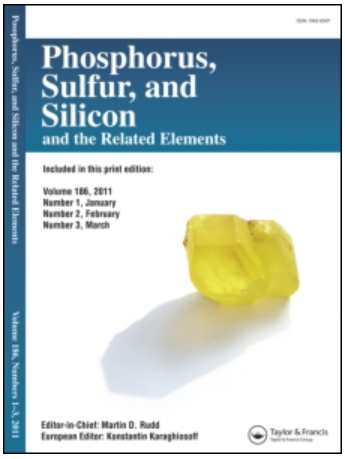


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ONE-POT SYNTHESIS OF NOVEL 1,1'- AND 1,4-BRIDGED BIS-THIAZOLIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

Rafat M. Shaker[a]
[a] Chemistry Department, Faculty of Science, El-Minia University, El-Minia, EGYPT

To cite this Article Shaker, Rafat M.(1999) 'ONE-POT SYNTHESIS OF NOVEL 1,1'- AND 1,4-BRIDGED BIS-THIAZOLIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 149: 1, 7 — 14
To link to this Article: DOI: 10.1080/10426509908037017
URL: http://dx.doi.org/10.1080/10426509908037017

Phosphorus, Sulfur and Silicon, 1999, Vol. 149, pp. 7-14
Reprints available directly from the publisher
Photocopying permitted by license only

ONE-POT SYNTHESIS OF NOVEL 1,1′- AND 1,4-BRIDGED BIS-THIAZOLIDINONE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

RAFAT M. SHAKER*

Chemistry Department, Faculty of Science, El-Minia University, El-Minia, EGYPT

(Received 07 October, 1998; In final form 14 November, 1998)

Several bis-thiazolidinone derivatives **6a-e, 9a,b** and **13a,b** have been synthesized and have discussed the IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra of these compounds. Compounds **6a-e** have also been screened *in vitro* for antibacterial activities.

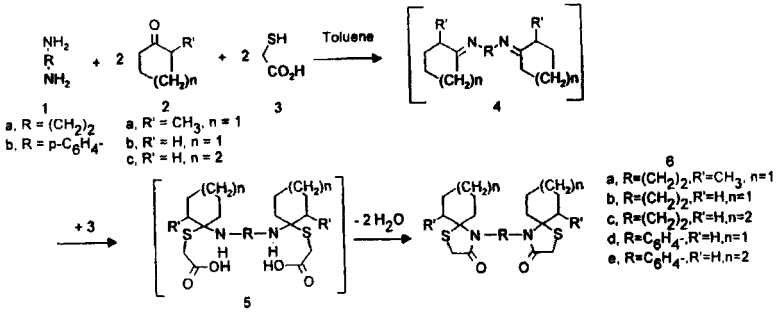
Keywords: 1,2-ethanediamine; 1,4-benzenediamine; mercaptoacetic acid; terephthalaldehyde; bis-spirothiazolidinone

Several thiazolidinone derivatives are well known for their amoebicidal,[1] hypnotic,[2]anticonvulsant,[3] anaesthetic[3] properties and other biological activities[4–6]. Although the chemistry of thiazolidinones have been studied extensively,[7] it was surprising that there is no general and/or facile method for the preparation of 1,1′- and 1,4-bridged bis-spirothiazolidinone derivatives. The present work constitutes an extension of the previous work[8] and in continuation of our interest at the synthesis of polyfunctionally substituted heteroaromatics from simple and laboratory available starting materials,[9–13] the synthesis of novel bridged bis-thiazolidinone derivatives was undertaken with the hope of enhanced biological activities of these compounds.

Thus, the direct condensation of 1,2-ethanediamine (**1a**) with 2-methylcyclohexanone (**2a**) and mercaptoacetic acid (**3**) in a molar ratio 1:2:2 using dry toluene as a solvent led to 4,4′-(1,1′-ethane-1,2-yl)-bis-[6-methyl-1-thia-4-azaspiro[4.5]decan-3-one] (**6a**) (Scheme 1).

* Correspondence Author.

The structural assignments of compound **6a** was established by spectroscopic studies and elemental analysis.



SCHEME 1

Thus, its IR spectrum revealed a strong band at 1680 cm^{-1} (CO) and a bands in the range of 2900–2850 cm^{-1} (-CH_2-). Its ^1H NMR spectrum showed a four-proton singlet at δ 3.46 due to the two thiazolidinone rings, a four-proton singlet at δ 3.39 assignable for-CH_2-CH_2- group, a two-proton multiplet at δ 2.29 assigned for the two methine groups, a sixteen-proton multiplet in the region δ 1.23–2.13 due to the two cyclohexyl rings and a doublet at δ 0.79 ppm (J = 6.5 Hz) for the two methyl groups. The structure **6a** was further confirmed by ^{13}C-NMR spectrum which revealed resonances at δ 78.29 and 172.16 ppm. These resonances were consistent with the two quaternary sp^3 carbon (spiro carbon) and the two carbonyl groups, respectively (Fig. 1). Also, the ^{13}C-DEPT NMR spectrum showed a negative signals at δ 39.54 and 15.59 ppm confirming the presence of the two methine groups and the two methyl groups, respectively, while the positive signals at δ = 23.34, 24.09, 31.4, 32.09, 39.76 and 40.21 ppm were assigned to the twelve methylene carbons in **6a.** Furthermore, the mass spectrum of **6a** gave the molecular ion peak at m/z 396 (M^+, 98 %) which found to be in good agreement with the assigned structure (see Experimental).

The formation of **6a** was rationalized in terns of the initial formation of the bis-ketimine **4** followed by the nucleophilic addition of mercaptoacetic

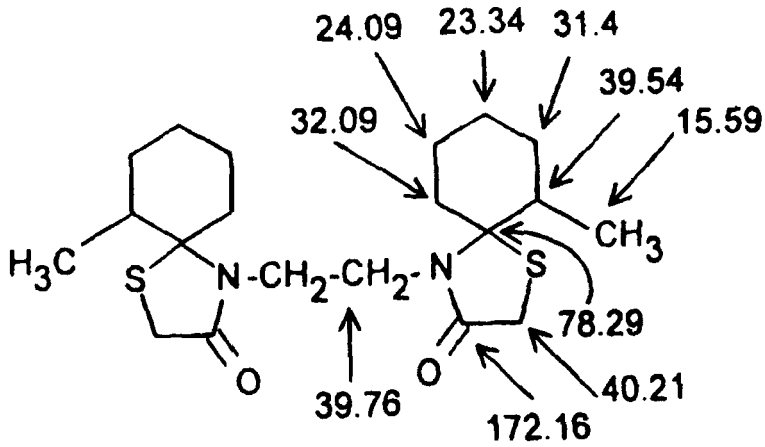


FIGURE 1 ^{13}C NMR data for compound **6a**

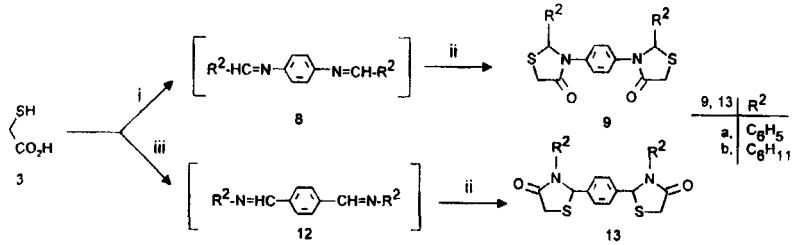
acid (**3**) to the imine bond forming an acyclic intermediate **5** which then cyclized to yield the final product **6a** (Scheme 1).

In order to generalize the previous one-pot synthesis, compounds **6b-e** were prepared by refluxing the diamine **1a,b** with cycloalkanones **2b,c** and mercaptoacetic acid (**3**) under the same reaction conditions (Scheme 1). The structure of **6b-e** were confirmed on the same line as for **6a** (see Experimental).

The applicability of this reaction in ternary condensation of either diamines with aldehydes and mercaptoacetic acid affording N-bis-thiazolidinone derivatives or dialdehydes with amines and mercaptoacetic acid to give the C-bis-thiazolidinone derivatives investigated. Thus, mercaptoacetic acid (**3**) reacted with 1,4-benzenediamine (**1b**) and aldehydes **7a,b** or terephthalaldehyde (**10**) and amines **11a,b** to afford 3,3′(1,4-phenylene)-bis-[2-aryl-1,3-thiazolidin-4-one] (**9**) and 2,2′(1,4-phenylene)-bis-[3-aryl-1,3-thiazolidin-4-one] (**13**), respectively, without isolating the bisaldimines **8** or **12** (Scheme 2). The structure of compounds **9a,b** and **13a,b** were established by elemental analysis and spectral data (see Experimental).

ANTIMICROBIAL SCREENING

The antimicrobial activity was tested in vitro against the microorganisms *Bacillus cereus*(gram positive bacteria) and *Pseudomonas aurginosae* (gram negative bacteria) using a 1 mg/ml solution in dimethylformamide on the nutrient broth and nutrient agar media following the Kirby-Bauer filter paper disc method[14]. The diameters of the inhibition zones were measured per applied disc after 24 hours incubation at 37 °C, A control disc with dimethylformamide was also performed. The resultes were recorded by measuring the inhibition zones (in millmeters) caused by various compounds on the tested microorganisms. Compounds **6a-e** were active against the Gram positive bacteria *(Bacillus cereus)* and only **6c,d** were active against Gram negative bacteria *(Pseudomonas aurginosae).* The test results are shown in Table I.



i) 1b,2R^2CHO (7) ii) compound 3 iii) Terphthalaldehyde (10), 2R^2NH_2 (11)

SCHEME 2

TABLE I Antibacterial Activity

Compound No.	*Bacillus cereus G + ve*	*Pseudomonas aurginosae G – ve*
6a	+ ve	- ve
6b	++ ve	- ve
6c	++ ve	++ ve
6d	+ ve	++ ve
6e	+ ve	- ve

(+ve) Indicates zone diameter of growth inhibition in mm.
(-ve) Indicates no inhibition zone around the filter paper disc.
(+) Zone diameter less than 10mm.
(++) zone diameter in the range 10–20 mm.

EXPERIMENTAL

All mps. were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with a Bruker AM 400 (400 MHz) spectrometer using TMS as an internal standard; the ^{13}C NMR spectra were recorded at 100 MHz. The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan Mat 8430 mass spectrometer operating at 70 eV. Microanalysis were performed by the Microanalytical Data Unit at Cairo University.

General Procedure for the Synthesis of Compounds 6, 9 and 13

Mercaptoacetic acid **3** (0.025 mol) was added to a well stirred solution of a mixture of each of diamine **1a,b** (0.01 mol) and cycloalkanones **2a-c** or aldehydes **7a,b** (0.02 mol)and/or terephthalaldehyde (**10**) (0.01 mol) and amines **11a,b** (0.02 mol) in 30 ml of dry toluene at room temperature. The mixture was then refluxed with a Dean and Stark water separator for 10 hrs till no more water collected; the progress of the reaction was monitored by means of analytical tlc. Excess of mercaptoacetic acetic acid and solvent was removed under vacuun and the solid residue recrystallized from the appropriate solvent.

4,4′-(1,1 ′-Ethane-1,2-diyl)-bis-[6-methyl-1-thia-4-azaspiro[4. 5]-decan-3-one] (6a)

Obtained in 78 % yield, m.p. 212–214 °C (from EtOH); (found: C, 60.40; H, 8.10; N, 7.10; S, 15.90. $C_{20}H_{32}N_2O_2S_2$ requires C, 60.56; H, 8.13; N, 7.06; S, 16.16 %); υ_{max} / cm^{-1} 2900,2850 (-CH_2-) and 1680 (CO); δ_H ($CDCl_3$) 0.79 (d, J 6.5 Hz, 6H, 2 CH_3), 1.23–2.13 (m, 16H, 2 cyclohexyl -CH_2-), 2.29 (m, 2H, 2 CH), 3.39 (s, 4H, -CH_2-CH_2-), 3.46 (s, 4H, 2 thiazolidinone protons); δ_c 15.59, 23.34, 24.09, 31.4, 32.09, 39.54, 39.76, 40.21, 78.29, 172.16; m/z 396 (M^+, 98 %).

4,4′-(1,1′-Ethane-1,2-diyl)-bis-[1-thia-4-azaspiro[4.5]decan-3-one] (6b)

Obtained in 82 % yield, m.p. 260–262 °C (from EtOH); (found: C, 58.70; H, 7.70; N, 7.50; S, 17.50. $C_{18}H_{28}N_2O_2S_2$ requires C, 58.65 ; H, 7.65; N,

7.60; S, 17.39 %); υ_{max} / cm^{-1} 2900,2840 (-CH_2-) and 1680 (CO); δ_H ($CDCl_3$) 1.12–2.10 (m, 20H, 2 cyclohexyl -CH_2-), 3.43 (s, 4H, -CH_2-CH_2-), 3.52 (s, 4H, 2 thiazolidinone protons); δ_c 23.34, 24.18, 31.22, 38.01, 40.08, 73.88, 171.89; m/z 368 (M^+, 74%).

4,4′-(1,1′-Ethane-1,2-diyl)-bis-[1-thia-4-azaspiro[4.6]undecan-3-one] (6c)

Obtained in 74 % yield, m.p. 225–227 °C (from EtOH); (found: C, 60.60; H, 7.90; N, 6.90; S, 16.20. $C_{20}H_{32}N_2O_2S_2$ requires C, 60.56; H, 8.13; N, 7.06; S, 16.16%); υ_{max} / cm^{-1} 2900,2850 (-CH_2-) and 1680 (CO); δ_H ($CDCl_3$) 1.61–2.2 (m, 24H, 2 cycloheptyl -CH_2-), 3.48 (s, 4H, -CH_2-CH_2-), 3.49 (s, 4H, 2 thiazolidinone protons); δ_c 22.67, 27.5, 31.35, 40.42, 41.63, 76.72, 171.56; m/z 396 (M^+, 72 %).

4,4′-(1,4-phenylene)-bis-[1-thia-4-azaspiro[4.5[decan-3-one] (6d)

Obtained in 71 % yield, m.p. 298–300 °C (from DMF/EtOH); (found: C, 63.50; H, 6.80; N, 6.60; S, 15.20. $C_{22}H_{28}N_2O_2S_2$ requires C, 63.42; H, 6.77; N, 6.72; S, 15.39%); υ_{max} / cm^{-1} 2900,2850 (-CH_2-) and 1680 (CO); δ_H (DMSO-d_6) 1.20–2.10 (m,20H,2cyclohexyl -CH_2-), 3.6 (s, 4H, 2 thiazolidinone protons); 7.1–7.4 (m, 4H, Ar-H).

4,4′-(1,4-phenylene)-bis-[1-thia-4-azaspiro[4. 6]undecan-3-one] (6e)

Obtained in 68 % yield, m.p. 285–287 °C (from DMF/EtOH); (found: C, 64.90; H, 7.10; N, 6.40; S, 14.30. $C_{24}H_{32}N_2O_2S_2$ requires C, 64.82; H, 7.25; N, 6.30; S, 14.42 %); υ_{max} / cm^{-1} 2900,2850 (-CH_2-) and 1680 (CO); δ_H (DMSO-d_6) 1.5–2.1 (m,24H, 2 cycloheptyl -CH_2-), 3.6 (s, 4H, 2 thiazolidinone protons); 7.2–7.4 (m,4H, Ar-H).

3,3′-(1,4-phenylene)-bis-[2-phenyl-1,3-thiazolidin-4-one] (9a)

Obtained in 79 % yield, m.p. >300 °C (from DMF); (found: C, 66.50; H, 4.70; N, 6.50; S, 14.70. $C_{24}H_{20}N_2O_2S_2$ requires C, 66.63; H,4.66; N, 6.47; S, 14.82 %); υ_{max} / cm^{-1} 1680 (CO); δ_H (DMSO-d_6) 3.84 (s, 4H, 2 thiazolidinone protons); 6.43 (s, 2H, 2CH); 7.18–7.41(m, 14H, Ar-H); δ_c 40.19,

63.06, 124.83, 125.02, 126.53, 128.16, 128.37, 135.16, 139.66, 170.22; m/z 432 (M^+, 88 %).

3,3′-(1,4-phenylene)-bis-[2-cyclohexyl-1,3-thiazolidin-4-one] (9b)

Obtained in 73 % yield, m.p. >300 °C (from DMF); (found: C, 64.70; H, 7.30; N, 6.20; S, 14.50. $C_{24}H_{32}N_2O_2S_2$ requires C, 64.82; H, 7.25; N, 6.30; S, 14.42 %); υ_{max} / cm^{-1} 1680 (CO); δ_H (DMSO-d_6) 1.09–1.53 (m, 22H, 2 cyclohexyl protons); 3.32 (s, 4H, 2 thiazolidinone protons); 5.35 (s, 2H, 2CH); 7.15–7.52 (m, 4H, Ar-H); m/z 444 (M^+,31 %).

2,2′-(1,4-phenytene)-bis-[3-phenyl-1,3-thiazolidin-4-one] (13a)

Obtained in 69 % yield, m.p. >300 °C (from DMF); (found: C, 66.60; H, 4.50; N, 6.30; S, 14.80. $C_{24}H_{20}N_2O_2S_2$ requires C, 66.63; H,4.66; N, 6.47; S, 14.82 %); υ_{max} / cm^{-1} 1680 (CO); δ_H (DMSO-d_6) 3.86 (s, 4H, 2 thiazolidinone protons); 6.39 (s, 2H, 2CH); 7.16–7.68(m, 14H, Ar-H); m/z 432 (M^+, 100 %).

2,2′-(1,4-phenylene)-bis-[3-cyclohexyl-1,3-thiazolidin-4-one] (13b)

Obtained in 67 % yield, m.p. >300 °C (from DMF); (found: C, 64.90; H, 7.20; N, 6.20; S, 14.30. $C_{24}H_{32}N_2O_2S_2$ requires C, 64.82; H, 7.25; N, 6.30; S, 14.42 %); υ_{max} / cm^{-1} 1680 (CO); δ_H (DMSO-d_6) 0.78–1.68(m, 22H, 2 cyclohexyl protons); 3.96 (s, 4H, 2 thiazolidinone protons); 5.88 (s, 2H, 2CH); 7.21–7.48(m, 4H, Ar-H); δ_c 25.24, 31.89, 38.54, 40.20, 54.86, 60.41, 126.71, 131.28, 143.29, 170.29; m/z 444 (M^+, 75 %).

Acknowledgements

The author wish to express his gratitude to Prof. Dr. F.F. Abdel-Latif, Professor of Organic Chemistry, Chemistry Department, Faculty of Science, El-Minia University, for his encouragement throughout this work and Prof. Dr. E.M. Fadl-Allah Professor of Microbiology, Botany Department, Faculty of Science, El-Minia University, for evaluation of antibacterial activity.

References

[1] A. R. Surrey and R. A. Cutler; *J. Am. Chem. Soc.*, **76**, 578 (1958).

[2] W. J. Doran and H. A. Shonle; *J. Org. Chem.;* **3**, 193 (1938).
[3] H. D. Troutmann and L. M. Long; *J. Am. Chem. Soc.;* **70**, 3436 (1948).
[4] C. L. Patel and H. Parekh; *J. Indian Chem. Soc.*, **65(4)**, 282 (1988).
[5] S. P. Singh, S. S. Parmar, K. Raman and V. I. Stenberg; *Chem. Rev.;* **81,** 175 (1981) and references therein.
[6] A. D. Dunn and R. Norries; *J. Prakt. Chem.;* **329,** 321 (1987).
[7] G.C. Barrett, *Tetrahedron,* **36,** 2023 (1980).
[8] R. M. Shaker and F. F. Abdel-Latif; *J. Chem. Res.(S),* 294 (1997).
[9] R. M. Shaker; *Die pharmazie,* 148 (1996).
[10] R. Mekheimer, R.M. Shaker, K.U. Sadek and H. H. Otto; *Heterocyclic communications,* **3,** 217 (1997).
[11] F.F. Abdel-Latif and R. M. Shaker; *Phosphorus Sulfur Silicon Relat. Elem.,* **48**, 217 (1990).
[12] F.F. Abdel-Latif and R. M. Shaker; *J. Chem. Res.(S);* 146 (1995).
[13] F.F. Abdel-Latif and R.M. Shaker; and Naglaa S. Abdel-Aziz; *Heterocyclic communications,* **3,** 245 (1997).
[14] L. Jack Bradshow:Laboratory microbiology 3rd edition (WB standers company Philadelphia, London, Toronto, 1979).