

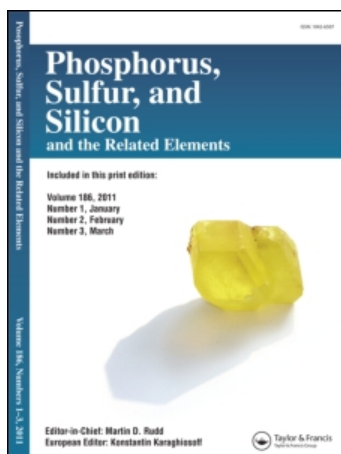
This article was downloaded by:

On: 28 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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>

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

Henryk Foks^a; Barbara Milczarska^a

^a Department of Organic Chemistry, Medical University of Gdańsk, Poland

To cite this Article Foks, Henryk and Milczarska, Barbara(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

To link to this Article: DOI: 10.1080/104265090508217

URL: <http://dx.doi.org/10.1080/104265090508217>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

Barbara Mileczarska

Henryk Foks

Department of Organic Chemistry, Medical University of Gdańsk,
Poland

A universal method of 4,5-disubstituted S-triazolo-3-thiones synthesis from methyl esters of arylothiocarbazic 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.

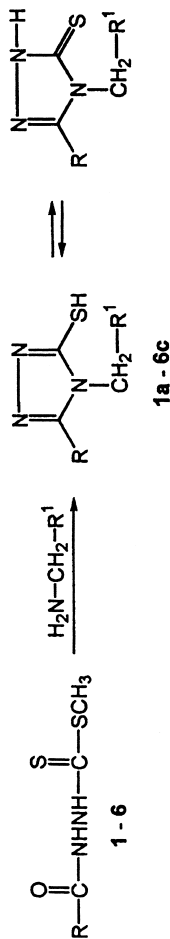
RESULTS AND DISCUSSION

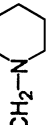
The method presented herein, foretold by Foks et al.,⁷ was based on the primary amines reaction with methyl esters of aryldithiocarbazic acids. The majority of 34 derivatives were obtained in very good yields (Table I).

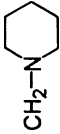
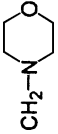
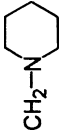
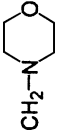
Received June 1, 2004; in final form June 15, 2004.

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

TABLE I Characteristics of the Synthesized Compounds

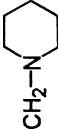
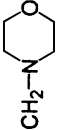
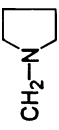


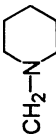
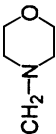
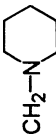
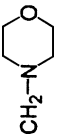
Compound	R	R ¹	Formula Molecular weight	M.p. [°C] Solvent for crystallization	Reaction yield [%]	¹ H-NMR (A—80 MHz, B—200 MHz) δ[ppm] (C—CDCl ₃ , D—CD ₃ OD, E—d ₆ -DMSO)
1	C ₆ H ₅	—	C ₉ H ₁₀ N ₃ OS ₂ 226,0	167–9 MeOH	42,0	A, D: 2.7 (s, 3H CH ₃); 7.4 (m, 5H Ar)
2	2-Cl–C ₆ H ₄	—	C ₉ H ₉ ClN ₃ OS ₂ 260,5	129–130 MeOH	45,0	A, C: 2.7 (s, 3H CH ₃); 7.5–7.9 (m, 4H Ar)
3	3-Cl–C ₆ H ₄	—	C ₉ H ₉ ClN ₃ OS 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 ₆ H ₄	—	C ₉ H ₉ ClN ₃ OS 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 ₈ H ₉ N ₃ OS 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 ₈ H ₉ N ₃ OS 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 ₆ H ₅	CH ₂ OH	C ₁₀ H ₁₁ N ₃ OS 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 ₂ O); 7.5–7.8 (m, 5H Ar)
1b	C ₆ H ₅	(CH ₂) ₂ OH	C ₁₀ H ₁₃ N ₃ OS 235,0	114–7 MeOH + H ₂ O	59,6	B, D: 1.8 (m, 2H CH ₂); 3.3 (s, 1H OH); 3.5 (t, 2H CH ₂ O); 4.2 (t, 2H NCH ₂); 7.5–7.7 (m, 5H Ar)
1c	C ₆ H ₅	(CH ₂) ₂ OC ₂ H ₅	C ₁₃ H ₁₇ N ₃ OS 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 ₂ OC ₂ H ₅); 4.25 (t, 2H NCH ₂); 7.5–7.65 (m, 5H Ar); 12.0 (1H NH)
1d	C ₆ H ₅		C ₁₅ H ₂₀ N ₄ S 288,0	124–7 Benzene	58,3	B, D: 1.4–1.6 (m, 6H (CH ₂) ₃); 2.55 (m, 4H CH ₂ NCH ₂); 2.8 (t, 2H CH ₂); 4.3 (t, 2H CH ₂); 7.5–7.7 (m, 5H Ar)
1e	C ₆ H ₅		C ₁₄ H ₁₈ N ₄ OS 290,0	176–8 MeOH	78,6	B, C: 2.3 (t, 4H CH ₂ NCH ₂); 2.7 (t, 2H CH ₂); 3.5 (t, 4H CH ₂ OCH ₂); 4.25 (t, 2H CH ₂); 7.5–7.65 (m, 5H Ar)

2a	2-Cl-C ₆ H ₄	CH ₂ OH	C ₁₀ H ₁₀ CIN ₃ OS 255,5	160-1 MeOH + H ₂ O	96,5	A, D: 3.8 (t, 2H CH ₂ N); 4.0 (t, 2H CH ₂ O); 7.4-7.8 (m, 4H Ar)
2b	2-Cl-C ₆ H ₄	(CH ₂) ₂ OH	C ₁₁ H ₁₂ CIN ₃ OS 269,5	157-8 MeOH + H ₂ O	90,7	A, E: 1.6 (m, 2H CH ₂); 3.7 (t, 2H NCH ₂); 3.8 (t, 2H CH ₂ O); 4.4 (s, 2H OH); 7.5-7.8 (m, 4H Ar)
2c	2-Cl-C ₆ H ₄	(CH ₂) ₃ OH	C ₁₂ H ₁₄ CIN ₃ OS 283,5	104-5 MeOH + H ₂ O	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 ₂ O); 7.4-7.6 (m, 4H Ar)
2d	2-Cl-C ₆ H ₄	CH-OH CH ₃	C ₁₁ H ₁₂ CIN ₃ OS 269,5	156-7 MeOH + H ₂ O	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 ₆ H ₄	CH-OH CH ₂ -OH	C ₁₁ H ₁₂ CIN ₃ O ₂ S 285,5	138-41 MeOH + H ₂ O	77,2	A, D: 3.4 (t, 2H NCH ₂); 3.7-4.3 (m, 3H CH-CH ₂ O); 7.4-7.7 (m, 4H Ar)
2f	2-Cl-C ₆ H ₄	(CH ₂) ₂ -OC ₂ H ₅	C ₁₃ H ₁₆ CIN ₃ OS 297,5	127-8 MeOH + H ₂ O	87,8	A, D: 1.0 (t, 3H CH ₃); 1.9 (q, 2H CH ₂); 3.3 (m, 4H NCH ₂ CH ₂); 4.0 (t, 2H CH ₂ O); 7.5-7.7 (m, 4H Ar)
2g	2-Cl-C ₆ H ₄		C ₁₅ H ₁₉ CIN ₄ S 322,5	200-1 MeOH	25,0	A, D: 1.4 (m, 6H (CH ₂) ₃); 2.3 (m, 4H CH ₂ NCH ₂); 2.5 (t, 2H CH ₂ N); 4.0 (t, 2H NCH ₂); 7.5-7.7 (m, 4H Ar)
2h	2-Cl-C ₆ H ₄		C ₁₄ H ₁₇ CIN ₄ OS 324,5	63-4 MeOH	25,0	A, D: 2.2 (m, 4H CH ₂ NCH ₂); 2.5 (t, 2H CH ₂ N); 3.5 (m, 4H CH ₂ OCH ₂); 4.0 (t, 2H NCH ₂); 7.5-7.7 (m, 4H Ar)
3a	3-Cl-C ₆ H ₄	(CH ₂) ₂ OC ₂ H ₅	C ₁₃ H ₁₆ CIN ₃ OS 297,5	97-9 MeOH + H ₂ O	90,5	B, C: 1.1 (t, 3H CH ₃); 2.1 (m, 2H CH ₂); 3.4 (m, 4H CH ₂ OCH ₂); 4.25 (t, 2H NCH ₂); 7.4-7.7 (m, 4H Ar)
3b	3-Cl-C ₆ H ₄		C ₁₅ H ₁₉ CIN ₄ S 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 ₂ NCH ₂); 7.4-7.7 (m, 4H Ar)
3c	3-Cl-C ₆ H ₄		C ₁₄ H ₁₇ CIN ₄ OS 324,5	72-8 Aceton + H ₂ O	86,4	B, C: 2.3 (t, 4H CH ₂ NCH ₂); 2.7 (t, 2H NCH ₂); 3.5 (t, 4H CH ₂ OCH 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 ₃ OD, E—d ₆ -DMSO)
4a	4-Cl-C ₆ H ₄	CH ₂ OH	C ₁₀ H ₁₀ ClN ₃ OS 255,5	220–2 MeOH + H ₂ O	70,3	A, E: 3.8–4.1 (t, 4H (CH ₂) ₂); 5.0 (t, 1H OH) + D ₂ O decay; 7.6–7.9 (m, 4H Ar); 14.0 (s, 1H NH) + D ₂ O decay
4b	4-Cl-C ₆ H ₄	(CH ₂) ₂ OH	C ₁₁ H ₁₂ ClN ₃ OS 269,5	148–50 MeOH + H ₂ O	98,5	A, E: 1.7 (m, 2H CH ₂); 3.4 (t, 2H NCH ₂); 4.1 (t, 2H CH ₂ O); 4.5 (t, 1H OH); 7.7 (m, 4H Ar); 14.0 (s, 1H NH)
4c	4-Cl-C ₆ H ₄	(CH ₂) ₃ OH	C ₁₂ H ₁₄ ClN ₃ OS 283,5	147–9 MeOH + H ₂ O	87,3	A, E: 1.1–1.8 (m, 4H (CH ₂) ₂); 3.3 (m, 2H NCH ₂); 4.0 (t, 2H CH ₂ O); 4.4 (t, 1H OH); 7.6 (m, 4H Ar); 14.0 (s, 1H NH)
4d	4-Cl-C ₆ H ₄	CH-OH CH ₃	C ₁₁ H ₁₂ ClN ₃ OS 269,5	168–70 MeOH + H ₂ O	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 ₆ H ₄	CH-OH CH ₂ -OH	C ₁₁ H ₁₂ ClN ₃ O ₂ S 285,5	150–2 H ₂ O	94,4	A, E: 3.3 (m, 2H CH ₂ O); 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 ₆ H ₄	(CH ₂) ₂ OC ₂ H ₅	C ₁₃ H ₁₆ ClN ₃ OS 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 ₂ OCH ₂); 4.25 (t, 2H NCH ₂); 7.4–7.6 (m, 4H Ar); 12.0 (s, 1H NH)
4g	4-Cl-C ₆ H ₄		C ₁₅ H ₁₉ ClN ₄ S 322,5	224–8 Dioksan	48,4	B, C: 1.4 (t, 6H (CH ₂) ₃); 2.35 (t, 4H CH ₂ NCH ₂); 2.7 (t, 2H NCH ₂); 4.2 (t, 2H NCH ₂); 7.5–7.7 (m, 4H Ar)
4h	4-Cl-C ₆ H ₄		C ₁₄ H ₁₇ ClN ₄ OS 324,5	170–3 MeOH	59,4	B, C: 2.4 (t, 4H CH ₂ NCH ₂); 2.7 (t, 2H NCH ₂); 3.5 (t, 4H CH ₂ OCH ₂); 4.25 (t, 2H NCH ₂); 7.4–7.6 (m, 4H Ar)
4i	4-Cl-C ₆ H ₄		C ₁₄ H ₁₇ ClN ₄ S 308,5	205–8 MeOH	20,0	A, C: 1.7 (m, 4H CH ₂ CH ₂); 2.5 (m, 4H CH ₂ NCH ₂); 2.9 (t, 2H CH ₂ N); 4.2 (t, 2H NCH ₂); 7.5 (m, 4H Ar)

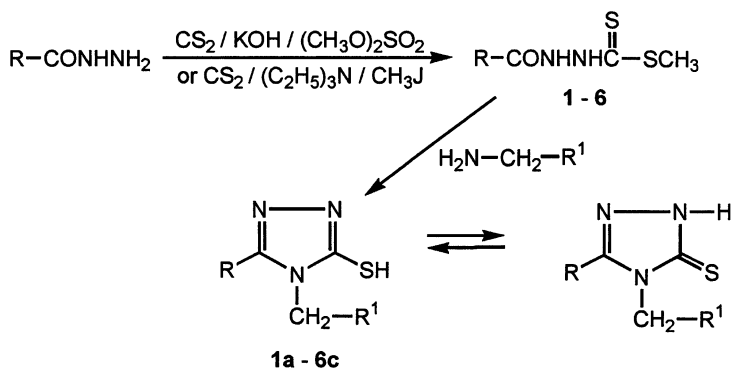
4j	4-Cl-C ₆ H ₄	C ₆ H ₁₁	C ₁₅ H ₁₈ ClN ₃ S 307,5	180–5 MeOH	54,5	A, C: 0.7–1.2 (m, 5H cyclic.); 1.3–1.8 (m, 6H cyclic.); 4.0 (d, 2H CH ₂); 7.5 (m, 4H Ar); 12.5 (s, 1H NH + D ₂ O decay)
5a	3-pyridyl	CH ₂ OCH ₃	C ₁₀ H ₁₂ N ₄ OS 236,3	166–9 Aceton + H ₂ O	60,4	B, C: 3.3 (s, 3H CH ₃); 3.9 (t, 2H CH ₂ O); 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) ₂ OCH ₃	C ₁₁ H ₁₄ N ₄ OS 250,32	137–9 Aceton + H ₂ O	77,7	B, C: 2.1 (m, 2H CH ₂); 3.2 (s, 3H CH ₃); 3.4 (t, 2H CH ₂ O); 4.3 (t, 2H NCH ₂); 7.5, 8.0, 8.8 (m, 4H Py)
5c	3-pyridyl	(CH ₂) ₂ OC ₂ H ₅	C ₁₂ H ₁₆ N ₄ OS 264,34	43–6 MeOH + H ₂ O	65,5	B, C: 1.1 (t, 3H CH ₃); 2.1 (m, 2H CH ₂); 3.3 (m, 4H CH ₂ OCH ₂); 4.3 (t, 2H NCH ₂); 7.5, 8.0, 8.8 (m, 4H Py)
5d	3-pyridyl		C ₁₄ H ₁₈ N ₅ S 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 ₂ N); 4.3 (t, 2H NCH ₂); 7.5, 8.1, 8.8 (m, 4H Py)
5e	3-pyridyl		C ₁₃ H ₁₇ N ₅ OS 291,4	75–8 MeOH + H ₂ O	30,6	B, C: 2.4 (m, 4H CH ₂ NCH ₂); 2.7 (t, 2H CH ₂ N); 3.5 (m, 4H CH ₂ OCH ₂); 4.3 (t, 2H NCH ₂); 7.5–8.8 (m, 4H, Py)
6a	4-pyridyl	(CH ₂) ₂ OC ₂ H ₅	C ₁₂ H ₁₆ N ₄ OS 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 ₂ OCH ₂); 4.3 (t, 2H NCH ₂); 7.5–8.8 (m, 4H, Py)
6b	4-pyridyl		C ₁₄ H ₁₈ N ₅ S 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 ₂ N); 7.7, 8.8 (m, 4H Py)
6c	4-pyridyl		C ₁₃ H ₁₇ N ₅ OS 291,4	201–3 Aceton	38,6	B, C: 2.2 (t, 4H CH ₂ NCH ₂); 2.7 (t, 2H CH ₂ N); 3.5 (t, 4H CH ₂ OCH 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 described^{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 Satellite spectrophotometer. The ^1H -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 ($\text{pH} = 3$) 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 ($\text{pH} 4\text{--}6$). The mixture was ice-cooled, the precipitate collected and recrystallized.

REFERENCES

- [1] F. Malbec, R. Milcent, and G. Barbier, *J. Heterocycl. Chem.*, **21**, 1689 (1984).
- [2] M. Dobosz, *Acta Polon. Pharm.*, **41**, 451 (1984).
- [3] M. Dobosz and A. Pachuta-Stec, *Acta Polon. Pharm.*, **51**, 457 and **53**, 123 (1996); **52**, 103 (1955).
- [4] S. Bahadur, S. P. Singh, M. K. Shukla, *Arch. Pharm. (Weinheim)* **315**, 312 (1982).
- [5] X. Collin, A. Saulean, and J. Coulon, *Bioorganic and Medicinal Chemistry Letters* **13**, 2601 (2003).
- [6] B. S. Holla, B. Veerendra, M. K. Shivananda, and B. Poojary, *European Journal of Medicinal Chemistry* **38**, 759 (2003).
- [7] H. Foks, A. Czarnocka-Janowicz, W. Rudnicka, and H. Trzeciak, *Phosphorus, Sulfur and Silicon* **164**, 67 (2000).
- [8] H. Foks and M. Janowiec, *Polski patent* 1984, nr 121508.
- [9] F. Sączewski and H. Foks, *Acta Polon. Pharm.*, **45**, 465 (1988).
- [10] W. Rudnicka, H. Foks, M. Janowiec, and Z. Zwolska-Kwiec, *Acta Polon. Pharm.*, **43**, 523 (1986).