 ml) and acidified with 3 M hydrochloric acid. The precipitate was collected by filtration, washed with water and purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 4:1) to give the corresponding compound 5 or 6.

3-(3-Ethoxy-3-oxo)propyl-7-nitro-2-(2-thienyl)-1,4-benzoxathiin 4,4-Dioxide 5.

This compound was obtained as white needles in 74% yield, mp 150-152°; ir: 1732 (CO), 1616 (C=C), 1537 and 1352 (NO_2), 1296 and 1156 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3 , $J = 6.5$ Hz), 2.58-3.40 (m, 4H, CH_2CH_2), 4.20 (q, 2H, OCH_2 , $J = 6.5$ Hz), 7.33-8.46 (m, 6H, phenyl protons); ms: m/z 409 (M^+ , 18.1%), 335 (100.0%), 111 (75.7%).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}_7\text{S}_2$: C, 49.86; H, 3.69; N, 3.42. Found: C, 49.99; H, 3.96; N, 3.52.

3-(3-Methoxy-2-methyl-3-oxo)propyl-7-nitro-2-(2-thienyl)-1,4-benzoxathiin 4,4-Dioxide 6.

This compound was obtained as white needles in 68% yield, mp 156°; ir: 1749 (CO), 1620 (C=C), 1531 and 1355 (NO_2), 1301 and 1155 (SO_2) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.01 (d, 3H, CH_3 , $J = 6.5$ Hz), 2.01-2.56 (br, 3H, CH_2CH), 3.40 (s, 3H, OCH_3), 7.17-8.32 (m, 6H, phenyl protons); ms: m/z 409 (M^+ , 15.0%), 111 (100.0%).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}_7\text{S}_2$: C, 49.86; H, 3.69; N, 3.42. Found: C, 50.10; H, 3.89; N, 3.63.

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- * Author to whom correspondence should be addressed.
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