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A new series of seven-membered cyclic sulfamides containing thiophene or pyridine units

Tahar Abbaz^{1,*}, Amel Bendjeddou², Abdelkrim Gouasmia¹, Zine Regainia² and Didier Villemain³

¹Laboratoire des Matériaux Organiques et hétérochimie, Université de Tébessa, Route de Constantine, Tébessa, 12000, Algérie

²Laboratoire de Chimie Organique Appliquée, Groupe de chimie Hétérocyclique, Département de Chimie, Faculté des Sciences, Université d'Annaba, BP 12, 23000, Algérie

³Laboratoire de Chimie Moléculaire et Thioorganique (LCMT), UMR CNRS 6507, INC3M, FR 3038, Labex EMC³, ENSICAEN & Université de Caen, 14050 Caen, France

ABSTRACT

A new series of 1,4,3,5-oxathiadiazepanes 4, 4-dioxydes containing thiophene or pyridine ring have been synthesized by the reactions of *N*-benzyl-*N*-(2-hydroxyethyl)-sarcosine or proline sulfamide with thiophenecarboxaldehyde or pyridinecarboxaldehyde in a cyclodehydration reaction through two methods.

Key words: Cyclic sulfamide; Oxathiadiazepane; Thiophene; Pyridine.

INTRODUCTION

Heterocycles are important structural units found in a wide range of biologically active compounds [1-3]. There have been many calls for the synthesis of novel heterocyclic systems to be used as building blocks for the next generation of pharmaceuticals [4-7]. Recently, a variety of aromatic sulfides [8, 9] and sulfones [10-13] have been shown to possess anti-HIV activity. In addition, Sulfonamide derivatives have been also reported to show substantial antitumor and anti-HIV activities [14-17]. We reported in previous work the synthesis of certain sultams [18-21] and substituted 1,4,3,5-oxathiadiazepanes-4,4-dioxides [22], so we aimed to continue the previous syntheses in this work. Substituted aminoalcohol derivative of sarcosine or proline was refluxed with pyridinecarboxaldehyde in toluene at reflux, or condensed with thiophenecarboxaldehyde in dichloromethane in a reaction of cyclodehydration.

MATERIALS AND METHODS

General

All commercial chemicals and solvents were used as received. Melting points were determined in open tubes on a Büchi apparatus and are uncorrected. Microanalyses were performed in the Microanalysis Laboratory of ENSCM (Montpellier). ¹H and ¹³C-Nuclear Magnetic Resonance spectra were determined on a Bruker AC 250 spectrometer. Chemical shifts are recorded in ppm (δ) and coupling constants in Hertz, relative to tetramethylsilane used as internal standard. Multiplicity is indicated as s (singlet), d (doublet), q (quadruplet), m (multiplet) and combinations of these signals. Fast-atom bombardment mass spectra (FAB) were recorded in positive or negative mode with glycerol (G), thioglycerol (GT), or 3-nitrobenzylalcohol (NOBA) as matrix. Optical rotations for solutions in CHCl₃ were measured with a POLAX model 2L digital polarimeter. All reactions were monitored by thin Layer Chromatography (TLC) on silica gel Merck 60 F254 precoated aluminium plates, developed by spraying with ninhydrin solution. Column chromatography was performed using silica gel 60 (203-400 mesh).

General procedure for the preparation of 1,4,3,5-oxathiadiazepanes 4,4-dioxydes 1b-6b

Amino alcohol **1a** or **2a** (0.01 mol) was refluxed separately with an equimolar amount of pyridinecarboxaldehyde (0.01 mol) in dry toluene (30 ml). When no more starting material could be detected on TLC (4h-6h), the solvent was evaporated off and the residual oil crystallized on treatment with Et₂O. The crystalline product was filtered off and recrystallized from hexane.

2-(4-pyridyl), *N*³-benzyl, *N*⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**1b**): Green powder; Yield = 48%; TLC: Rf = 0.60 (hexane/CH₂Cl₂ 1:1); mp = 93°C; ¹H-NMR (CDCl₃) δ ppm: 8.70 (d, 2H, J = 4.60 Hz, pyr); 7.44 (d, 2H, J = 4.62 Hz, pyr); 7.27 (m, 5H, Ar-ph); 6.35(s, 1H, CH*); 4.33 (t, 2H, CH₂O); 4.20 and 4.25 (2d, 1H, J = 15.75 Hz and 1H, J = 15.80 Hz, CH₂-ph); 3.33 (t, 2H, CH₂-N); 2.93 (s, 3H, CH₃-N); ¹³C-NMR(CDCl₃) δ ppm: 37.77; 49.70; 52.75; 68.01; 86.89; 125; 128; 148; M.S: (ESI⁺): 356 [M+Na]⁺; M = 333; Anal.Calcd for C₁₆H₁₉O₃N₃S: C, 57.63; H, 5.74; N, 12.60; S, 9.61; found: C, 57.70; H, 5.80; N, 12.58; S, 9.59.

2-(3-pyridyl), *N*³-benzyl, *N*⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**2b**): Green powder; Yield = 40%; TLC: Rf = 0.60 (hexane/CH₂Cl₂ 1:1); mp = 96°C; ¹H-NMR (CDCl₃) δ ppm: 8.72 (s, 1H, pyr); 8.52 (d, 1H, pyr); 7.83 (d, 1H, pyr); 7.34 (t, 1H, pyr); 7.25 (m, 5H, Ar-ph); 6.33 (s, 1H, CH*); 4.32 (t, 2H, CH₂O); 4.15 and 4.25 (2d, 1H, J = 15.70 Hz and 1H, J = 17.75 Hz, CH₂-ph); 3.32 (t, 2H, CH₂-N); 2.93 (s, 3H, CH₃-N); ¹³C-NMR(CDCl₃) δ ppm: 37.78; 49.70; 52.77; 68; 86.90; 125; 128; 135; 147; 150; M.S: (ESI⁺): 356 [M+Na]⁺; M = 333; Anal.Calcd for C₁₆H₁₉O₃N₃S: C, 57.63; H, 5.74; N, 12.60; S, 9.61; found: C, 57.72; H, 5.75; N, 12.33; S, 9.20.

2-(2-pyridyl), *N*³-benzyl, *N*⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**3b**): Green powder; Yield = 37%; TLC: Rf = 0.60 (hexane/CH₂Cl₂ 1:1); mp = 147°C; ¹H-NMR (CDCl₃) δ ppm: 8.69 (d, 1H, J = 4.60 Hz, pyr); 7.84 (t, 1H, J = 7.80 Hz, pyr); 7.52 (d, 1H, J = 7.80 Hz, pyr); 7.27 (t, 1H, J = 5.95 Hz, pyr); 7.23 (m, 5H, Ar); 6.30 (s, 1H, CH*); 4.35 (t, 2H, CH₂O); 4.0 and 4.2 (2d, 1H, J = 15.65 Hz and 1H, J = 15.70 Hz, CH₂-ph); 3.31 (t, 2H, CH₂-N); 2.93 (s, 3H, CH₃-N). ¹³C-NMR(CDCl₃) δ ppm: 37.79; 49.72; 52.79; 68.01; 86.90; 123; 127; 128; 136; 148; M.S: (ESI⁺): 356 [M+Na]⁺; M = 333; Anal.Calcd for C₁₆H₁₉O₃N₃S: C, 57.63; H, 5.74; N, 12.60; S, 9.61; found: C, 57.75; H, 5.84; N, 12.28; S, 9.27.

2-(4-pyridyl), *N*³-benzyl, (*N*^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**4b**): Green powder; Yield = 50%; TLC: Rf = 0.66 (hexane/CH₂Cl₂ 1:1); mp = 98°C; ¹H-NMR (CDCl₃) δ ppm: 1.92 (m, 4H, CH_{2β} et CH_{2γ}); 3.62 (m, 2H, CH₂-N); 3.84 (m, 2H, CH₂O); 4.00 (m, 1H, C₂H*); 4.43 (s, 2H, CH₂-ph); 6.40 (s, 1H, C₁H*); 8.50 (d, 2H, J = 4.56 Hz, pyr); 7.36 (d, 2H, J = 4.58 Hz, pyr); 7.25 (m, 5H, Ar-ph); ¹³C-NMR(CDCl₃) δ ppm: 24.75; 28.90; 41; 48.20; 59; 72.81; 98.97; 125; 128; 148; M.S: (NOBA, FAB>0): 360 [M+H]⁺, M = 359; Anal.Calcd for C₁₈H₂₁O₃N₃S: C, 60.14; H, 5.88; N, 11.69; S, 8.92; found: C, 60.18; H, 5.90; N, 11.66; S, 8.89.

2-(3-pyridyl), *N*³-benzyl, (*N*^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**5b**): Green powder; Yield = 41%; TLC: Rf = 0.66 (hexane/CH₂Cl₂ 1:1); mp = 104°C; ¹H-NMR (CDCl₃) δ ppm: 1.92 (m, 4H, CH_{2β} et CH_{2γ}); 3.61 (m, 2H, CH₂-N); 3.83 (m, 2H, CH₂O); 4.00 (m, 1H, C₂H*); 4.41 (s, 2H, CH₂-ph); 6.41 (s, 1H, C₁H*); 6.68 (s, 1H, pyr); 8.47 (d, 1H, pyr); 7.78 (d, 1H, pyr); 7.31 (t, 1H, pyr); 7.24 (m, 5H, Ar-ph); ¹³C-NMR(CDCl₃) δ ppm: 24.76; 28.90; 41.01; 48.18; 59; 72.80; 98.95; 125; 128; 135; 147; 150; M.S: (NOBA, FAB>0): 360 [M+H]⁺, M = 359; Anal.Calcd for C₁₈H₂₁O₃N₃S: C, 60.14; H, 5.88; N, 11.69; S, 8.92; found: C, 60.30; H, 6.12; N, 10.56; S, 8.24.

2-(2-pyridyl), *N*³-benzyl, (*N*^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**6b**): Green powder; Yield = 35%; TLC: Rf = 0.66 (hexane/CH₂Cl₂ 1:1); mp = 152°C; ¹H-NMR (CDCl₃) δ ppm: 1.93 (m, 4H, CH_{2β} et CH_{2γ}); 3.64 (m, 2H, CH₂-N); 3.85 (m, 2H, CH₂O); 4.02 (m, 1H, C₂H*); 4.45 (s, 2H, CH₂-ph); 6.45 (s, 1H, C₁H*); 8.65 (d, 1H, J = 4.58 Hz, pyr); 7.78 (t, 1H, J = 7.78 Hz, pyr); 7.49 (d, 1H, J = 7.78 Hz, pyr); 7.25 (t, 1H, J = 5.95 Hz, pyr); 7.20 (m, 5H, Ar-ph); ¹³C-NMR(CDCl₃) δ ppm: 24.75; 28.91; 41.01; 48.20; 59; 72.81; 98.95; 123; 127; 128; 136; 148; M.S: (NOBA, FAB>0): 360 [M+H]⁺, M = 359; Anal.Calcd for C₁₈H₂₁O₃N₃S: C, 60.14; H, 5.88; N, 11.69; S, 8.92; found: C, 60.33; H, 6.18; N, 10.43; S, 8.19.

General procedure for the preparation of 1,4,3,5-oxathiadiazepanes 4,4-dioxydes 7b-12b

Compounds **1a** and **2a** (0.01 mol) were dissolved separately in 25ml of dichloromethane, and the thiophenecarboxaldehyde (0.01 mol) was added. A drop of concentrated sulfuric acid was also added, and stirred the reaction mixture for 3h at room temperature. The reaction mixture was washed with a 5% solution of sodium bicarbonate, water and then with brine. The organic layer was dried over anhydrous sodium sulfate, and evaporated under reduced pressure on a rotary evaporator. The residue was purified by column chromatography eluting with hexane/dichloromethane (2:1) to give the 1,4,3,5-oxathiadiazepanes 4,4-dioxydes.

2-(2-thiophenyl), *N*³-benzyl, *N*⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**7b**): Red powder; Yield = 64%; TLC: Rf = 0.40 (hexane/CH₂Cl₂ 2:1); mp = 79°C; ¹H-NMR (CDCl₃) δ ppm: 7.27 (m, 5H, ph); 7.14 (d, 1H, J = 4.47 Hz,

thio); 6.87 (t, 1H, J = 4.45 Hz, thio); 6.82 (d, 1H, J = 3.6 Hz, thio); 6.50 (s, 1H, CH*); 4.40 (t, 2H, CH₂-O); 4.10 and 4.25 (2d, 1H, J = 15.80 Hz and 1H, J = 15.83 Hz, CH₂-ph); 3.35 (t, 2H, CH₂-N); 2.95 (s, 3H, CH₃-N); ¹³C-NMR(CDCl₃) δ ppm: 37.75; 49.66; 52.73; 67.95; 87.47; 126; 128; M.S: (ESI⁺): 361 [M+Na]⁺; M = 338; Anal.Calcd for C₁₅H₁₈O₃N₂S₂: C, 53.23; H, 5.36; N, 8.27; S, 18.97; found: C, 53.25; H, 5.50; N, 8.10; S, 19.00.

2-(5-ethyl, 2-thiophenyl), N³-benzyl, N⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**8b**): light-brown oil; Yield = 72%; TLC: Rf = 0.43 (hexane/CH₂Cl₂ 5:1); mp = oil; ¹H-NMR (CDCl₃) δ ppm: 7.25 (m, 5H, ph); 6.68 (d, 1H, J = 3.85 Hz, thio); 6.70 (d, 1H, J = 3.85 Hz, thio); 6.48 (s, 1H, CH*); 4.99 (t, 2H, CH₂-O); 4.0 and 4.15 (2d, 1H, J = 15.80 Hz and 1H, J = 15.82 Hz, CH₂-ph); 3.33 (t, 2H, CH₂-N); 3.0 (q, 2H, CH₂-thio); 2.93 (s, 3H, CH₃-N); 2.65 (t, 3H, CH₃-CH₂-thio); ¹³C-NMR(CDCl₃) δ ppm: 20.3; 29.5; 37.76; M.S: (ESI⁺): 389 [M+Na]⁺; M = 366; Anal.Calcd for C₁₇H₂₂O₃N₂S₂: C, 55.71; H, 6.05; N, 7.64; S, 17.49; found: C, 55.68; H, 5.98; N, 7.68; S, 17.54.

2-(3-thiophenyl), N³-benzyl, N⁵-methyl 1,4,3,5-oxathiadiazepane 4,4-dioxyde (**9b**): Brown-red powder; Yield = 63%; TLC: Rf = 0.40 (hexane/CH₂Cl₂ 2:1); mp = 118°C; ¹H-NMR (CDCl₃) δ ppm: 7.28 (m, 5H, ph); 7.18 (d, 1H, J = 6.00 Hz, thio); 6.89 (d, 1H, J = 6.00 Hz, thio); 6.84 (s, 1H, thio); 6.60 (s, 1H, CH*); 4.45 (t, 2H, CH₂O); 4.15 and 4.30 (2d, 1H, J = 15.90 Hz and 1H, J = 16.00 Hz, CH₂-ph); 3.38 (t, 2H, CH₂-N); 2.96 (s, 3H, CH₃-N); ¹³C-NMR(CDCl₃) δ ppm: 37.80; 49.68; 52.75; 68; 87.53; 124; 128; 129; 130; M.S: (ESI⁺): 361 [M+Na]⁺; M = 338; Anal.Calcd for C₁₅H₁₈O₃N₂S₂: C, 53.23; H, 5.36; N, 8.27; S, 18.97; found: C, 53.20; H, 5.60; N, 7.80; S, 18.70.

2-(2-thiophenyl), N³-benzyl, (N^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**10b**): Red powder; Yield = 65%; TLC: Rf = 0.42 (hexane/CH₂Cl₂ 2:1); mp = 105°C; ¹H-NMR (CDCl₃) δ ppm: 1.85 (m, 4H, CH_{2β} and CH_{2γ}); 3.54 (m, 2H, CH₂-N); 3.75 (m, 2H, CH₂O); 3.93 (m, 1H, C₂H*); 4.30 (s, 2H, CH₂ph); 6.48 (s, 1H, C₁H*); 6.80 (d, 1H, J = 3.7 Hz, thio); 6.85 (t, 1H, J = 4.40 Hz, thio); 7.10 (d, 1H, J = 4.42 Hz, thio); 7.25 (m, 5H, Ar-ph); ¹³C-NMR(CDCl₃) δ ppm: 24.78; 28.90; 41; 48.15; 59; 72.80; 89.95; 126; 128; M.S: (NOBA, FAB>0): 365 [M+H]⁺, M = 364; Anal.Calcd for C₁₇H₂₀O₃N₂S₂: C, 56.02; H, 5.53; N, 7.68; S, 17.59; found: C, 56.06; H, 5.56; N, 7.70; S, 17.51.

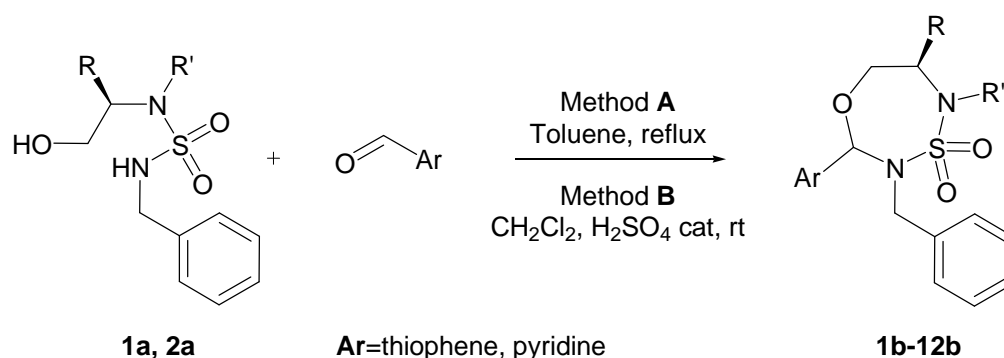
2-(5-ethyl, 2-thiophenyl), N³-benzyl, (N^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**11b**): light-brown oil; Yield = 75%; TLC: Rf = 0.45 (hexane/CH₂Cl₂ 5:1); mp = oil; ¹H-NMR (CDCl₃) δ ppm: 1.87 (m, 4H, CH_{2β} and CH_{2γ}); 3.75 (m, 2H, CH₂-N); 3.78 (m, 2H, CH₂O); 3.95 (m, 1H, C₂H*); 2.62 (t, 3H, CH₃-CH₂-thio); 3.15 (q, 2H, CH₂-thio); 4.20 (s, 2H, CH₂-ph); 6.50 (s, 1H, C₁H*); 6.68 (d, 1H, J = 4.30 Hz, thio); 6.65 (d, 1H, J = 4.30 Hz, thio); 7.25 (m, 5H, Ar-ph); ¹³C-NMR(CDCl₃) δ ppm: 20.5; 24.79; 28.92; 29.60; 41.01; 48.17; 57.02; 72.85; 89.93; 126; 128; M.S: (NOBA, FAB>0): 393 [M+H]⁺, M = 392; Anal.Calcd for C₁₉H₂₄O₃N₂S₂: C, 58.13; H, 6.16; N, 7.13; S, 16.33; found: C, 58.10; H, 6.12; N, 7.10; S, 16.35.

2-(3-thiophenyl), N³-benzyl, (N^{5,6})-trimethylene 1,4,3,5-oxathiadiazepane 4,4-dioxide (**12b**): Brown-red powder; Yield = 66%; TLC: Rf = 0.42 (hexane/CH₂Cl₂ 2:1); mp = 135°C; ¹H-NMR (CDCl₃) δ ppm: 1.86 (m, 4H, CH_{2β} and CH_{2γ}); 3.55 (m, 2H, CH₂-N); 3.77 (m, 2H, CH₂O); 3.94 (m, 1H, C₂H*); 4.10 (s, 2H, CH₂-ph); 6.48 (s, 1H, CH*); 6.82 (s, 1H, thio); 6.86 (d, 1H, J = 6.00 Hz, thio); 7.15 (d, 1H, J = 6.00 Hz, thio); 7.25 (m, 5H, ph); ¹³C-NMR(CDCl₃) δ ppm: 24.73; 28.88; 41.01; 48.20; 59; 72.82; 90; 124; 128; 129; 130; M.S: (NOBA, FAB>0): 365 [M+H]⁺, M = 364; Anal.Calcd for C₁₇H₂₀O₃N₂S₂: C, 56.02; H, 5.53; N, 7.68; S, 17.59; found: C, 55.82; H, 5.48; N, 7.45; S, 17.16.

RESULTS AND DISCUSSION

Twelve new oxathiadiazepanes 4,4-dioxides containing thiophene or pyridine unit were prepared in moderate to good yields starting from the same precursors **1a** or **2a** through two methods **A** and **B** (Scheme 1). Compounds **1a-2a** were synthesized from tert-butyloxycarbonylsulfamides in three steps alkylation under Mitsunobu conditions [23-26] using benzylic alcohol, selective cleavage of the *t*-butyloxycarbonyl protective group and reduction with NaBH₄ as previously described [22].

The reaction of substituted aminoalcohols (*N'*-benzyl-*N*-(2-chloroethyl)-proline or sarcosine sulfamides **1a** or **2a** with pyridinecarboxaldehydes have been carried out in molar ratio 1:1 in refluxing toluene for 4h-6h (Method **A**, Table 1), whereby it afforded oxathiadiazepanes 4,4-dioxides containing pyridine unit **1b-6b** in moderate yield. Compounds **7b-12b** were synthesized via cyclodehydration reaction of thiophencarboxaldehydes with compounds **1a** or **2a** in dichloromethane at room temperature (Method **B**, Table 1), The yields of compounds **1b-12b** are listed in (Table 1).



Scheme 1: Synthesis of substituted oxathiadiazepanes 4,4-dioxides.

Table 1: The reaction of (*N'*-benzyl-*N*-(2-chloroethyl)-proline or sarcosine sulfamides (1a, 2a) with pyridinecarboxaldehydes or thiophenecarboxaldehydes.

Entry	Substrate	Ar	Method ^a	Product	Yield (%)
1	1a, R=H, R'=CH ₃	4-pyridyl	A	1b	48
2	1a, R=H, R'=CH ₃	3-pyridyl	A	2b	40
3	1a, R=H, R'=CH ₃	2-pyridyl	A	3b	37
4	2a, R,R'=(CH ₂) ₃	4-pyridyl	A	4b	50
5	2a, R,R'=(CH ₂) ₃	3-pyridyl	A	5b	41
6	2a, R,R'=(CH ₂) ₃	2-pyridyl	A	6b	35
7	1a, R=H, R'=CH ₃	2-thiophenyl	B	7b	64
8	1a, R=H, R'=CH ₃	5-ethyl-2-thiophenyl	B	8b	72
9	1a, R=H, R'=CH ₃	3-thiophenyl	B	9b	63
10	2a, R,R'=(CH ₂) ₃	2-thiophenyl	B	10b	65
11	2a, R,R'=(CH ₂) ₃	5-ethyl-2-thiophenyl	B	11b	75
12	2a, R,R'=(CH ₂) ₃	3-thiophenyl	B	12b	66

^aMethod A: Toluene, reflux. Method B: CH₂Cl₂, H₂SO₄ cat, rt.

In the ¹H-NMR (CDCl₃) spectra the asymmetric carbon proton of oxathiadiazepanes 4,4-dioxides derivatives showed for pyridine derivatives **1b-6b** and thiophene derivatives **7b-12b** a singlet peak around 6.30-6.45 ppm and 6.48-6.60 ppm, respectively. The ¹H-NMR spectrum of **7b** as an example for thiophene derivatives, **C2**, **C4**, and **C5** protons of thiophene heterocycle, appear at 7.14 ppm as doublet with coupling constants of 4.47 Hz, at 6.87 ppm as triplet with coupling constants of 4.45 Hz and at 6.82 ppm as doublet with coupling constants of 3.60 Hz, respectively. While compound (**1b**) as an example for pyridine derivatives, **C2**, **C6** and **C3**, **C5** protons of pyridine heterocycle appear at 8.70 ppm as doublet with coupling constants of 4.60 Hz and at 7.44 ppm as doublet with coupling constants of 4.62 Hz, respectively.

CONCLUSION

In summary, we have successfully prepared via a simple strategy some new derivatives of 1,4,3,5-oxathiadiazepanes 4,4-dioxides containing thiophene or pyridine rings. The simplicity of the reaction conditions with short reaction times to obtain the pure products in high yields should make this method attractive for organic chemists. This strategy is suitable for preparing seven-membered cyclic sulfamides on a large scale and analogues for extensive biological evaluation, and structure-activity relationship study. Related work in this field is currently in progress and will be reported in due course.

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