Heteroatom Chemistry
Volume 18, Number 4, 2007

Original Recyclization of S-Phenacyl Derivatives of 4-Acylamino-2-mercapto-1,3-oxazoles and Their Analogues

Andrei G. Balia,[1] Aleksandr G. Belyuga,[1] Vladimir S. Brovarets,[1] Aleksandr N. Vasylenko,[1] Aleksandr V. Turov,[2] Andrei A. Gakh,[3] and Boris S. Drach[1]

[1]*Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanskaya Str., 02660 Kiev-94, Ukraine*

[2]*Department of Chemistry, Taras Shevchenko National University, 64 Vladimirskaya Str., 01033 Kiev, Ukraine*

[3]*Oak Ridge National Laboratory Washington, P.O. Box 2008, Oak Ridge, TN 37381-6242, USA*

Received 28 August 2006

ABSTRACT: *Readily accessible acylamino(chloro)-acetophenones, if treated with sodium rhodanide and α-halogenocarbonyl compounds, provide 4-acylamino-5-aryl-2-mercapto-1,3-oxazole derivatives which undergo recyclization on heating in polyphosphoric acid to give substituted 1,3-thiazol-2(3H)-ones or 1,3-thiazolidin-2,4-diones containing 2-alkyl(aryl)-5-aryl-1,3-oxazol-4-yl residues at the N^3 atom.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:432–437, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20317

INTRODUCTION

Amidophenacylating reagents of the general formula ArCOCHClNHCOR[1] **1a–f** have already found extensive application in the synthesis of functionalized 1,3-oxazoles [1–3], 1,3-thiazoles [4,5], imidazoles [6], and condensed systems such as imidazo[1,2-*a*]azines [7,8], and imidazo[2,1-*b*]azoles [9]. In the present work, we have developed a new line in the synthetic use of reagents **1a–f** based on the recyclization of 3-acylaminothiazolo[2,3-*b*]oxazolium cations convertible into new derivatives of 1,3-thiazol-2(3*H*)-one or 1,3-thiazolidin-2,4-dione.

RESULTS AND DISCUSSION

Treating amidophenacylating reagents **1a–f** with sodium rhodanide in tetrahydrofuran results, already at 20–25°C, in the formation of intermediate isothiocyanates **2a–f** undergoing intramolecular cyclization that affords 4-acylamino-5-aryl-1,3-oxazol-2(3*H*)-thiones **3a–f**. Their tautomers **4a–f** are formed, if at all, in so minor amount that they are undetectable during IR and ^{1}H NMR spectroscopy. Nonetheless, the formation of thiol form **4** should not be neglected because the equilibrium $3 \rightleftarrows 4$, even strongly shifted toward **3**, can be of significance in some conversions. It is quite evident that deprotonation of both tautomeric forms leads to the same mesomeric thiolate anions that react

Correspondence to: Boris S. Drach; e-mail: Drach@bpci.kiev.ua.

regioselectively with, for example, chloroacetone, phenacyl bromide, 4-halogenophenacyl bromides, and methyl chloroacetate to give the corresponding 2-mercapto-1,3-oxazole derivatives **5a–i** and **6a–c**.

Structures **3, 5, 6** are supported by the IR and ^{1}H NMR spectral data, which suggest that the conversion $1 \rightrightarrows 3$ involves the carbonyl group of the phenacyl moiety and the proton of the methine group is eliminated from the moiety >CH–NH– in the course of the thioamide group formation. At the same time, the spectral data summarized in Table 1 demonstrate that the conversions **3**→**5** and **3**→**6** are completely regioselective and result in the introduction of the groups CH_2COMe, CH_2COAr, and $CH_2C(O)OMe$ at the sulfur atom.

It should also be noted that the two-step conversion **1**→**2**→**3**, shown in Scheme 1, closely resembles the formerly studied cyclocondensation of α-ethylthio substituted α-chloroketones with potassium rhodanide [10] (see Scheme 2).

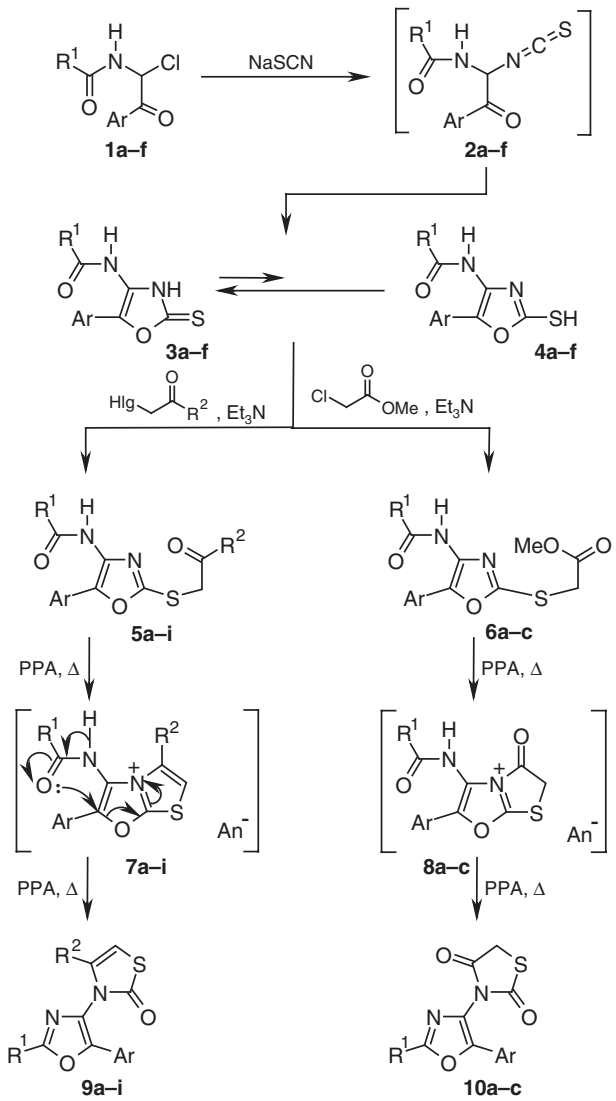
Thus, the constitution of compounds **3a–f, 5a–i**, and **6a–c** is determined quite unequivocally, which enables the treatment of the further complex conversions, **5**→**7**→**9** and **6**→**8**→**10**, occurring on heating the reaction mixture to 140°C in polyphosphoric acid.

As was shown previously [11], substituted oxazoles bearing an acetonylthio- or phenacylthio group at position 2 can be converted on heating in polyphosphoric acid into fairly stable

TABLE 1 Spectroscopic Data of Compounds **3, 5, 6, 9**, and **10**

	IR (KBr)(cm^{-1})	*^{1}H NMR (DMSO-d_6/TMS)δ*
3a	1190(C=S), 1670 (NC=O), 3050 (NH), 3300 (NH)	2.08 (s, 3H, CH_3), 7.29–7.65 (m, 5H, C_6H_5), 10.10 (s, 1H, NH), 13.44 (s, 1H, NH)
3b	1190(C=S), 1670 (NC=O), 3050 (NH), 3250 (NH)	7.34–8.02 (m, 10H, $2C_6H_5$), 10.57 (s, 1H, NH), 13.62 (s, 1H, NH)
5a	1680 (NC=O), 1700(C=O), 3300 (NH)	2.03 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 7.26–8.07 (m, 10H, $2C_6H_5$), 9.87 (s, 1H, NH)
5b	1670 (NC=O), 1700(C=O), 3300 (NH)	5.03 (s, 2H, CH_2), 7.25–8.08 (m, 15H, $3C_6H_5$), 10.39 (s, 1H, NH)
5c	1650 (NC=O), 1690(C=O), 3300 (NH)	2.40 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 7.27–8.08 (m, 14H, $2C_6H_5$, C_6H_4), 10.29 (s, 1H, NH)
5g	1670 (NC=O), 1730(C=O), 3300 (NH)	2.04 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 7.25–7.49 (m, 5H, C_6H_5), 9.87 (s, 1H, NH)
5h	1670 (NC=O), 1730(C=O), 3300 (NH)	2.30 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.25–8.01 (m, 10H, $2C_6H_5$), 10.39 (s, 1H, NH)
5i	1650 (NC=O), 1725(C=O), 3300 (NH)	2.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.27–7.89 (m, 9H, C_6H_5, C_6H_4), 10.28 (s, 1H, NH)
6a	1680 (NC=O), 1750(C=O), 3300 (NH)	2.05 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 7.25–7.52 (m, 5H, C_6H_5), 9.89 (s, 1H, NH)
6b	1660 (NC=O), 1740(C=O), 3300 (NH)	3.71 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 7.28–8.02 (m, 10H, $2C_6H_5$), 10.42 (s, 1H, NH)
6c	1650 (NC=O), 1750(C=O), 3300 (NH)	2.41 (s, 3H,CH_3), 3.71 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 7.31–7.89 (m, 9H, C_6H_5, C_6H_4), 10.31 (s, 1H, NH)
9a	1700(C=O)	2.46 (s, 3H, CH_3), 6.75 (s, 1H, CH), 7.16–7.45 (m, 10H, $2C_6H_5$)
9b	1700(C=O)	6.81 (s, 1H, CH), 7.23–8.02 (m, 15H, $3C_6H_5$)
9c	1700(C=O)	2.40 (s, 3H, CH_3), 6.80 (s, 1H, CH), 7.23–7.92 (m, 14H, $2C_6H_5$, C_6H_4)
9d	1690(C=O)	6.82 (s, 1H, CH), 7.00–8.03 (m, 13H, C_6H_5, $2C_6H_4$)
9e	1685(C=O)	
9f[a]	1685(C=O)	2.40 (s, 3H, CH_3), 6.89 (s, 1H, CH), 7.26–7.92 (m, 12H, $3C_6H_4$)
9g	1690(C=O)	1.89 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.32 (s, 1H, CH), 7.26–7.45 (m, 5H, C_6H_5)
9h	1690(C=O)	1.97 (s, 3H, CH_3), 6.40 (s, 1H, CH), 7.42–7.58 (m, 10H, $2C_6H_5$)
9i	1680(C=O)	1.96 (s, 3H,CH_3), 2.42 (s, 3H, CH_3), 6.38 (s, 1H, CH), 7.36–8.00 (m, 10H, $2C_6H_5$)
10a	1700(C=O), 1780(C=O)	2.53 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 7.26–7.53 (m, 5H, C_6H_5)
10b	1700(C=O), 1780(C=O)	4.54 (s, 2H, CH_2), 7.45–8.10 (m, 10H, $2C_6H_5$)
10c[b]	1700(C=O), 1780(C=O)	

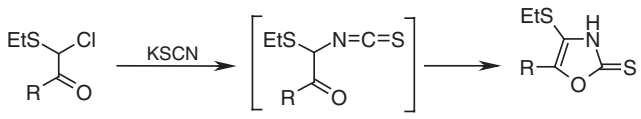
[a]MS: *m/z* (M^+) 479.
[b]MS: *m/z* (M^+) 350.



1-10	a	b	c	d	e	f	g	h	i
R^1	Me	Ph	4-MeC_6H_4	4-ClC_6H_4	Ph	4-MeC_6H_4	Me	Ph	4-MeC_6H_4
Ar	Ph	Ph	Ph	Ph	4-MeC_6H_4	4-ClC_6H_4	Ph	Ph	Ph
R^2	Ph	Ph	Ph	4-FC_6H_4	Ph	4-ClC_6H_4	Me	Me	Me

SCHEME 1

thiazolo[2,3-*b*]oxazolium salts of aromatic character. However, attempted introduction of acylamine residues at position 3 of this condensed system by the cyclization **5**→**7** resulted in unstable intermediates **7** recyclizing to products **9**. The conversion **7**→**9** is probably facilitated by the appropriate relative disposition of the nucleophilic center at the oxygen atom in the acylamino residue and the electrophilic center C^2 in the substituted thiazolo[2,3-*b*]oxazol-4-ium cation **7**. As a result of the interaction between the two centers, the oxazolium nucleus is cleaved to form the thiazolo-2(3*H*)-one ring and a new oxazole ring closes involving the acylamino residue; these



R = Me, Ph, $PhCH_2$.

SCHEME 2

processes can be detected by IR and ^{1}H NMR spectroscopy (see Table 1). In a similar manner, we successfully performed the conversion **6**→**8**→**10** which afforded novel N-hetaryl substituted 1,3-thiazolidin-2,4-diones.

TABLE 2 ^{1}H and ^{13}C NMR Signal Assignments and Correlations in the NOESY, HMQC, and HMBC Spectra for Compound **10c**

	^{1}H, δ	*^{13}C, δ*	
^{1}H, δ	*NOESY*	*HMQC*	*HMBC*
2.37 (CH_3)	7.38 (C^{3a}-H)	21.80 (CH_3)	21.80 (CH_3), 142.34 (C^{4a}), 130.59 (C^{4b})
7.38 (C^{3a}-H)	2.37 (CH_3)	130.59 (C^{3a})	130.59 (C^{5a}), 123.78 (C^{1a})
7.96 (C^{2a}-H)	—	126.82 (C^{2a})	126.82 (C^{6a}), 159.61 (C^{2b}), 142.34 C^{4a})
7.67 (C^{2c}-H)	—	125.52 (C^{2c})	125.52 (C^{6c}), 146.39 (C^{5b}), 130.43 (C^{4c})
7.52 (C^{3c}-H)	—	130.09 (C^{3c})	130.09 (C^{5c}), 126.16 (C^{1c})
7.45 (C^{4c}-H)	—	130.43 (C^{4c})	125.52 (C^{2c})
4.59 (CH_2)	—	35.26 (C^{5d})	171.66 (C^{4d}), 171.32 (C^{2d})

On comparing the IR spectra for the related representatives of structures **9** and **10**, it is seen that the former exhibits only one band of the carbonyl valence vibrations in the region 1650–1800 cm^{-1}, whereas the thiazolidin-2,4-dione moiety of the latter gives rise to two such bands. Furthermore, elimination of water or methanol in the conversion **5** $\rightrightarrows$ **9** or **6** $\rightrightarrows$ **10**, respectively, is evidenced by mass spectrometry (see Table 1). Moreover, the structure of compound **10c**, one of the final recyclization products, is consistent with the experimentally established one bond and long-range (two or three bond) proton-carbon connectivities derived from ^{1}H-^{13}C HMQC and HMBC spectra, respectively. These spectra also enable assignment of ^{13}C resonances. A complete list of the correlations determined is presented in Table 2. Interestingly, the atom $^{13}C^{4b}$ displays no correlation. Its NMR signal found at 130.34 ppm is further upfield than expected (about 150 ppm), which may be attributable to the effect of two carbonyl groups in the ring "d" (see Table 2 and Fig. 1).

In conclusion, it is notable that recyclizations of functionalized thiazolo[2,3-*b*]oxazolium cations demonstrate, even at the very outset of the applicational research on them, great preparative value, for example, in the synthesis of some N-hetaryl substituted thiazolo-2(3*H*)-ones and 1,3-thiazolidin-2,4-diones, pharmaceutically important S,N-heterocycles promising in bioregulator design.

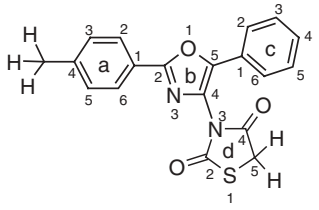


FIGURE 1 Atom and ring labeling for compound **10c**.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz using TMS as an internal standard. ^{1}H and ^{13}C NMR spectral measurements combined with NOESY, HMQC, and HMBC experiments for **10c** were performed on a Varian mercury 400 spectrometer 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.

N-(2-Aryl-1-chloro-2-oxoethyl)carboxamides **1a–f**. These compounds were obtained by using the known procedure [4,5].

4-Acylamino-5-aryl-1,3-oxazol-2 (3H)-thiones **3a–f**. To a stirred suspension of sodium rhodanide (22 mmol) in anhydrous tetrahydrofuran (10 mL), a warm solution of one of compounds **1a–f** (20 mmol) in tetrahydrofuran (20 mL) was added. The stirred mixture was held at 20–25°C for 72 h. On evaporating tetrahydrofuran in vacuo, the residue was mixed with ethyl acetate (30 mL) and heated to 50–60°C. After filtering off sodium chloride and removing most of solvent, compounds **3a–f** were obtained and recrystallized from acetic acid prior to analysis (see Table 3).

4-Acy1amino-2-acylmethylthio-5-aryl-1,3-oxazoles **5a–i**. To a solution of **3a–f** (2.5 mmol) in absolute methanol (30 mL), triethylamine (0.35 mL) and chloroacetone or bromoacetophenone, or 4-chloro(fluoro)acetophenone (2.5 mmol) were successively added. After stirring the mixture at 20–25°C for 24 h, most of methanol was removed in vacuo and water (100 mL) was added. The resulting precipitate was filtered off and was purified by recrystallization from ethanol (see Table 3).

TABLE 3 Physical and Analytical Data of Compounds **3, 5, 6, 9**, and **10**

	M.P. (°C)	Yield (%)	Molecular Formula (Molecular Weight)	Analysis (%) Found (Calcd.)				
				C	H	N	S	Cl
3a	196–198[a]	65	$C_{11}H_{10}N_2O_2S$ (234.27)	56.23 (56.39)	4.31 (4.30)	11.89 (11.95)	13.64 (13.68)	–
3b	192–193[a]	55	$C_{16}H_{12}N_2O_2S$ (296.34)	64.79 (64.84)	4.11 (4.08)	9.39 (9.45)	10.81 (10.82)	–
3c	212–214[a]	61	$C_{17}H_{14}N_2O_2S$ (310.37)	65.71 (65.78)	4.51 (4.54)	8.99 (9.02)	10.21 (10.33)	–
3d	151–152[a]	69	$C_{16}H_{11}ClN_2O_2S$ (330.79)	58.03 (58.09)	3.41 (3.35)	8.39 (8.47)	9.59 (9.69)	10.65 (10.71)
3e	183–185[a]	71	$C_{17}H_{14}N_2O_2S$ (310.37)	65.72 (65.78)	4.53 (4.54)	8.97 (9.02)	10.26 (10.33)	–
3f	167–169[a]	74	$C_{17}H_{13}ClN_2O_2S$ (344.82)	59.15 (59.21)	3.82 (3.80)	8.09 (8.12)	9.25 (9.29)	10.21 (10.28)
5a	129–131[b]	71	$C_{19}H_{16}N_2O_3S$ (352.41)	64.69 (64.75)	4.53 (4.57)	7.89 (7.95)	9.01 (9.09)	–
5b	151–152[b]	70	$C_{24}H_{18}N_2O_3S$ (414.48)	69.48 (69.54)	4.41 (4.37)	6.68 (6.75)	7.65 (7.73)	–
5c	86–88[b]	72	$C_{25}H_{20}N_2O_3S$ (428.51)	70.03 (70.07)	4.75 (4.70)	6.45 (6.53)	7.41 (7.48)	–
5d	200–202[b]	85	$C_{24}H_{16}FClN_2O_3S$ (466.91)	61.65 (61.73)	3.47 (3.45)	5.93 (6.00)	6.83 (6.87)	7.51 (7.59)
5e	158–160[b]	83	$C_{25}H_{20}N_2O_3S$ (428.51)	69.98 (70.07)	4.71 (4.70)	6.47 (6.53)	7.43 (7.48)	–
5f	223–225[b]	82	$C_{25}H_{18}Cl_2N_2O_3S$ (497.40)	60.46 (60.63)	3.68 (3.78)	5.81 (5.85)	6.63 (6.68)	14.75 (14.79)
5g	154–156[b]	69	$C_{14}H_{14}N_2O_3S$ (290.34)	57.85 (57.91)	4.81 (4.86)	9.58 (9.64)	10.98 (11.04)	–
5h	173–174[b]	59	$C_{19}H_{16}N_2O_3S$ (352.41)	64.66 (64.75)	4.51 (4.57)	7.86 (7.95)	9.01 (9.09)	–
5i	165–167[b]	63	$C_{20}H_{18}N_2O_3S$ (366.43)	65.49 (65.55)	4.91 (4.95)	8.55 (7.64)	8.69 (8.75)	–
6a	156–158[b]	58	$C_{14}H_{14}N_2O_4S$ (306.34)	54.81 (54.89)	4.53 (4.60)	9.08 (9.14)	10.39 (10.46)	–
6b	135–137[b]	53	$C_{19}H_{16}N_2O_4S$ (368.41)	61.87 (61.94)	4.41 (4.37)	7.51 (7.60)	8.64 (8.70)	–
6c	134–135[b]	61	$C_{20}H_{18}N_2O_4S$ (382.43)	62.75 (62.81)	4.69 (4.74)	7.25 (7.32)	8.29 (8.38)	–
9a	186–188[c]	58	$C_{19}H_{14}N_2O_2S$ (334.39)	68.20 (68.24)	4.15 (4.22)	8.28 (8.37)	9.43 (9.58)	–
9b	146–148[b]	59	$C_{24}H_{16}N_2O_2S$ (396.46)	72.65 (72.70)	4.11 (4.06)	7.01 (7.06)	8.02 (8.08)	–
9c	180–182[b]	62	$C_{25}H_{18}N_2O_2S$ (410.49)	73.09 (73.14)	4.39 (4.42)	6.73 (6.82)	7.73 (7.81)	–
9d	148–150[b]	79	$C_{24}H_{14}FClN_2O_2S$ (484.93)	59.35 (59.44)	2.96 (2.91)	5.71 (5.77)	6.53 (6.61)	7.25 (7.31)
9e	143–145[b]	74	$C_{25}H_{18}N_2O_2S$ (410.49)	73.11 (73.14)	4.43 (4.42)	6.75 (6.82)	7.76 (7.81)	–
9f	223–225[d]	82	$C_{25}H_{16}Cl_2N_2O_2S$ (479.38)	62.57 (62.63)	3.41 (3.36)	5.78 (5.84)	6.61 (6.68)	14.71 (14.79)
9g	92–94[c]	56	$C_{14}H_{12}N_2O_2S$ (272.32)	61.68 (61.74)	4.45 (4.44)	10.21 (10.28)	11.69 (11.77)	–
9h	152–154[b]	61	$C_{19}H_{14}N_2O_2S$ (334.39)	68.15 (68.24)	4.18 (4.22)	8.31 (8.37)	9.51 (9.58)	–
9i	138–139[c]	59	$C_{20}H_{16}N_2O_2S$ (248.42)	68.89 (68.94)	4.59 (4.62)	7.98 (8.04)	9.15 (9.20)	–
10a	116–117[c]	55	$C_{13}H_{10}N_2O_3S$ (274.29)	56.87 (56.92)	3.71 (3.67)	10.16 (10.21)	11.63 (11.69)	–
10b	213–215[b]	58	$C_{18}H_{12}N_2O_3S$ (336.36)	64.15 (64.27)	3.61 (3.59)	8.25 (8.33)	9.46 (9.53)	–
10c	217–219[b]	65	$C_{19}H_{14}N_2O_3S$ (350.39)	65.09 (65.12)	4.01 (4.02)	8.01 (7.99)	9.07 (9.15)	–

[a]Recrystallization from MeC (O)OH.
[b]Recrystallization from EtOH.
[c]Recrystallization from *i*-PrOH.
[d]Recrystallization from DMF.

Methyl esters of S-(4-acylamino-5-phenyl-1,3-oxazol-2-yl)mercaptoacetic acids **6a–c**. These compounds were obtained like compounds **5a–i** starting from **3a–c** (3 mmol) and methyl chloroacetate (3 mmol).

4-Aryl(methyl)-3-[5-aryl-2-methyl(aryl)-1,3-oxazol-4-yl]-1,3-thiazol-2(3H)-ones **9a–i**. A mixture of one of compounds **5a–i** (1 mmol) and polyphosphoric acid (3.5 g) was held at 140°C for 6 h before cooling and pouring onto crushed ice (20 g). The resulting precipitate was filtered off and purified by recrystallization from an appropriate solvent (see Table 3).

3-[2-Methyl(aryl)-5-phenyl-1,3-oxazol-4-yl]-1,3-thiazolidine-2,4-diones **10a–c.** These compounds were obtained like compounds **9a–i** starting from **6a–c** (1 mmol) (see Table 3).

ACKNOWLEDGMENTS

This research was supported in part by the IPP program through the Science and Technology Center in Ukraine (STCU). Oak Ridge National Laboratory is managed by UT-Battelle, LLC, under contract DE-AC05-00OR22725 for the U.S. Department of Energy. Contribution 20, the Discovery Chemistry Project.

REFERENCES

[1] Drach, B. S.; Dolgushina, I. Yu.; Sinitsa, A. D. Zh Org Khim 1973, 9, 2368–2372.
[2] Drach, B. S.; Dolgushina, I. Yu.; Sinitsa, A. D. Zh Obshch Khim 1975, 45, 1251–1255.
[3] Belyuga, A. G.; Brovarets, V. S.; Drach, B. S. Zh Obshch Khim 2005, 75, 561–564.

[4] Drach, B. S.; Dolgushina, I. Yu.; Kirsanov, A. V. Zh Org Khim 1973, 9, 414–419.
[5] Belyuga, A. G.; Brovarets V. S.; Drach, B. S. Zh, Obshch Khim 2004, 74, 1529–1533.
[6] Belyuga, A. G. Synthesis of novel bioregulators, derivatives of nitrogen-containing heterocycles on the basis of amidophenacylic reagents; Ph.D. Thesis, Institute of Bioorganic Chemistry and Petrochemistry, Kyiv, Ukraine, 2006, pp 7–8.
[7] Drach, B. S.; Dolgushina, I. Yu.; Sinitsa, A. D. Khim Geterotsikl Soed 1975, 45, 2387–2390.
[8] Belyuga, A. G.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. Zh Org Farm Khim 2004, 2(4), 25–34.
[9] Belyuga, A. G.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. Zh Org Farm Khim 2004, 3(4), 38–42.
[10] Weygand, F.; Bestmann, H. J.; Steden, F. Chem Ber 1958, 91, 2537–2542.
[11] Bradsher, C. K.; Jones, W. J., Jr. J Org Chem 1967, 32, 2079–2081.