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Synthesis, Characterization and Antibacterial Activity of Cyclic Sulfamide Linked to Tetrathiafulvalene (TTF)

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Abstract: We herein describe the synthesis and antibacterial activity of cyclic sulfamide linked to tetrathiafulvalene (TTF). This approach exploits the inherent chemistry of biomolecules and π-donors compounds to generate symmetric bis-trimethyltetrathiafulvalenyl-2-thiophenyl cyclic sulfamides. Two strategies are revealed, one centres on the Ring-closing olefin metathesis using the Grubbs catalyst a second strategy based on the direct alkylation of dibromoalkane derivatives with symmetric sulfamide under basic conditions. All the newly synthesized compounds were screened for their antimicrobial activities and some of them were found to possess good or moderate antimicrobial activity.

Keywords: Antibacterial activity, cyclic sulfamides, olefin metathesis, sultams, sulfur heterocycles, tetrathiafulvalenes.

INTRODUCTION

Sulphur has a long history of application in medicine as a result of scabicidal, insecticidal, fungicidal and purgative properties [1]. The chemical versatility of organosulphur compounds has led to its incorporation into a number of projects in several different areas of medicinal chemistry. The discovery of sulfonamide [2] as an antibacterial drug marks an important milestone in the development of medicinal chemistry.

The application of organosulphur compounds is not only used as drugs but it has also plunged into the field of electronics and superconductors [3], the tetrathiafulvalenes are the most representative examples. Only a very limited number of non-metals can be used by biological systems as a reversible redox switch, and sulfur is one of those [4]. It can be attached to different biomolecules.

Tetrathiafulvalene (TTF) derivatives have been the most intensively studied species during the past 25 years [5-7]. Its utility as building blocks in macromolecular and supramolecular structures [8-9], as ferromagnetic compounds [10], as synthetic intermediates in organic chemistry [11-12]. It has also been incorporated in a number of macrocyclic systems for use as molecular sensors, enzyme biosensors, switches, wires and shuttles, exploiting the inherent electron donor properties [13].

On the other hand, the sulfonamide moiety ($-SO_2NHR$) has become an important pharmacophore which has gained widespread use in medicinal chemistry, It has been observed that the introduction of the sulfonamide moiety induces an increase in metabolic stability towards protease-catalyzed degradation of peptidosulfonamides [14] and it has been reported as nonhydrolyzable peptidomimetics [15], metalloprotease inhibitors [16], they have also shown antibacterial, diuretic, hypoglycemic, antithyroid, antitumor activity [17]. These interesting properties have promoted the incorporation of the sulfonamide group into a growing number of compounds, many of which have demonstrated biological activity.

Our research has been devoted to the development of a new series of bis TTF systems which incorporate the cyclic sulfamide moiety in the hope that they may be biologically active. Moreover, TTF derivatives are planar [18] and therefore might possibly intercalate with DNA or even influence membrane transport. These properties could be of use in the treatment of diseases or affect metabolic pathways. However, the biological importance of sulfur-containing heterocycles is still minor compared to the very wide applications of sulfur-based heterocycles in modern materials chemistry [19]. No studies have been made so far on the possible application of TTF to biological systems. This work deals with the synthesis of novel series of cyclic sulfamides, where we have incorporated a series of seven, eight, nine and ten membered heterocyclic compounds containing sulfonamide moiety linked to TTF derivatives, synthesized via two different methods, the first involved a direct reaction between n-dibromoalkanes derivatives and N,N'-disubstituted symmetric sulfamide, the second involved the ring-closing metathesis strategy.

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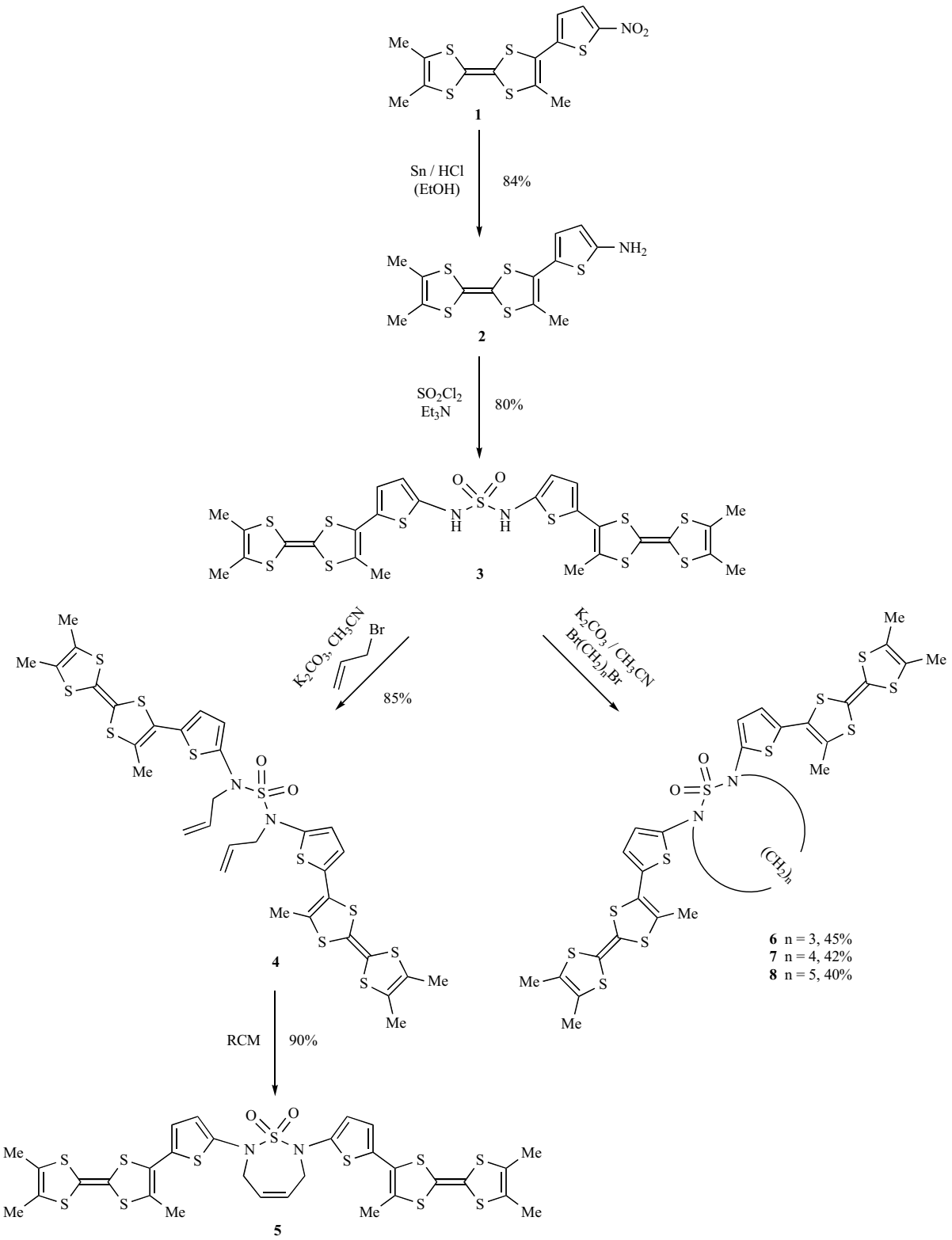

Scheme 1. Synthetic route for the preparation of n-membered symmetric cyclic sulfamide **5-8**.

RESULTS AND DISCUSSION

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes **1**. In the present study, 2-nitro-5-trimethyltetrathiafulvalenylthiophene **1** which was reported in previous work of our group [20] was reduced into an amino group in ethanol at reflux in the presence of tin and hydrochloric acid. The 2-amino-5-trimethyltetrathiafulvalenylthiophene **2** was obtained after purification by column chromatography in 84% yield.

Table 1. Sensitivity of *Escherichia coli* Towards Sulfamides 3-8

µg/mL sulfamides	2	3	5	8	10	15	20	30	40	50	80	100
3	+	+	+	+	MIC	-	-	-	-	-	-	-
4	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	MIC	-	-
6	+	+	+	+	+	+	+	+	+	MIC	-	-
7	+	+	+	+	+	+	+	+	+	MIC	-	-
8	+	+	+	+	+	+	+	+	+	+	+	+

Table 2. Sensitivity of *Staphylococcus aureus* Towards Sulfamides 3-8

µg/mL sulfamides	2	3	5	8	10	15	20	30	40	50	80	100
3	+	+	+	+	+	MIC	-	-	-	-	-	-
4	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+

The route to the symmetric sulfamide **3** center on the condensation of two equivalents of the amine compound **2** with Sulfuryl chloride (SO_2Cl_2) in the presence of triethylamine in dichloromethane, yields the N,N'-Bis (5-trimethyltetrathiafulvalenyl-2-thiophenyl)sulfamide **3** (80% yield).

The treatment of compound **3** in acetonitrile with one equivalent of various dibromoalkane (n=3, 4 and 5) under basic conditions (potassium carbonate K_2CO_3) and reflux gave symmetric cyclosulfamides **6**, **7** and **8** in 45%, 42% and 40% yield, respectively after purification by column chromatography.

Diallylation of **3** with allyl bromide in the presence of K_2CO_3 in CH_3CN at 70°C afforded N,N'-allylated symmetric sulfamide **4** in 85% yield, after purification by flash chromatography.

RCM has found great applicability for the synthesis of heterocyclic rings, including sulphur heterocycles [21]. It has also been used extensively for the formation of small to medium-sized rings as well as macrocycles [22, 23]. Using this synthetic method, a seven membered ring has been obtained using the Grubbs benzylidene catalyst to give excellent yield of the symmetric cyclic sulfamide **5**.

Biological Activity

All the synthesized compounds in this work are tested for solubility (tested using various solvents) and the results show that they are soluble in methanol, ethanol and acetone but insoluble in water. The bacterial strains used in this study were *Staphylococcus aureus* and *Escherichia coli* species. They were isolated from an aquatic medium, followed by successive isolations carried out periodically in the specific media in order to obtain strains as pure as possible. The solid media of MacConkey and Chapman have been used for *Escherichia coli* and *Staphylococcus aureus*, respectively. Microscopic study, after Gram coloration, was carried out after incubation at 37°C for 24 hours. The biochemical characteristics of each strain have been determined using a classic biochemical gallery. Finally, the pathogenic power of Staphylococcus aureus has been confirmed by showing that the coagulase of this strain was hemolytic, in vitro, towards rabbit or human plasma [24].

In vitro Evaluation of the Bacterial Sensitivity of the Strains to Sulfamides 3-8

To draw the antibiogram, the dilution in a liquid medium method was chosen. It is based on putting innoculums of each studied strain in contact with increasing concentrations of the sulfamides **3-8**. In a glucose medium, each bacterial inoculum (100 µL per suspension) was distributed in a series of tubes (macro-dilution method) containing increasing sulfamide concentrations [25]. The bacterial innoculum corresponding to the two studied strains was previously prepared from a colony that was collected from a solid medium and then put in suspension in a glucose medium for 18 hours at 37°C. After the incubation of the whole tubes at 37°C for 24 hours, the MIC (minimal inhibited concentration) of each of sulfamides **3-8** with respect to each strain (*Escherichia coli and/or Staphylococcus aureus*) was measured as indicated by the tube that contained the lower concentration of the product and where no apparent bacterial growth is noticed. The results of the *in vitro* evaluation of the sensitivity of the bacteria *Escherichia coli* and *Staphylococcus aureus* towards sulfamides **3-8** are presented in Tables **1** and **2**, respectively.

The antimicrobial activity results showed compounds **4** and **8** shows no activity towards the test microorganisms, whereas other sulfonamides **5**, **6** and **7** exhibited activity against the gram-negative bacteria Escherichia coli but do not show any inhibitory effect on the growth of the Staphylococcus aureus strain. In contrast, the sulfonamide **3** was the most active against all the test microorganisms

EXPERIMENTAL

General

NMR spectra were recorded on a Brucker AC 250 instrument. FAB mass spectra were recorded on a JOEL JMS-DX 300 spectrometer. Uncorrected melting points were measured on a 510 Buchi apparatus. All solvents were dried by standard methods and all commercial reagents used without purification. All reactions were performed under an inert atmosphere of nitrogen.

Synthesis of 2-amino-5-trimethyltetrathiafulvalenylthiophene 2

A stirred mixture of 2-nitro-5-trimethyltetrathiafulvalenylthiophene **1** (2.75g, 8 mmol), tin (1.88 g, 16 mmol), and aqueous solution of HCl (35%) (3.6 ml, 40 mmol) in ethanol (50 ml) was refluxed for 3h under nitrogen. During this time the initial black solution turned light yellow. The solution was then concentrated in vacuo and treated with an aqueous solution (150 ml) of sodium hydroxide (0.1 M) and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 2:1) affording the expected compounds **2** as orange red powder. Yield = 84%; TLC: Rf = 0.90 (hexane/CH_2Cl_2) (2:1); mp = 132°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.96 (s, 6H, CH_3); 2.15 (s, 3H, CH_3); 4.27 (s, 2H, NH_2); 6.83 (d, 1H$_{thioph.}$, J= 8.14 Hz); 7.28 (d, 1H$_{thioph.}$, J= 8.14 Hz); M.S: (NOBA, FAB > 0): 344 $[M + H]^+$; M = 343.

Synthesis of N,N'-Bis (5-trimethyltetrathiafulvalenyl-2-thiophenyl)sulfamide 3

2-amino-5-trimethyltetrathiafulvalenylthiophene **2** (2 g, 5.83 mmol) and CH_2Cl_2 (100 mL) were added sequentially to a round-bottom flask. The solution was cooled to 0°C, Et_3N (1.8 mL, 12.82 mmol) added slowly, and the resulting solution was stirred for 15 min. SO_2Cl_2 (233 µL, 2.90 mmol) was added slowly over 45 min and the resulting was then warmed to room temperature over 3 h. The solvent was concentrated to15 mL under reduced pressure, EtOAc (100 mL) was added, and the solution was washed with 10% $NaHSO_4$ (2x), aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). The solution was filtered, concentrated under reduced pressure to leave a crude oil. Flash chromatography (Hexane/ CH_2Cl_2, 2:1) afforded 1.74 g of sulfamide **3** as orange solid. Yield = 80%; TLC: Rf = 0.78 (hexane/CH_2Cl_2) (2:1); mp = 103°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.94 (s, 12H, CH_3); 2.12 (s, 6H, CH_3); 5.3 (s, 2H, NH); 7.61 (d, J= 8.34 Hz, 2H$_{thioph.}$); 7.65 (d, J= 8.34 Hz, 2H$_{thioph.}$); M.S: (NOBA, FAB > 0): 750 $[M + H]^+$; M = 749.

Synthesis of N,N'-Bis(2-propenyl)- N,N'-bis[(5-trimethyltetrathiafulvalenyl-2-thiophenyl)] sulfamide 4

To a stirring solution of sulfamide **3** (1 g, 1.33 mmol) in CH_3CN (40 mL) in a 100 mL round-bottom flask was added K_2CO_3 (0.55 g, 4 mmol) and allyl bromide (0.46 mL, 5.32 mmoL). The flask was fitted with a condenser, and the mixture was heated to 70°C for 14 h. The resulting yellow red mixture was filtered by suction, and the solvent removed under reduced pressure to give yellow oil. Flash chromatography (Hexane/ CH_2Cl_2, 2:1) afforded 937 mg of N,N-diallylated sulfamide **4** as orange solid. Yield = 85%; TLC: Rf = 0.75 (hexane/CH_2Cl_2) (2:1); mp = 67°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.94 (s, 12H, CH_3); 2.12 (s, 6H, CH_3); 3.80-4.20 (m, 4H, NCH_2), 5.21 (m, 4H, $=CH_2$), 5.92 (m, 2H, =CH), 7.61 (s, J= 8.30 Hz, 2H$_{thioph.}$); 7.65 (d, J= 8.30 Hz, 2H$_{thioph.}$); M.S: (NOBA, FAB > 0): 830 $[M + H]^+$; M = 829.

Synthesis of 2,2'-(2S,2'S)-[(2,3,6,7-Tetrahydro-1,2,7-thiadiazepine-1,1-dioxido-2,7-diyl)] bis 5-trimethyltetrathia fulvalenyl-2-thiophene 5

A stirring solution of the diallylated sulfamide **4** (250 mg, 0.30 mmol) in CH_2Cl_2 (50 mL) in a round-bottom flask was degassed by bubbling nitrogen gas through the solution for 15 min. The Grubbs metathesis catalyst benzylidene-dichloro-bis(tricyclohexylphosphoranyl) ruthenium (7.41 mg, 0.01 mmol, 3 mol%) was added, the flask was quickly fitted with a condenser containing a nitrogen balloon, and the solution was heated to reflux for 1.5 h. The solution was cooled to room temperature and the flask opened up to the air. CH_2Cl_2 (40 mL) and Celite (5.0 g) were added, and the solution was stirred for 18 h. The solvent was removed under reduced pressure, EtOAc (100 mL) was added, and the solution was filtered through a plug of silica. The solvent was again removed under reduced pressure to leave a crude solid. Flash chromatography (hexane/CH_2Cl_2) (2:1) gave 216 mg of the cyclic sulfamide **5** as beige solid. Yield = 90%; TLC: Rf = 0.73(hexane/CH_2Cl_2) (2:1); mp = 88°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.94 (s, 12H, CH_3); 2.12 (s, 6H, CH_3); 3.92 (dd, 2H, J=14.48, 3.52 Hz, NCH_2), 4.35 (dd, 2H, J=14.48, 1.84 Hz, NCH_2), 5.43 (t, 2H, J=1.84, =CH); 7.63 (d, J= 8.28 Hz, 2H$_{thioph.}$); 7.66 (d, J= 8.28 Hz, 2H$_{thioph.}$); M.S: (NOBA, FAB > 0): 802 $[M + H]^+$; M = 801.

Synthesis of Symmetric Cyclosulfamides 6-8

Compounds **6-8** were synthesized by employing the same experimental process as **5** from 1 equiv. of **5** and 1 equiv. of various dibromoalkane (n=3, 4 and 5).

*2,2'-(2S,2'S)- [(2,3,5,6-Tetrahydro-1,2,6-thiadiazinane-1,1-dioxide-2,6-diyl)] bis 5-trimethyltetrathia fulvalenyl-2-thiophene **6**:* Yield = 45%; TLC: Rf = 0.75 (hexane/CH_2Cl_2) (2:1); beige powder, mp = 91°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.94 (s, 12H, CH_3); 2.00 (m, 2H, CH_2); 2.12 (s, 6H, CH_3); 3.6 (m, 4H, NCH_2); 7.60 (d, 2H$_{thioph}$, J = 8.25 Hz); 7.63 (d, 2H$_{thioph}$, J = 8.25 Hz); M.S: (NOBA, FAB > 0): 790 $[M + H]^+$; M = 789.

2,2'-(2S,2'S)- [(2,3,6,7-Tetrahydro-1,2,7-Thiadiazepane 1,1-dioxide-2,7-diyl)] bis 5-trimethyltetrathia fulvalenyl-2-thiophene 7: Yield = 42%; TLC: Rf = 0.74 (hexane/CH_2Cl_2) (2:1); beige powder, mp = 87°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.85 (m, 4H, CH_2CH_2); 1.94 (s, 12H, CH_3); 2.12 (s, 6H, CH_3); 3.58 (m, 4H, NCH_2); 7.59 (d, 2H$_{thioph}$, J = 8.27 Hz); 7.62 (d, 2H$_{thioph}$, J = 8.27 Hz); M.S: (NOBA, FAB > 0): 804 $[M + H]^+$; M = 803.

2,2'-(2S,2'S)- [(2,3,7,8-Tetrahydro-1,2,8-Thiadiazocane 1,1-dioxide-2,8-diyl)] bis 5-trimethyltetrathia fulvalenyl-2-thiophene ***8****:* Yield = 40%; TLC: Rf = 0.74 (hexane/CH_2Cl_2) (2:1); beige powder, mp = 85°C; ^{1}H NMR ($CDCl_3$) δ ppm: 1.50 (m, 2H, CH_2) ; 1.75 (m, 4H, CH_2); 1.94 (s, 12H, CH_3); 2.12 (s, 6H, CH_3); 3.59 (m, 4H, NCH_2); 7.58 (d, $2H_{thioph}$, J = 8.25 Hz); 7.61 (d, $2H_{thioph}$, J = 8.25Hz); M.S: (NOBA, FAB > 0): 818 $[M + H]^+$; M = 817.

CONCLUSION

With this research, we have successfully linked between cyclic sulfamide and tetrathiafulvalene. Same new n-membered symmetric cyclic sulfamide containing TTF derivatives have been synthesized, and characterized during the course of this work. Sulfamide derivatives were screened for their antibacterial activity against few bacterial strains and it was observed that some of the compounds showed good to moderate biological activity. A study to test their action against other microorganisms is currently underway and will be reported in due course.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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