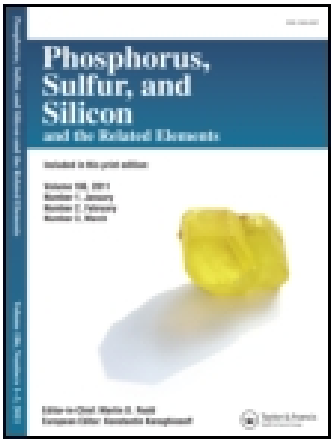

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

New Method of 4,5-Disubstituted 1,2,4-triazolo-3-thiones Synthesis

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Published online: 01 Feb 2007.

To cite this article: Henryk Foks & Barbara Milczarska (2005) New Method of 4,5-Disubstituted 1,2,4-triazolo-3-thiones Synthesis, Phosphorus, Sulfur, and Silicon and the Related Elements, 180:1, 197-204, DOI: 10.1080/104265090508217

To link to this article: http://dx.doi.org/10.1080/104265090508217

Phosphorus, Sulfur, and Silicon, 180:197–204, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090508217

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New Method of 4,5-Disubstituted 1,2,4-triazolo-3-thiones Synthesis

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A universal method of 4,5-disubstituted S-triazolo-3-thiones synthesis from methyl esters of arylothiocarbazoic acids and some primary amines is presented.

Keywords 1,2,4-Triazole-3-thiones; 4,5-disubstituted-1,2,4-triazolo-3-thiones; new method synthesis

INTRODUCTION

The 4,5-disubstituted 1,2,4-triazolo-3-thione derivatives have been produced mainly by two methods: (a) the imidoesters treatment with thiosemicarbazide and amines,[1] (b) the reaction of hydrazides with isothiocyanates, followed by cyclization of the compounds obtained in alkaline environment.[2,3]

Since the 1,2,4-triazolo-3-thione derivatives have shown widespread pharmacological activity[4–6] the efficient method of preparation of these compounds was worked out.

RESULTS AND DISCUSSION

The method presented herein, foretold by Foks et al.,[7] was based on the primary amines reaction with methyl esters of aryldithiocarbazoic acids. The majority of 34 derivatives were obtained in very good yields (Table I).

Received June 1, 2004; in final form June 15, 2004.

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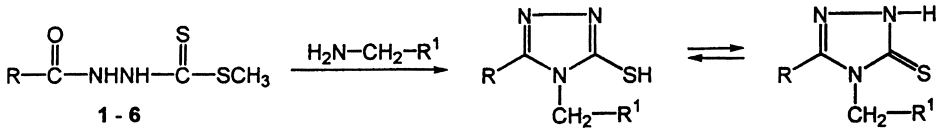
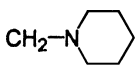
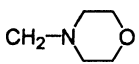
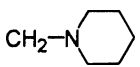
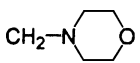
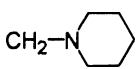
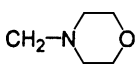
TABLE I Characteristics of the Synthesized Compounds

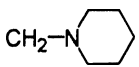
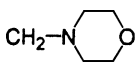
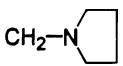


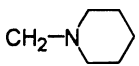
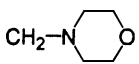
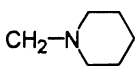
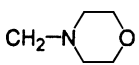
Compound	R	R^1	Formula Molecular weight	M.p. [°C] Solvent for crystallization	Reaction yield [%]	^{1}H-NMR (A—80 MHz, B—200 MHz) δ[ppm] (C—$CDCl_3$, D—CD_3OD, E—d_6-DMSO)
1	C_6H_5	—	$C_9H_{10}N_2OS_2$ 226,0	167–9 MeOH	42,0	A, D: 2.7 (s, 3H CH_3); 7.4 (m, 5H Ar)
2	2-Cl—C_6H_4	—	$C_9H_9ClN_2OS_2$ 260,5	129–130 MeOH	45,0	A, C: 2.7 (s, 3H CH_3); 7.5–7.9 (m, 4H Ar)
3	3-Cl—C_6H_4	—	$C_9H_9ClN_2OS_2$ 260,5	172–8 MeOH	43,6	A, D: 2.5 (s, 3H CH_3); 7.4–7.9 (m, 4H Ar)
4	4-Cl—C_6H_4	—	$C_9H_9ClN_2OS_2$ 260,5	177–180 MeOH	50,0	A, E: 2.6 (s, 3H CH_3); 7.6–7.9 (m, 4H Ar); 11.1 (s, 1H NH—C=S); 11.6 (s, 1H NH)
5	3-pyridyl	—	$C_8H_9N_3OS_2$ 227,0	160–2 MeOH	70,0	B, D: 2.6 (s, 3H CH_3); 7.5–9 (m, 4H Py)
6	4-pyridyl	—	$C_8H_9N_3OS_2$ 227,0	183–4 MeOH	63,0	B, C: 2.5 (s, 3H CH_3); 7.7–8.8 (m, 4H Py)
1a	C_6H_5	CH_2OH	$C_{10}H_{11}N_3OS$ 221,0	190–2 MeOH	63,3	B, D: 3.3 (s, 1H OH); 3.9 (t, 2H CH_2); 4.2 (t, 2H CH_2O); 7.5–7.8 (m, 5H Ar)
1b	C_6H_5	$(CH_2)_2OH$	$C_{10}H_{13}N_3OS$ 235,0	114–7 MeOH + H_2O	59,6	B, D: 1.8 (m, 2H CH_2); 3.3 (s, 1H OH); 3.5 (t, 2H CH_2O); 4.2 (t, 2H NCH_2); 7.5–7.7 (m, 5H Ar)
1c	C_6H_5	$(CH_2)_2OC_2H_5$	$C_{13}H_{17}N_3OS$ 263,0	118–120 MeOH	28,2	B, C: 1.05 (t, 3H CH_3); 2.05 (m, 2H CH_2); 3.2–3.4 (m, 4H CH_2OCH_2); 4.25 (t, 2H NCH_2); 7.5-7.65 (m, 5H Ar); 12.0 (1H NH)
1d	C_6H_5		$C_{15}H_{20}N_4S$ 288,0	124–7 Benzene	58,3	B, D: 1.4–1.6 (m, 6H $(CH_2)_3$); 2.55 (m, 4H CH_2NCH_2); 2.8 (t, 2H CH_2); 4.3 (t, 2H CH_2); 7.5–7.7 (m, 5H Ar)
1e	C_6H_5		$C_{14}H_{18}N_4OS$ 290,0	176–8 MeOH	78,6	B, C: 2.3 (t, 4H CH_2NCH_2); 2.7 (t, 2H CH_2); 3.5 (t, 4H CH_2OCH_2); 4.25 (t, 2H CH_2); 7.5–7.65 (m, 5H Ar)

2a	2-Cl–C_6H_4	CH_2OH	$C_{10}H_{10}ClN_3OS$ 255,5	160–1 MeOH + H_2O	96,5	A, D: 3.8 (t, 2H CH_2N); 4.0 (t, 2H CH_2O); 7.4–7.8 (m, 4H Ar)
2b	2-Cl–C_6H_4	$(CH_2)_2OH$	$C_{11}H_{12}ClN_3OS$ 269,5	157–8 MeOH + H_2O	90,7	A, E: 1.6 (m, 2H CH_2); 3.7 (t, 2H NCH_2); 3.8 (t, 2H CH_2O); 4.4 (s, 2H OH); 7.5–7.8 (m, 4H Ar)
2c	2-Cl–C_6H_4	$(CH_2)_3OH$	$C_{12}H_{14}ClN_3OS$ 283,5	104–5 MeOH + H_2O	67,2	A, C: 1.3–1.9 (m, 4H CH_2–CH_2); 3.6 (t, 2H NCH_2); 4.0 (t, 2H CH_2O); 7.4–7.6 (m 4H, Ar)
2d	2-Cl–C_6H_4	CH(OH)CH_3	$C_{11}H_{12}ClN_3OS$ 269,5	156–7 MeOH + H_2O	54,1	A, C: 1.1 (d, 3H CH_3); 3.9 (d, 2H CH_2); 4.2 (m, 1H CH); 7.4–7.6 (m, 4H Ar)
2e	2-Cl–C_6H_4	CH(OH)CH_2–OH	$C_{11}H_{12}ClN_3O_2S$ 285,5	138–41 MeOH + H_2O	77,2	A, D: 3.4 (t, 2H NCH_2); 3.7–4.3 (m, 3H CH–CH_2O); 7.4–7.7 (m, 4H Ar)
2f	2-Cl–C_6H_4	$(CH_2)_2$–OC_2H_5	$C_{13}H_{16}ClN_3OS$ 297,5	127–8 MeOH + H_2O	87,8	A, D: 1.0 (t, 3H CH_3); 1.9 (q, 2H CH_2); 3.3 (m, 4H NCH_2CH_2); 4.0 (t, 2H CH_2O); 7.5–7.7 (m, 4H Ar)
2g	2-Cl–C_6H_4		$C_{15}H_{19}ClN_4S$ 322,5	200–1 MeOH	25,0	A, D: 1.4 (m, 6H $(CH_2)_3$); 2.3 (m, 4H CH_2NCH_2); 2.5 (t, 2H CH_2N); 4.0 (t, 2H NCH_2); 7.5–7.7 (m, 4H Ar)
2h	2-Cl–C_6H_4		$C_{14}H_{17}ClN_4OS$ 324,5	63–4 MeOH	25,0	A, D: 2.2 (m, 4H CH_2NCH_2); 2.5 (t, 2H CH_2N); 3.5 (m, 4H CH_2OCH_2); 4.0 (t, 2H NCH_2); 7.5–7.7 (m, 4H Ar)
3a	3-Cl–C_6H_4	$(CH_2)_2OC_2H_5$	$C_{13}H_{16}ClN_3OS$ 297,5	97–9 MeOH + H_2O	90,5	B, C: 1.1 (t, 3H CH_3); 2.1 (m, 2H CH_2); 3.4 (m, 4H CH_2OCH_2); 4.25 (t, 2H NCH_2); 7.4–7.7 (m, 4H Ar); 12.3 (s, 1H NH)
3b	3-Cl–C_6H_4		$C_{15}H_{19}ClN_4S$ 322,5	124–7 Benzene + E_N	82,6	B, C: 1.5 (m, 6H $(CH_2)_3$); 2.8 (t, 2H CH_2); 4.3 (t, 2H CH_2); 4.5 (t, 4H CH_2NCH_2); 7.4–7.7 (m, 4H Ar)
3c	3-Cl–C_6H_4		$C_{14}H_{17}ClN_4OS$ 324,5	72–8 Aceton + H_2O	86,4	B, C: 2.3 (t, 4H CH_2NCH_2); 2.7 (t, 2H NCH_2); 3.5 (t, 4H CH_2OCH_2); 4.2 (t, 2H NCH_2); 7.4–7.7 (m, 4H Ar)

(Continued on next page)

TABLE I Characteristics of the Synthesized Compounds *(Continued)*

Compound	R	R^1	Formula 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—CD_3OD, E—d_6-DMSO)
4a	4-Cl—C_6H_4	CH_2OH	$C_{10}H_{10}ClN_3OS$ 255,5	220–2 MeOH + H_2O	70,3	A, E: 3.8–4.1 (t, 4H $(CH_2)_2$); 5.0 (t, 1H OH) + D_2O decay; 7.6–7.9 (m, 4H Ar); 14.0 (s, 1H NH) + D_2O decay
4b	4-Cl—C_6H_4	$(CH_2)_2OH$	$C_{11}H_{12}ClN_3OS$ 269,5	148–50 MeOH + H_2O	98,5	A,E: 1.7 (m, 2H CH_2); 3.4 (t, 2H NCH_2); 4.1 (t, 2H CH_2O); 4.5 (t, 1H OH); 7.7 (m, 4H Ar); 14.0 (s, 1H NH)
4c	4-Cl—C_6H_4	$(CH_2)_3OH$	$C_{12}H_{14}ClN_3OS$ 283,5	147–9 MeOH + H_2O	87,3	A, E: 1.1–1.8 (m, 4H $(CH_2)_2$); 3.3 (m, 2H NCH_2); 4.0 (t, 2H CH_2O); 4.4 (t, 1H OH); 7.6 (m, 4H Ar); 14.0 (s, 1H NH)
4d	4-Cl—C_6H_4	CH—OH | CH_3	$C_{11}H_{12}ClN_3OS$ 269,5	168–70 MeOH + H_2O	61,2	A, C: 1.2 (d, 3H CH_3); 4.0 (d, 2H CH_2); 4.5 (m, 1H CH); 7.5–7.7 (m, 4H Ar)
4e	4-Cl—C_6H_4	CH—OH | CH_2—OH	$C_{11}H_{12}ClN_3O_2S$ 285,5	150–2 H_2O	94,4	A, E: 3.3 (m, 2H CH_2O); 3.7–4.2 (m, 3H NCH_2–CH); 4.7 (t, 1H OH); 5.1 (d, 1H OH); 7.6–7.9 (m, 4H Ar); 14.0 (s, 1H NH)
4f	4-Cl—C_6H_4	$(CH_2)_2OC_2H_5$	$C_{13}H_{16}ClN_3OS$ 297,5	119–20 MeOH	82,4	B, C: 1.1 (t, 3H CH_3); 2.05 (m, 2H CH_2); 3.35 (q + t, 4H CH_2OCH_2); 4.25 (t, 2H NCH_2); 7.4–7.6 (m, 4H Ar); 12.0 (s, 1H NH)
4g	4-Cl—C_6H_4		$C_{15}H_{19}ClN_4S$ 322,5	224–8 Dioksan	48,4	B, C: 1.4 (t, 6H $(CH_2)_3$); 2.35 (t, 4H CH_2NCH_2); 2.7 (t, 2H NCH_2); 4.2 (t, 2H NCH_2); 7.5–7.7(m, 4H Ar)
4h	4-Cl-C_6H_4		$C_{14}H_{17}ClN_4OS$ 324,5	170–3 MeOH	59,4	B, C: 2.4 (t, 4H CH_2NCH_2); 2.7 (t, 2H NCH_2); 3.5 (t, 4H CH_2OCH_2); 4.25 (t, 2H NCH_2); 7.4–7.6 (m, 4H Ar)
4i	4-Cl-C_6H_4		$C_{14}H_{17}ClN_4S$ 308,5	205–8 MeOH	20,0	A, C: 1.7 (m, 4H CH_2CH_2); 2.5 (m, 4H CH_2NCH_2); 2.9 (t, 2H CH_2N); 4.2 (t, 2H NCH_2); 7.5 (m, 4H Ar)

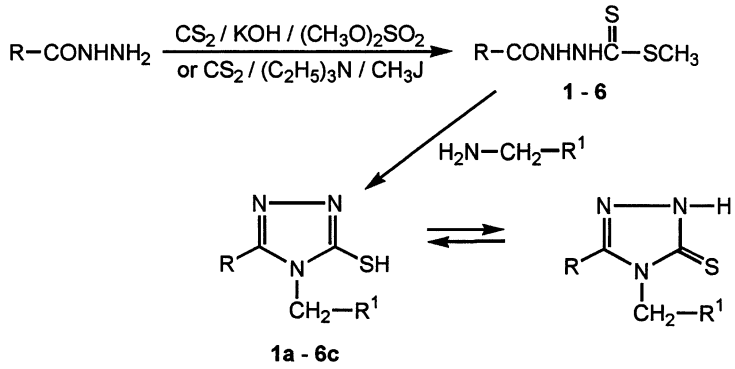
4j	4-Cl—C_6H_4	C_6H_{11}	$C_{15}H_{18}ClN_3S$ 307,5	180–5 MeOH	54,5	A, C: 0.7–1.2 (m, 5H cyclic.); 1.3–1.8 (m, 6H cyclic.); 4.0 (d, 2H CH_2); 7.5 (m, 4H Ar); 12.5 (s, 1H NH + D_2O decay)
5a	3-pyridyl	CH_2OCH_3	$C_{10}H_{12}N_4OS$ 236,3	166–9 Aceton + H_2O	60,4	B, C: 3.3 (s, 3H CH_3); 3.9 (t, 2H CH_2O); 4.3 (t, 2H NCH_2); 7.5, 8.2, 8.8 (m, 4H Py); 12.0 (s, 1H NH)
5b	3-pyridyl	$(CH_2)_2OCH_3$	$C_{11}H_{14}N_4OS$ 250,32	137–9 Aceton + H_2O	77,7	B, C: 2.1 (m, 2H CH_2); 3.2 (s, 3H CH_3); 3.4 (t, 2H CH_2O); 4.3 (t, 2H NCH_2); 7.5, 8.0, 8.8 (m, 4H Py)
5c	3-pyridyl	$(CH_2)_2OC_2H_5$	$C_{12}H_{16}N_4OS$ 264,34	43–6 MeOH + H_2O	65,5	B, C: 1.1 (t, 3H CH_3); 2.1 (m, 2H CH_2); 3.3 (m, 4H CH_2OCH_2); 4.3 (t, 2H NCH_2); 7.5, 8.0, 8.8 (m, 4H Py)
5d	3-pyridyl		$C_{14}H_{19}N_5S$ 289,4	125–9 Aceton	51,8	B, C: 1.5 (m, 6H $(CH_2)_3$); 2.4 (m, 4H $(CH_2)_2$); 2.8 (t, 2H CH_2N); 4.3 (t, 2H NCH_2); 7.5, 81, 8.8 (m, 4H Py)
5e	3-pyridyl		$C_{13}H_{17}N_5OS$ 291,4	75–8 MeOH + H_2O	30,6	B, C: 2.4(m, 4H CH_2NCH_2); 2.7(t, 2H CH_2N); 3.5(m, 4H CH_2OCH_2); 4.3(t, 2H NCH_2), 7.5–8.8 (m, 4H, Py)
6a	4-pyridyl	$(CH_2)_2OC_2H_5$	$C_{12}H_{16}N_4OS$ 264,3	168–70 Aceton	85,7	B, C: 1.1(t, 3H CH_3); 2.15(m, 2H CH_2); 3.4(m, 4H CH_2OCH_2); 4.3(t, 2H NCH_2); 7.6, 8.8(m, 4H Py); 12.2(s, 1H NH)
6b	4-pyridyl		$C_{14}H_{19}N_5S$ 289,4	188–90 MeOH	82,0	B, C: 1.4(m, 6H $(CH_2)_3$); 2.4(m, 4H $(CH_2)_2$); 2.8(t, 2H NCH_2); 4.3(t, 2H CH_2N); 7.7, 8.8(m, 4H Py)
6c	4-pyridyl		$C_{13}H_{17}N_5OS$ 291,4	201–3 Aceton	38,6	B, C: 2.2(t, 4H CH_2NCH_2); 2.7(t, 2H CH_2N); 3.5(t, 4H CH_2OCH_2); 4.15(t, 2H NCH_2); 7.6, 8.9(m, 4H Py)

Ar = aromatic, Py = pyridine.

The method presented was the only way of obtaining the triazolothiones when the isothiocyanates were hardly available.

The method failed, however, in the case of amines having their primary functional group bounded to a secondary carbon atom. These amines used to give hydrazides and N,N′-disubstituted thioureas as the reaction products, e.g. with cyclohexylamine the methyl esters of dithiocarbazoic acids decomposed, giving the corresponding acid hydrazide and N,N′-dicyclohexylthiourea.

The methyl monoesters of aryldithiocarbazoic acids were obtained from the corresponding (benzoic, 2-, 3-, and 4-chlorobenzoic, nicotinic and isonicotinic) hydrazides by means of methylation with dimethyl sulphate or methyl iodide (Scheme 1).



SCHEME 1

The methylation course was established experimentally with a view to the highest possible yields, and a minimum dimethyl derivative content in the ester obtained.

Dimethyl sulphate was used as the methylating agent in the syntheses of phenyl-, 2-chloro-, 3-chloro-, and 4-chlorodithiocarbazoic acid methyl esters, whereas methyl iodide—in the syntheses of 3-pyridilo- and 4-pyridilodithiocarbazoic acid methyl esters.

For some of the 1,2,4-triazolo-3-thione derivatives, tuberculostatic activity has been descriebed[3,8–10] therefore the newly obtained compounds will be tested for their activity against *Mycobacterium tuberculosis.* The results together with other group of triazoles will be given in a separate paper.

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with a Satelite spectrophotometer. The ^{1}H-NMR spectra were taken with Tesla BS-487 spectrometer at 80 MHz in $CDCl_3$, CD_3OD, and DMSO-d_6, or with Varian Gem 200 spectrometer at 200 MHz in $CDCl_3$ and CD_3OD.

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

Reaction yields and the physical constants of the new compounds are given in the Table I.

Preparation of Methyl 2-Acylodithiocarbazates (1–6)

Method A (1–4)

To a solution of KOH (0.06 mol) in water (40 cm^3) and ethanol (30 cm^3), the corresponding hydrazide (0.03 mol) was added and then, through a reflux condenser carbon disulfide (0.03 mol) was added with stirring. After the oily drops of carbon disulfide disappeared, dimethyl sulfate (0.015 mol) was added portionwise with stirring. After 3 h the solution was acidified with acetic acid (pH = 3) and the precipitated esters (**1**–**4**) were collected, washed with water and recrystallized.

Method B (5, 6)

To a suspension of the corresponding hydrazide (0.05 mol) in methanol (25 cm^3), triethyloamine (0.05 mol) was added. Then, carbon disulfide (0.05 mol) was added dropwise through a reflux condenser. After the reaction mixture cleared, methyl iodide (0.05 mol) was added drop by drop with stirring.

After 2 h to the solution water (150 cm^3) was added and the mixture was allowed to stand overnight at room temperature. The precipitated esters (**5, 6**) were filtered off and recrystallized.

Preparation of 4,5-Disubstituted S-Triazole-3-thione Derivatives (1a–6c)

Compounds **1–6** (0.005 mol) and the corresponding amines (0.015 mol) were refluxed for 1–1.5 h. On cooling down, 10 cm^3 of water was added and the solution was acidified with acetic acid (pH 4–6). The mixture was ice-cooled, the precipitate collected and recrystallized.

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