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A Facile Synthesis of New Thieno[2,3-*b*][1,4]-thiazine Derivatives Starting from 2-Acylamino-3,3-dichloroacrylonitriles

Sergey V. Popil'nichenko,[1] Vladimir S. Brovarets,[1] Alexander N. Chernega,[2] Denis V. Poltorak,[2] and Boris S. Drach[1]

[1]*Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanskaya Str., 02094 Kiev, Ukraine*

[2]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanskaya Str., 02094 Kiev, Ukraine*

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ABSTRACT: *Readily available 2-acylamino-3,3-dichloroacrylonitriles are sequentially treated with methyl mercaptoacetate in the presence of sodium methylate and with sulfuric acid to furnish the methyl ester of 7-amino-2-oxo-3H-thieno[2,3-b][1,4]thiazine-6-carboxylic acid. Treating it first with triethyl orthoformate and then with ammonia or primary amines, the pyrimidine-4-one nucleus is annelated to the thienothiazine system, which is corroborated by spectroscopic methods and X-ray diffraction analysis.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:411–415, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20232

INTRODUCTION

Readily available 2-acylamino-3,3-dichloroacrylonitriles are known to be unique reagents for heterocyclizations, which were already employed in the synthesis of 1,3-oxazole [1–8], 4*H*-imidazole [9], pyrazole [10], 1,3,4-oxadiazole [11], and 1,3,4-thiadiazole [12] functional derivatives. In the present study, we have developed a new line in the synthetic application of reagents **1a,b** using them to obtain a number of condensed heterocycles derived from the thieno[2,3-*b*][1,4]thiazine-2(3*H*)-one system (Table 1).

RESULTS AND DISCUSSION

On treating chloro-substituted enamidonitriles **1a,b** first with methyl mercaptoacetate in the presence of sodium methylate and then with sulfuric acid, the conversions **1** → **2** → **3** → **4** proceed as shown in Scheme 1. The first stage of the process resembles the reaction of compounds **1a,b** with thiophenols [7], and the conversion **2** → **3** is a special case of the well-known type of heterocyclizations involving a C≡N bond and an active methylene group [13,14]. The cyclocondensation **3** → **4** represents a more original reaction that can be regarded as an intramolecular reacylation leading to the annelation of the 2-oxo-1,4-thiazine system to the thiophene ring. In the course of the reaction, the acyl residue is eliminated from the nitrogen atom at the 3-position of the thiophene ring; as a result, two different enamidonitriles **1a,b** yield the same product **4**, the methyl ester of 7-amino-2-oxo-3*H*-thieno[2,3-*b*][1,4]thiazine-6-carboxylic acid, which is evidenced

Correspondence to: Boris S. Drach; e-mail: drach@bpci.kiev.ua.
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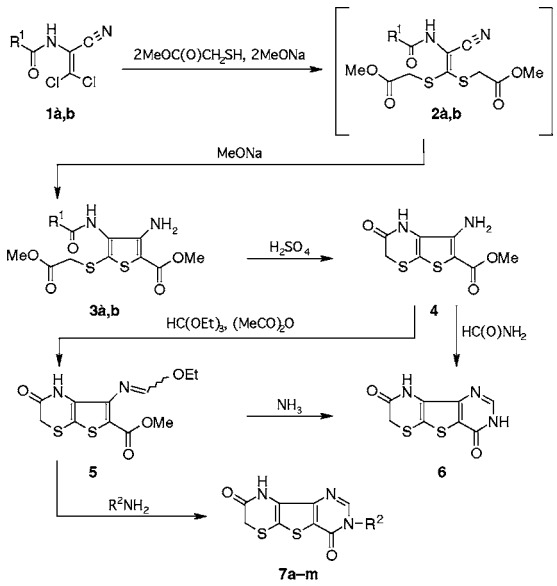
TABLE 1 Physical and Analytical Data of Compounds **3–7**

	M.P. (°C)	Yield (%)	Molecular Formula (molecular weight)	Analysis (%) found (calcd.)			
				C	H	N	S
3a	128—129[a]	66	$C_{11}H_{14}N_2O_5S_2$ (318.37)	41.31 (41.50)	4.60 (4.43)	8.68 (8.80)	19.99 (20.14)
3b	130—133[a]	74	$C_{16}H_{16}N_2O_5S_2$ (380.44)	50.39 (50.51)	4.02 (4.24)	7.05 (7.36)	16.74 (16.86)
4	280—282[b]	75	$C_8H_8N_2O_3S_2$ (244.29)	39.17 (39.33)	3.02 (3.30)	11.59 (11.47)	25.98 (26.25)
5	157—160[a]	64	$C_{11}H_{12}N_2O_4S_2$ (300.35)	43.66 (43.99)	4.20 (4.03)	9.12 (9.33)	21.26 (21.35)
6	>300[c]	65	$C_8H_5N_3O_2S_2$ (239.27)	39.91 (40.16)	2.38 (2.11)	17.41 (17.56)	26.66 (26.80)
7a	275—278[b]	65	$C_9H_7N_3O_2S_2$ (253.30)	41.93 (42.67)	2.91 (2.78)	16.34 (16.59)	25.28 (25.32)
7b	241—244[b]	67	$C_{10}H_9N_3O_2S_2$ (267.33)	44.65 (44.93)	3.50 (3.39)	15.46 (15.72)	23.75 (23.99)
7c	172—175[b]	66	$C_{11}H_{11}N_3O_2S_2$ (281.35)	46.66 (46.96)	4.10 (3.94)	14.85 (14.93)	22.61 (22.79)
7d	>290[b]	75	$C_{14}H_9N_3O_2S_2$ (315.37)	52.95 (53.32)	2.79 (2.88)	13.25 (13.32)	20.35 (20.33)
7e	>290[b]	67	$C_{15}H_{11}N_3O_2S_2$ (329.40)	54.11 (54.69)	3.28 (3.37)	12.69 (12.76)	19.42 (19.47)
7f	>290[b]	70	$C_{15}H_{11}N_3O_3S_2$ (345.40)	51.95 (52.16)	3.09 (3.21)	12.21 (12.17)	18.49 (18.57)
7g	228—231[b]	63	$C_{15}H_{11}N_3O_2S_2$ (329.40)	54.54 (54.69)	3.54 (3.37)	12.35 (12.76)	19.39 (19.47)
7h	217—220[b]	68	$C_{16}H_{13}N_3O_3S_2$ (359.42)	53.63 (53.47)	3.81 (3.64)	11.45 (11.69)	17.82 (17.84)
7i	240—243[b]	66	$C_{15}H_{10}ClN_3O_2S_2$ (363.84)	50.01 (49.52)	2.83 (2.77)	11.46 (11.55)	17.59 (17.62)
7j	234—237[b]	69	$C_{15}H_{10}FN_3O_2S_2$ (347.39)	51.92 (51.86)	3.05 (2.90)	12.15 (12.10)	18.51 (18.46)
7k	209—212[b]	70	$C_{13}H_9N_3O_3S_2$ (319.36)	48.74 (48.89)	3.02 (2.84)	13.21 (13.16)	20.01 (20.08)
7l	219—222[b]	72	$C_{16}H_{13}N_3O_2S_2$ (343.42)	55.82 (55.96)	3.98 (3.81)	12.11 (12.23)	18.62 (18.67)
7m	235—238[b]	69	$C_{13}H_{13}N_3O_2S_2$ (307.39)	50.50 (50.79)	4.32 (4.26)	13.71 (13.67)	20.64 (20.86)

[a]Recrystallization from EtOH.
[b]Recrystallization from MeC(O)OH.
[c]Recrystallization from the mixture acetic acid—DMSO



1–3: R^1 = Me(a), Ph(b).

7: R^2 = Me(a), Et(b), *n*-Pr(c), Ph(d), 4-MeC_6H_4(e), 4-$MeOC_6H_4$(f), $PhCH_2$(g), 4-$MeOC_6H_4CH_2$(h), 4-$ClC_6H_4CH_2$(i), 4-$FC_6H_4CH_2$(j),  –CH_2 (k), $PhCH_2CH_2$(l), *cyclo*-C_5H_9(m).

SCHEME 1

by the spectral and mass spectrometric data (Table 2). Starting from the key substrate **4**, which contains the appropriately positioned amino and methoxycarbonyl groups, we succeeded in conducting the steps **4** → **5** → **6** and **4** → **5** → **7** presented in Scheme 1. Both reaction sequences end in the annelation of the pyrimidine-4-one nucleus to the thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one system.

The cascade process **4** → **5** → **7** has proved to be applicable rather extensively, because a variety of aliphatic, alicyclic, and aromatic primary amines readily enter into this condensation (Table 1). Moreover, it is conveniently conducted in one step without isolation of intermediate compound **5**.

The structures of compounds **5, 6**, and **7a–m** are supported by the IR and ^{1}H NMR spectral data listed in Table 2. In addition, an unequivocal structural determination using X-ray diffraction analysis has been performed for compound **7i** (R^2 = 4-$ClC_6H_4CH_2$). As seen from Fig. 1, the molecule of compound **7i** is essentially nonplanar, with the moiety $S^2N^2N^3C^{3-8}$ being planar accurate to 0.027 Å and the benzene ring twisted through 86.0° out of this plane. The six-membered heterocycle $S^1C^{1,2}N^1C^{3,8}$ exhibits a strongly distorted halfbath conformation, with the following modified Cremer–Pople parameters [15]: $S = 0.66$, $\theta = 57.2°$, $\Psi = 19.4°$. The bond lengths in the molecule concerned (Table 3) suggest a significant delocalization of electronic density within the tricyclic moiety $S^1S^2N^{1-3}C^{1-8}$ (except that the conjugation is broken by the atom C^1). A crystal of compound **7i** contains the molecules bound in centrosymmetric dimers by fairly weak [16] intermolecular hydrogen bonds N^1—H···N^2 (N^1···N^2 3.184(3) Å, N^1—H 0.89(4) Å, N^2···H 2.36(4) Å, N^1HN^2 155(2)°).

In summary, it may be noted that the easily accessible key substrate **4** is appropriate for derivatizing not only the pyrimido[4′,5′:4,5]thieno[2,3-*b*][1,4]thiazine system but also analogous tricyclic N,S-containing nuclei being the subject of our further study.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz using TMS as an internal standard. IR spectra were measured on a Specord M-80 spectrometer for KBr disks. Mass spectra were measured on a Varian MAT-311A instrument.

Methyl 4-Acylamino-3-amino-5-(methoxycarbonylmethylthio)thiophene-2-carboxylates **3a,b**

To a solution of **1a,b** (4 mmol) obtained by the known procedure [1,2] in absolute methanol (30 mL), methyl mercaptoacetate (8.2 mmol) and solution of sodium methylate (1.2 mmol) in MeOH (1.5 mL) were added. The mixture was refluxed for 10 h, and MeOH was removed in vacuo. For crystallization, the residue was treated with H_2O; then it was filtered off and recrystallized from an appropriate solvent (Table 1).

Methyl 7-Amino-2-oxo-3H-thieno[2,3-b][1,4]-thiazine-6-carboxylate **4**

A mixture of **3a** and **3b** (2 mmol) in H_2SO_4 (5 mL) was heated at 110–120°C under stirring for 5 min. After pouring the solution onto ice, the precipitate was filtered off and recrystallized from acetic acid. The samples of compound **4** obtained from **3a** and **3b** demonstrated identical IR and ^{1}H NMR spectra.

Methyl 7-Etoxymethylidenamino-2-oxo-3H-thieno[2,3-b][1,4]thiazine-6-carboxylate **5**

A mixture of compound **4** (4 mmol), triethyl orthoformate (8 mL), and acetic anhydride (0.3 mL) was refluxed for 2 h. The precipitate formed was filtered off and recrystallized from ethanol (Table 1).

TABLE 2 Spectroscopic Data of Compounds **3–7**

	IR (KBr) (cm^{-1})	*^1H NMR (DMSO-d_6/TMS)δ*
3a	1655[a] (NC═O, OC═O), 1740 (OC═O), 3150—3340(NH)	2.03 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.73 (s, 5H, CH_2, OCH_3), 6.16 (br s, 2H, NH_2), 9.26 (s, 1H, NH)
3b	1640 (NC═O), 1675 (OC═O), 1745 (OC═O), 3250—3400(NH)	3.66 (s, 3H, OCH_3), 3.75 (s, 5H, CH_2, OCH_3), 6.28 (br s, 2H, NH_2), 7.50—8.02(m, 5H, C_6H_5), 9.75 (s, 1H, NH)
4[b]	1680 (NC═O, OC═O), 1620 (δ, NH_2) 3100—3480(NH, NH_2)	3.60 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 6.45 (br s, 2H, NH_2), 10.32 (s, 1H, NH)
5[c]	1635 (C═N), 1675 (NC═O), 1725 (OC═O), 3225 (NH)	1.34 (t, 3H, CH_3), 3.52 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 4.35 (q, 2H, OCH_2), 7.81 (s, 1H, CH), 10.15 (s, 1H, NH)
6	1650 (NC═O), 1675 (NC═O), 3100—3250 (NH)	3.59 (s, 2H, CH_2), 8.09 (s, 1H, CH), 10.45 (br s, 1H, NH), 12.45 (br s, 1H, NH)
7a	1675[a] (NC═O), 3200—3320(NH)	3.52 (s, 3H, NCH_3), 3.66 (s, 2H, CH_2), 8.48 (s, 1H, CH), 10.81 (br s, 1H, NH)
7b	1680[a] (NC═O), 3170—3280(NH)	1.63 (t, 3H, CH_3), 3.87 (s, 2H, CH_2), 4.49 (q, 2H, CH_2), 8.45 (s, 1H, CH), 9.39 (s, 1H, NH)
7c	1675 (NC═O), 1700 (NC═O), 3250 (NH)	1.13 (t, 3H, CH_3), 2.01 (m, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.37 (t, 2H, CH_2), 8.46 (s, 1H, CH), 9.37 (s, 1H, NH)
7d	1690[a] (NC═O), 3300 (NH)	3.70 (s, 2H, CH_2), 7.00—7.55(m, 5H, C_6H_5), 8.47 (s, 1H, CH), 10.99 (s, 1H, NH)
7e	1685[a] (NC═O), 3295 (NH)	2.39 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 7.20—7.45(m, 4H, C_6H_4), 8.43 (s, 1H, CH), 10.98 (s, 1H, NH)
7f	1690[a] (NC═O), 3320 (NH)	3.63 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 7.10 (d, 2H, 2CH), 7.45 (d, 2H, 2CH), 8.40 (s, 1H, CH), 10.98 (s, 1H, NH)
7g	1690[a] (NC═O), 3300 (NH)	3.86 (s, 2H, CH_2), 5.52 (s, 2H, CH_2), 7.48 (s, 5H, C_6H_5), 8.55 (s, 1H, CH), 9.23 (s, 1H, NH),
7h	1680[a] (NC═O), 3200—3300(NH)	3.66 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 6.92 (d, 2H, 2CH), 7.34 (d, 2H, 2CH), 8.69 (s, 1H, CH), 10.65 (s, 1H, NH)
7i	1685[a] (NC═O), 3350 (NH)	3.86 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 7.44 (s, 4H, C_6H_4), 8.48 (s, 1H, CH), 9.34 (s, 1H, NH)
7k	1685[a] (NC═O), 3340 (NH)	3.86 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6.47—7.50(m, 3H, 3CH), 8.42 (s, 1H, CH), 9.42 (s, 1H, NH)
7l	1660 (NC═O), 1685 (NC═O), 3300 (NH)	3.26 (t, 2H, CH_2), 3.86 (s, 2H, CH_2), 4.65 (t, 2H, CH_2), 7.14—7.34(m, 5H, C_6H_5), 8.46 (s, 1H, CH), 9.32 (s, 1H, NH)
7m	1655 (NC═O), 1680 (NC═O), 3325 (NH)	1.97 (m, 6H, $3CH_2$), 2.49 (m, 2H, CH_2), 3.87 (s, 2H, CH_2), 5.34 (m, 1H, CH), 8.40 (s, 1H, CH), 9.48 (s, 1H, NH)

[a]A band with a shoulder.
[b]MS: m/z (M^+) 244.
[c]The data refer to the mainly formed geometric isomer.

7H-Pyrimido[4′,5′:4,5]thieno[2,3-b][1,4]-thiazine-4,8(3H,9H)-dione **6**

(A) A mixture of compound **4** (4 mmol) and formamide (10 mL) was refluxed for 5 h. The precipitate formed was filtered off, washed with ethanol, and recrystallized from the mixture acetic acid–DMSO ~3:1.

(B) A solution of compound **5** in dioxane (30 mL) was refluxed and saturated with anhydrous ammonia for 3 h. Methanol released was removed in vacuo. The precipitate was recrystallized from the mixture acetic acid–DMSO ~3:1. The IR and ^1H NMR spectra for the samples of compound **6** obtained from **4** and **5** were identical.

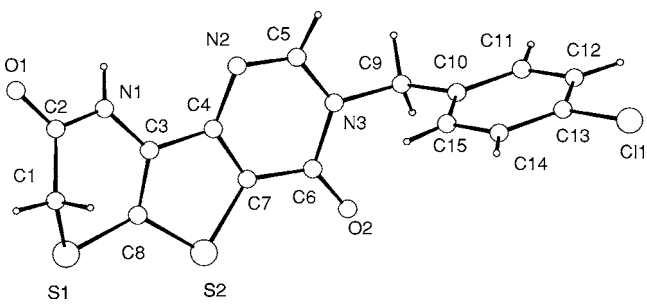


FIGURE 1 Perspective view and labeling scheme for the molecule of compound **7i**.

7H-3-Alkyl(aralkyl,aryl,cycloalkyl)pyrimido-[4′,5′:4,5]thieno[2,3-b][1,4]thiazine-4,8(3H,9H)-diones **7a–m**

A mixture of compound **4** (4 mmol), triethyl orthoformate (8 mL), and acetic anhydride (0.3 mL) was refluxed for 2 h, cooled to 50°C, and treated

TABLE 3 Selected Bond Lengths (Å) and Bond Angles (°) of Compound **7i**

S(1)—C(1) 1.825(3)	C(1)—S(1)—C(8) 95.60(13)
S(1)—C(8) 1.739(3)	C(7)—S(2)—C(8) 90.43(12)
S(2)—C(7) 1.727(3)	C(2)—N(1)—C(3) 124.3(2)
S(2)—C(8) 1.740(3)	C(4)—N(2)—C(5) 114.0(2)
N(1)—C(2) 1.360(4)	C(5)—N(3)—C(6) 122.9(2)
N(1)—C(3) 1.395(3)	S(1)—C(1)—C(2) 114.1(2)
N(2)—C(4) 1.370(3)	N(1)—C(2)—C(1) 116.1(2)
N(2)—C(5) 1.295(4)	N(1)—C(3)—C(8) 123.9(2)
N(3)—C(5) 1.362(4)	C(4)—C(3)—C(8) 113.0(2)
N(3)—C(6) 1.417(3)	N(2)—C(4)—C(7) 124.6(2)
C(1)—C(2) 1.504(4)	C(3)—C(4)—C(7) 111.5(2)
C(3)—C(4) 1.423(4)	N(2)—C(5)—N(3) 126.4(3)
C(3)—C(8) 1.360(4)	N(2)—C(5)—N(3) 126.4(3)
C(4)—C(7) 1.378(4)	N(3)—C(6)—C(7) 110.9(2)
C(6)—C(7) 1.440(3)	S(2)—C(7)—C(4) 112.74(19)
	C(4)—C(7)—C(6) 121.2(2)
	S(1)—C(8)—C(3) 121.1(2)
	S(2)—C(8)—C(3) 112.26(19)
	N(3)—C(9)—C(10) 113.3(2)

with an appropriate primary amine (6 mmol). The mixture was refluxed for 2 h. The precipitate was filtered off and recrystallized from acetic acid (Table 1).

X-ray Structure Determination for **7i**

Crystal Data. $C_{15}H_{10}ClN_3O_2S_2$, $M = 363.85$, triclinic, $a = 6.951(1)$ Å, $b = 7.616(1)$ Å, $c = 14.698(5)$ Å, $\alpha = 104.31(2)^\circ$, $\beta = 92.81(2)^\circ$, $\gamma = 95.46(1)^\circ$, $V = 748.4(3)$ Å^3, $Z = 2$, $d = 1.61$ g cm^{-3}, space group $P\bar{1}(N2)$, $\mu = 4.987$ cm^{-1}, $F(0\ 0\ 0) = 372$, crystal size ca. 0.16 mm × 0.28 mm × 0.41 mm.

Data Collection. All crystallographic measurements were performed at 20°C on a CAD-4 Enraf-Nonius diffractometer operating in the ω–2θ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.0$). Intensity data were collected within the range $3^\circ < \theta < 67^\circ$ ($0 \le h \le 8$, $-9 \le k \le 9$, $-17 \le l \le 17$) using graphite-monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). Intensities of 2828 reflections (2343 unique reflections, $R_{int} = 0.020$) were measured. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction based on azimuthal scan data was applied [17].

Structure Solution and Refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package [18]. In the refinement, 2343 reflections with $I > 4\sigma(I)$ were used. All hydrogen atoms were located in the difference Fourier maps and included in the final refinements with fixed positional and thermal parameters. Convergence was obtained at $R(F) = 0.056$ and $R_w(F^2) = 0.136$, GOF = 0.120 (248 refined parameters; obs/variabl. = 9.5; the largest and minimal peaks in the final difference map are 0.46 and −0.40 e/Å^{-3}). The Chebyshev weighting scheme [19] with the parameters 472, 798, 530, 243, and 74.3 was used [20].

REFERENCES

[1] Drach, B. S.; Sviridov, E. P.; Kisilenko, A. A.; Kirsanov, A. V. Zh Org Khim 1973, 9, 1818–1824.

[2] Drach, B. S.; Sviridov, E. P.; Lavrenyuk, T. Ya. Zh Org Khim 1974, 10, 1271–1274.

[3] Matsumura, K.; Sarai, T.; Hashimoto, N. Chem Pharm Bull 1976, 24, 924–940.

[4] Matsumura, K.; Miyashita, O.; Shimadzu, H.; Hashimoto, N. Chem Pharm Bull 1976, 24, 948–959.

[5] Drach, B. S.; Mis'kevich, G. N. Zh Org Khim 1977, 13, 1398–1404.

[6] Drach, B. S.; Mis'kevich, G. N. Zh Org Khim 1978, 14, 501–507.

[7] Pilyo, S. G.; Brovarets, V. S.; Vinogradova, T. K.; Golovchenko, A. V.; Drach, B. S. Zh Obshch Khim 2002, 72, 1818–1824.

[8] Pilyo, S. G.; Brovarets, V. S.; Romanenko, Ye. A.; Drach, B. S. Zh Obshch Khim 2002, 72, 1828–1833.

[9] Vinogradova, T. K.; Mis'kevich, G. N.; Drach, B. S. Zh Org Khim 1980, 16, 1869–1874.

[10] Brovarets, V. S.; Pilyo, S. G.; Chernega, A. N.; Romanenko, Ye. A.; Drach, B. S. Zh Obshch Khim 1999, 69, 1646–1651.

[11] Pilyo, S. G.; Brovarets, V. S.; Vinogradova, T. K.; Chernega, A. N.; Drach, B. S. Zh Obshch Khim 2001, 71, 310–315.

[12] Golovchenko, O. V.; Pilyo, S. G.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. Heteroatom Chem 2004, 15, 454–458.

[13] Rossy, Ph.; Vogel, F. C. M.; Haffmann, W.; Paust, J.; Nurrenbach, A. Tetrahedron Lett 1981, 22, 3493–3496.

[14] Stephens, Ch. E.; Price, M. B.; Sowell, J. W. J. Heterocycl Chem 1999, 36, 659–665.

[15] Zefirov, N. S.; Palyulin, V. A. Dokl Akad Nauk SSSR 1980, 252, 111–115.

[16] Kuleshova, L. N.; Zorkii, P. M. Acta Crystallogr Sect B 1981, 37, 1363–1366.

[17] North, A. C. T.; Phillips, D. C.; Mathews, F. S. Acta Crystallogr Sect A 1968, 24, 351–359.

[18] Watkin, D. J.; Prout, C. K.; Caruthers, J. R.; Betteridge, P. W. CRYSTALS, Issue 10; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.

[19] Caruthers, J. R.; Watkin, D. J. Acta Crystallogr Sect A 1979, 35, 698–699.

[20] Full crystallographic details have been deposited at Cambridge Crystallographic Data Center (CCDC). Any request to the CCDC for this material should quote the full literature citation and reference number CCDC 292925.