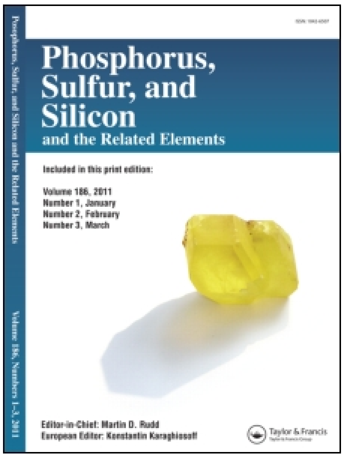


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Tuberculostatic Activity of 1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles

Barbara Milczarska[a]; Henryk Foks[a]; Urszula Dobrzycka[a]; Zofia Zwolska[b]; Ewa Augustynowicz-Kopeć[b]
[a] Department of Organic Chemistry, Medical University of Gdańsk, Poland [b] Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, Warsaw, Poland

To cite this Article Milczarska, Barbara , Foks, Henryk , Dobrzycka, Urszula , Zwolska, Zofia and Augustynowicz-Kopeć, Ewa(2005) 'Synthesis and Tuberculostatic Activity of 1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 12, 2793 — 2799

To link to this Article: DOI: 10.1080/104265090968244

URL: http://dx.doi.org/10.1080/104265090968244

Phosphorus, Sulfur, and Silicon, 180:2793–2799, 2005
Copyright © Taylor & Francis Inc.
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090968244

Synthesis and Tuberculostatic Activity of 1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles

Barbara Milczarska
Henryk Foks
Urszula Dobrzycka
Department of Organic Chemistry, Medical University
of Gdańsk, Poland

Zofia Zwolska
Ewa Augustynowicz-Kopeć
Department of Microbiology, Institute of Tuberculosis
and Pulmonary Diseases, Warsaw, Poland

The 4-hydroxyalkyl-1,2,4-triazole-3-thiones cyclization allowed us to work out the effective method of 1,3-thiazacycloalkyl[3,2-b]-1,2,4-triazoles synthesis. Some of the compounds that were obtained were tested for their tuberculostatic activity.

Keywords 1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles; 4-hydroxyalkyl-1,2,4-triazole-3-thiones; methyl 2-acylodithiocarbazates; tuberculostatic

INTRODUCTION

The heterocyclic derivatives of 1,2,4-triazole-3-thiones were reported[2–4,11] to have large bactericidal activity and some influence on the circulatory system. These compounds exhibited antiphlogistic, antimycotic and antidepressive activity[5–7] as well.

The most often used methods for the preparation of the 1,2,4-triazole derivatives containing the cyclic dihydrothiazole or dihydro-1,3-triazine system are the following: reactions of the corresponding hydrazides with halogeno-alkanoisothiocyanates;[8] reactions of 1,2,4-triazolo-3-thione derivatives with dihalogeno compounds;[9,10,12] reactions of dihalogenoalkanes with aryloylthiosemicarbazide

Received February 15, 2005; in final form March 8, 2005.

Address correspondence to H. Foks, Department of Organic Chemistry, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland. E-mail: hfoks@amg.gda.pl

derivatives;[12] and reactions of 3-aryldithiocarbazaic acid methyl ester with halogenoamines.[10,11]

All these reactions used to give the previously mentioned cyclic compounds; their yields, however, were often below 10–20%.

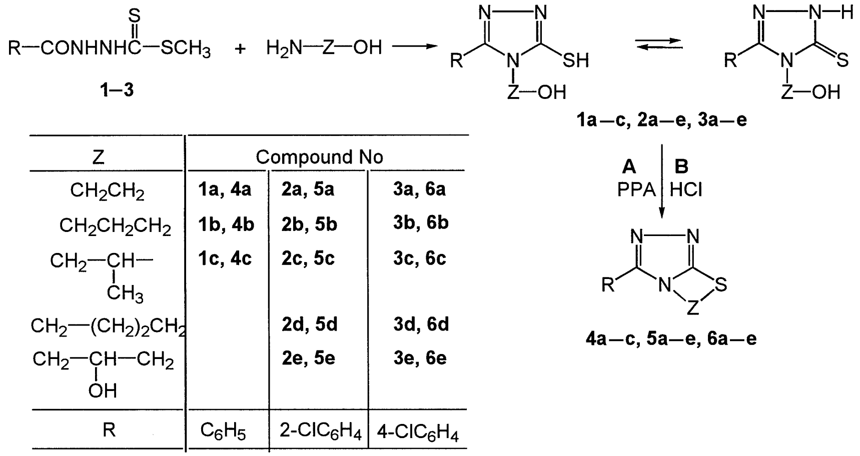
RESULTS AND DISCUSSION

In continuation of our works on the syntheses of biologically active 1,2,4-triazolo-3-thione derivatives, the compounds with hydroxyalkyl substituents in position 4 were obtained.[1] The transformation of these compounds into the derivatives containing the condensed 1,3-thiazacycloalkyl[3,2-b]-1,2,4-triazole systems is reported below.

The synthesis presented, unlike the till now described ones, is the method of high yield (on the average of above 70%).

The cyclization of 4-hydroxyalkyl-1,2,4-triazolo-3-thiones took place in concentrated hydrochloric acid, or polyphosphoric acid surroundings. Under these circumstances the compounds **1a–c**, **2a–e** and **3a–e** gave **4a–e**, **5a–e**, and **6a–e**, respectively. The products of **1c**, **2e**, and **3e** cyclization (i.e., **4c**, **5e**, and **6e**) were obtained in higher yields, while in a concentrated HCl medium.

The reactions realized are shown in Scheme 1.



Z	Compound No		
CH_2CH_2	**1a, 4a**	**2a, 5a**	**3a, 6a**
$CH_2CH_2CH_2$	**1b, 4b**	**2b, 5b**	**3b, 6b**
$CH_2—CH(CH_3)—$	**1c, 4c**	**2c, 5c**	**3c, 6c**
$CH_2—(CH_2)_2CH_2$		**2d, 5d**	**3d, 6d**
$CH_2—CH(OH)—CH_2$		**2e, 5e**	**3e, 6e**
R	C_6H_5	2-ClC_6H_4	4-ClC_6H_4

SCHEME 1

The reaction paths of **2e** and **3e** cyclization had to be considered: one, with the participation of primary alcoholic group in the ring closure, or two with secondary group participation.

While analyzing the registered ^{1}H NMR spectra, taken in DMSO at 500 MHz, a doublet for the 1H secondary alkoholic group —CH—O$\underline{H}$ at 5.62 ppm and a multiplet for the 1H C$\underline{H}$ at 4.35 ppm were observed.

Furthermore, with the use of the Distortionless Enhancement by Polarisation Transfer method, the positive signals of two methylene groups and negative signals of methine groups (aromatic system methine groups at 7.5–7.7 ppm and C$\underline{H}$—OH at 4.35 ppm) were observed.

The spectrum at the simultaneous decoupling of protons (Spin Decoupling method) was registered as well. The singlet of the alcoholic group's protons and the simplification of the methine group signal were registered. These observations proved unequivocally the participation of the primary alcoholic group in the cyclization process.

MICROBIOLOGY

The major part of 4-(hydroxyalkyl)-1,2,4-triazolo-3-thione[1] derivatives and of the cyclic compounds obtained was tested *in vitro* for the tuberculostatic activity with the classical method described elsewhere.[13]

Some of the compounds were tested for their tuberculostatic activity towards the standard Mycobacterium tuberculosis $H_{37}Rv$ strain and two "wild" strains, isolated from the tuberculotic patients (Table I): one, Myc. species 210, resistant to P-aminosalicylic Acid (PAS), Isonicotinic Acid Hydrazide (INH), Etambutol (EMB) and Rifampycine (RFP); the other, Myc. species 192, fully susceptible to the drugs administered.

The results showed that the major part of the compounds tested was active towards Myc. spec. 210 strain—resistant to the drugs

TABLE I Tuberculostatic Activity (μg/mL)

Compound number	Myc.tbc. $H_{37}Rv$	Myc.spec. 192 (susceptible)	Myc.spec. 210 (resistant)	Compound number	Myc.tbc. $H_{37}Rv$	Myc.spec. 192 (susceptible)	Myc.spec. 210 (resistant)
1a	50	50	50	**4a**	50	100	50
1b	100	100	100	**4c**	50	100	50
2a	100	100	50	**5a**	100	100	100
2b	50	100	50	**5b**	100	100	100
2c	100	100	100	**5c**	100	100	100
2d	100	100	50	**5d**	6.2	25	25
2e	100	100	50	**5e**	50	50	50
3a	100	100	50	**6a**	50	25	50
3b	100	100	50	**6b**	100	50	50
3c	100	100	50	**6c**	50	100	50
3d	50	100	50	**6d**	25	100	50
3e	100	100	50	**6e**	50	100	50

TABLE II Characteristics of the Synthesized Compounds

Compound number	R	Z	Formula and molecular weight	M.P. [°C] solvent for crystallization	Reaction yield [%]	^{1}H-NMR (**A**—80 MHz, **B**—200 MHz δ[ppm] **C**—$CDCl_3$, **D**—DMSO-d_6	IR KBr ν [cm^{-1}]
4a	C_6H_5	$-CH_2-CH_2-$	$C_{10}H_9N_3S$ 203	190–3 Benzene	59	**AC**: 4.05(t, 2H CH_2); 4.4(t, 2H CH_2); 7.5–7.8(m, 5H Ph)	750, 1440, 1540, 1620, 1650, 2950, 3020
4b	C_6H_5	$-CH_2-CH_2-CH_2-$	$C_{11}H_{11}N_3S$ 217	195–9 Benzene	46	**BD**: 2.2(m, 2H CH_2); 3.25(t, 2H SCH_2); 4.15(t, 2H NCH_2); 7.5–7.7(m, 5H Ph)	760, 1450, 1560, 1600, 1640, 2960, 3050
4c	C_6H_5	$-CH_2-\underset{\vert}{C}H-CH_3$	$C_{11}H_{11}N_3S$ 217	171–5 Methanol	60	**BC**: 1.65(d, 3H CH_3); 4.0(q, 1H CH_2); 4.5(q, 1H CH_2); 4.7(m, 1H CH); 7.5–7.8(m, 5H Ph)	760, 1440, 1550, 1620, 1650, 2920–2970, 3010
5a	2-ClC_6H_4	$-CH_2-CH_2-$	$C_{10}H_8ClN_3S$ 238	184–5 Methanol + H_2O	90	**BC**: 3.9–4.3(m, 4H CH_2CH_2); 7.4–7.7(m, 4H Ph)	700, 1450, 1550, 1600, 1650, 2900–2950, 3300–3600
5b	2-ClC_6H_4	$-CH_2-CH_2-CH_2-$	$C_{11}H_{10}ClN_3S$ 252	151–2 Methanol + H_2O	90	**BC**: 2.3(m, 2H CH_2); 3.2(t, 2H NCH_2); 3.9(t, 2H SCH_2); 7.4–7.6(m, 4H Ph)	750, 1460, 1550, 1580, 1620, 2800–2900, 3300–3600
5c	2-ClC_6H_4	$-CH_2-\underset{\vert}{C}H-CH_3$	$C_{11}H_{10}ClN_3S$ 252	104–106 Methanol + H_2O	97	**CD**: 1.5(d, 3H CH_3); 4.2(d, 2H CH_2); 4.75(m, 1H CH); 7.5–7.7(m, 4H Ph)	780, 1450, 1500, 1580, 1620, 2900, 3300–3600
5d	2-ClC_6H_4	$-CH_2-(CH_2)_2-CH_2-$	$C_{12}H_{12}ClN_3S$ 266	130–2 Methanol + H_2O	71	**BD**: 1.9–2.2(m, 4H CH_2CH_2); 2.9(t, 2H CH_2N); 4.0(t, 2H SCH_2); 7.4–7.7(m, 4H Ph)	760, 1440, 1540, 1580, 1620, 1650, 2975, 3300–3600
5e	2-ClC_6H_4	$-CH_2-\underset{\underset{OH}{\vert}}{C}H-CH_2-$	$C_{11}H_{10}ClN_3OS$ 268	192–5 Methanol + H_2O	96	**BD**: 3.5(d, 2H SCH_2); 3.7(d, 2H NCH_2); 4.35(m, 1H CH); 5.65(q, 1H OH); 7.6(m, 4H Ph)	760, 1100, 1210, 1480, 1580, 1620, 2900, 3300–3600

6a	4-ClC_6H_4	$-CH_2-CH_2-$	$C_{10}H_8ClN_3S$ 238	210–3 Methanol	97	**AC**: 4.1–4.3(m, 4H CH_2CH_2); 7.4–7.7 (m, 4H Ph)	835, 1080, 1440, 1480, 1530, 1605, 2900, 3040
6b	4-ClC_6H_4	$-CH_2-CH_2-CH_2-$	$C_{11}H_{10}ClN_3S$ 252	185–7 H_2O	71	**AC**: 2.3(m, 2H CH_2); 3.1(t, 2H CH_2S); 4.1(t, 2H NCH_2); 7.5(m, 4H Ph)	840, 1080, 1440, 1520, 1560, 1620, 2960
6c	4-ClC_6H_4	$-CH_2-\underset{\vert}{C}H-CH_3$	$C_{11}H_{10}ClN_3S$ 252	191–2 Methanol + H_2O	71	**AC**: 1.6(d, 3H CH_3); 3.8–4.8(m, 3H CH_2-CH); 7.4–7.7(m, 4H Ph)	825, 1000, 1080, 1460, 1640, 2950
6d	4-ClC_6H_4	$-CH_2-(CH_2)_2-CH_2-$	$C_{12}H_{12}ClN_3S$ 266	172–5 Methanol	95	**AC**: 1.9–2.2(m, 4H CH_2CH_2); 2.9(t, 2H CH_2S); 4.1(t, 2H NCH_2); 7.5(m, 4H Ph)	840, 1000, 1080, 1185, 1380, 1460, 1570, 2920, 2960
6e	4-ClC_6H_4	$-CH_2-\underset{\underset{OH}{\vert}}{C}H-CH_2-OH$	$C_{11}H_{10}ClN_3OS$ 268	237–9 Methanol	64	**AC**: 2.4(d, 2H SCH_2); 3.3(m, 2H CH_2N); 4.0(m, 1H CH); 4.3(s, 1H OH); 7.6(m, 4H Ph)	830, 1050, 1080, 1240, 1270, 1300, 1440, 1520, 1600, 1640, 2900, 3130, 3200

commonly used PAS, INH, EMB, and RFP—with Minimum Growth Inhibiting Concentration (MIC) value of 50 μg/mL. The bicyclic compounds were even more active. The MIC for the compound **5d** was 6.2–25 μg/mL, and for the compounds **6a**, **c**, **d**, **e**, from 25–50 μg/mL.

EXPERIMENTAL

All melting points were obtained with a Boëtius apparatus and are uncorrected. The IR spectra were taken with a Satellite spectrophotometer. The ^{1}H NMR spectra were taken with a Tesla BS-487 spectrometer at 80 MHz in $CDCl_3$ and DMSO-d_6, or with Varian Gemini 200 and Varian Unity 500 MHz spectrometers at 200 MHz in $CDCl_3$ and DMSO-d_6.

The results of elemental analyses (% C, H, and N) for all the compounds obtained were in good agreement with the data calculated.

The reaction yields and the physical constants of the new compounds were given in Table II. Methyl 2-acylodithiocarbazates **1–3** and 4,5-disubstituted s-triazole-3-thiones **1a–c**, **2a–e**, and **3a–e** were obtained according to the method described elsewhere.[1]

1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles (4a–c, 5a–e, and 6a–e)

Method A

The corresponding 4-hydroxyalkyl-5-aryl-1,2,4-triazole-3-thiones **1a–b**, **2a–d**, or **3a–d** (2.5 mmole) were heated to 100°C in polyphosphoric acid (6–7 g) for 2 h. After cooling, water (25 mL) was added and alkalified with ammonia to pH 6.5–7.0. The products precipitated were filtered and crystallized.

Method B

The reaction was carried out in a similar way: compounds **1c**, **2e**, and **3e** were refluxed with concentrated HCl (6 mL) for 2 h.

REFERENCES

[1] B. Milczarska and H. Foks, *Phosphorus, Sulfur and Silicon*, **180,** 197 (2005).

[2] H. Foks, W. Rudnicka, M. Główka, R. Kaliszan, A. Nasal, B. Damasiewicz, A. Rodwanska, J. Petrusewicz, H. Trzeciak, B. Okopien, M. Jarowiec, and Z. Zwaska-Kweik, *Pharmazie*, **47,** 770 (1992).

[3] H. Foks and F. Sączewski, *Acta Polon. Pharm.*, **45,** 465 (1988).

[4] W. Zhongyi, S. Haoxin, and S. Haijian, *Synthetic Commun.*, **31,** 2841 (2001).

[5] K. Sung and A. Lee, *J. Heterocyclic Chem.*, **29,** 1101 (1992).

[6] J. Mohan and P. Verma, *J. Indian Chem. Soc.*, **69,** 268 (1992).

[7] J. Kane and F. Miller, E. P. 221, 485 U.S (1985); *Chem. Abs.*, **107,** P 154339g (1987).

[8] L. G. Payne, M. T. Wu, and A. A. Patehett. *Heterocycles*, **12,** 1171 (1979).
[9] A. S. Ali, J. S. Wilkie, and K. N. Winzenberg, *Aust. J. Chem.*, **50,** 911 (1997).
[10] H. K. Sangita Pujari, *Indian J. Chem. Sect. B*, **17,** 364 (1979).
[11] H. Foks, A. Czarnocka-Janowicz, W. Rudnicka, B. Damasiewicz, and A. Nasal, *Acta Polon. Pharm.*, **52,** 415 (1995).
[12] K. Jain, R. N. Handa, *Indian J. Chem. Sect. B*, **21,** 732 (1982).
[13] D. Pancechowska-Ksepko, H. Foks, M. Janowiec, and Z. Zwolska-Kwiek, *Acta Polon. Pharm.*, **45,** 193 (1988).