Sulfur-containing heterocycles
14.* New synthesis of cyclic anhydrides of 3-sulfinocarboxylic acids

T. P. Vasil´eva, G. T. Shchetnikov, and S. N. Osipov*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085. E-mail: ikuper@yandex.ru

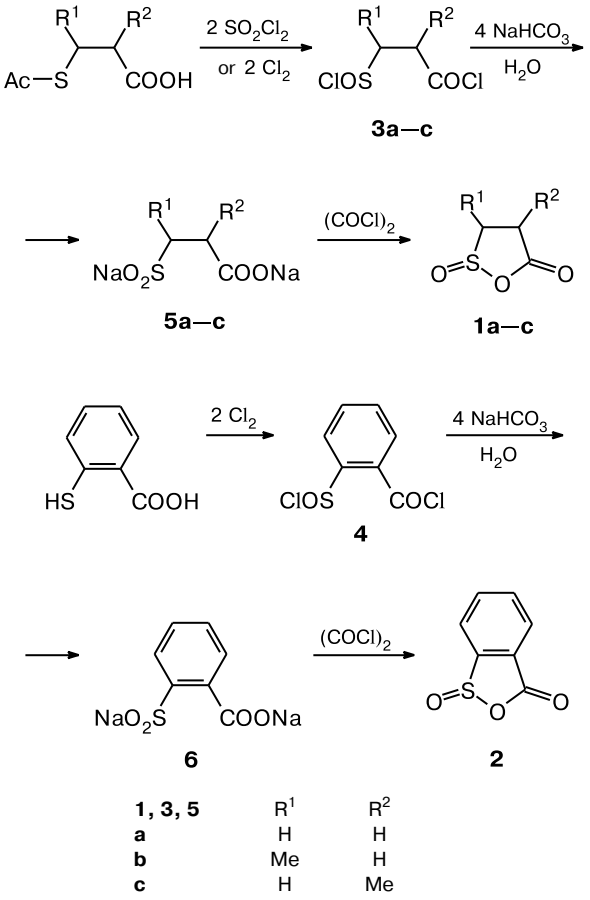
3-Chlorosulfinylalkanoyl chlorides undergo cyclization into the corresponding five-membered mixed anhydrides (1,2-oxathiolan-5-one 2-oxides) under the action of sodium or mercury acetates. 2-Chlorosulfinylbenzoyl chloride gives 3*H*-2,1-benzoxathiol-3-one 1-oxide in high yield.

Key words: 3*H*-2,1-benzoxathiol-3-one 1-oxide, 1,2-oxathiolan-5-one 2-oxides, anhydrides, sulfinic acids, 2-chlorosulfinylbenzoyl chloride, cyclization, ring-chain tautomerism.

In continuation of the investigations[1,2] into sulfur-containing heterocyclic compounds, *viz.*, cyclic anhydrides of 3-sulfinoalkanoic and 2-sulfinobenzoic acids (compounds **1** and **2**), we studied the possibility of their one-pot synthesis from the corresponding sulfinyl chlorides (**3** or **4**) obtained by chlorination of 3-(acetylthio)-alkanoic acids (adducts of thioacetic *S*-acid to acrylic acid) or thiosalicylic (2-mercaptobenzoic) acid.[3] The interest in mixed anhydrides **1** or **2** is related, first of all, with their extremely high reactivity, which allows one to use them as the building blocks for the concurrent introduction of two functional groups into an organic molecule.[4] Effective radioprotectors with moderate toxicity have been found among the reaction products of anhydrides **1** and **2** with some amines.[5—7] It turned out that 3*H*-2,1-benzoxathiol-3-one 1-oxide (**2**) is a potent oxidant; its use in stereospecific oxidation of nucleoside H-phosphonothioate diesters with retention of configuration was described.[8,9] Hence, investigations into convenient procedures for the synthesis of compounds **1** and **2** is topical.

The first representative of saturated anhydrides, *viz.*, 3,3,4,4-tetraphenyl-1,2-oxathiolan-5-one 2-oxide, was obtained[10] in low yield (18%) by the oxidation of tetraphenyl-β-thiolactone, but this method is not suitable for the oxidation of other β-thiolactones. Unsubstituted anhydride **1a**, its Me-substituted analogues (**1b,c**), as well as aromatic anhydride **2** were synthesized by us for the fist time[2] in 59—70% yields by the reaction of the corresponding 3-(chloro-sulfinyl)-alkanoyl chlorides **3a—c** or **4** with aqueous $NaHCO_3$ and subsequent reaction of dry bis-sodium salts **5a—c** or **6** with oxalyl chloride in benzene with heating (Scheme 1).

Scheme 1



This synthetic procedure often affords the hydrolysis products of anhydride **1** or **2** instead of the anhydrides themselves due to difficulties in the removal of crystal

* For Part 13, see Ref. 1.

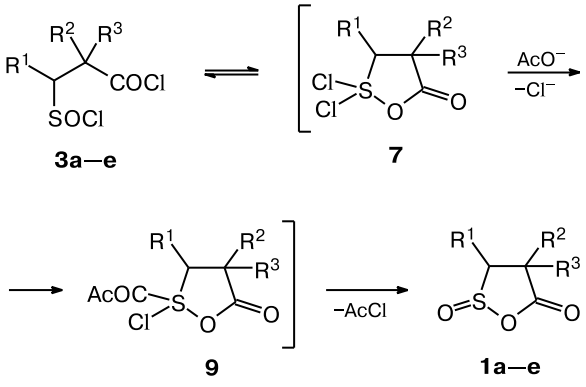
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2413—2417, December, 2009.

water from the salts **5a—c** and **6**. In addition, we failed to obtain chlorine-substituted anhydrides **1** using the oxalyl—chloride method, because saponification of the starting chlorine-substituted 3-(chlorosulfinyl)alkanoyl chlorides was accompanied by dehydrochlorination. Recently, other syntetic procedures for the synthesis of anhydride **2** from 3*H*-1,2-benzodithiol-3-one 1,1-dioxide under the action of trimethyl phosphite,[11] or Et_3N,[8,9] or a mixture of Et_3N with propane-1-thiol,[12] were described (without information on the yields); however, anhydride **2** can be contaminated with colloidal sulfur or trimethyl phosphothioate formed upon desulfurization.

Results and Discussion

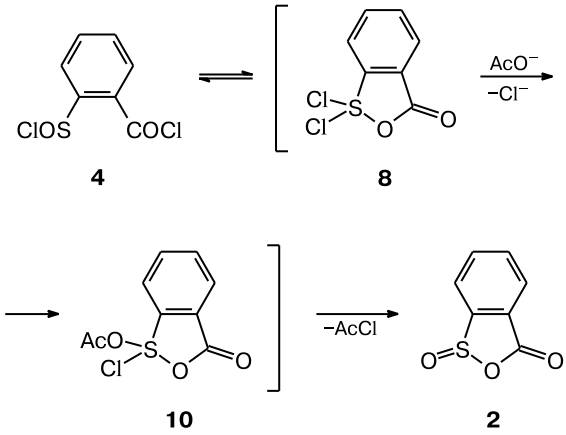
In the present study, a new method for the synthesis of five-membered carboxylic-sulfinic anhydrides, *vis.*, both oxathiolanone oxides **1** (including chlorosubstituted compounds **1d,e**) and aromatic anhydride **2** by the reaction of 3-(chlorosulfinyl)alkanoyl chlorides **3a—e** and **4** with AcONa or $Hg(OAc)_2$ in $CHCl_3$ or benzene (Schemes 2 and 3) is proposed. Optimum conditions of the reaction are found for various compounds. The procedure of choice for obtaining unsubstituted (**1a**), methyl-substituted (**1b,c**), and aromatic (**2**) anhydrides is the addition of 1.1 equiv. of the corresponding sulfinyl chloride (**3a—c**, **4**) to a suspension of AcONa (method *A*) or $Hg(OAc)_2$ (method *B*) in $CHCl_3$ followed by heating of the reaction mixture. With the reverse order of the reactant mixing, the yields and the purity of the obtained products **1** and **2** considerably decreased. Chloro-substituted anhydrides **1d,e** could not be obtained under the conditions of method *A* or method *B* due to dehydrochlorination, therefore, synthesis of compounds **1d,e** was carried out by addition of equimolar amount of AcONa (method *C*) or $Hg(OAc)_2$ (method *D*) to a solution of sulfinyl chlorides **3d,e** in $CHCl_3$ without heating.

Scheme 2



1, 3, 7, 9	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	H	H	Me
d	H	H	Cl
e	H	Me	Cl

Scheme 3



With AcONa as the cyclization agent, the process proceeds more selectively than in the case of $Hg(OAc)_2$ (see Schemes 2 and 3), and the target anhydrides **1**, **2** do not contain admixtures of the starting dichlorides **3**, **4**.

The putative mechanism envisages the realization of ring-chain tautomerism in the first step (see Schemes 2 and 3). As is known,[1,3] the starting sulfinyl chlorides containing the vicinal COCl group (compounds **3** and **4**) exist in the equilibrium with highly reactive cyclic dichlorosulfuranes **7** and **8**, it is the latter that react with acetate anion to produce intermediate acetoxysulfuranes **9** or **10**. The latter eliminate acetyl chloride (slowly at 20 °C, faster on heating) to afford anhydrides **1** or **2**. Analysis of the organic phase of the reaction mixtures (see Schemes 2 and 3) by IR spectroscopy showed the disappearance of absorption bands of both the sulfinyl chloride group (1152—1158 cm^{-1} for **3** or 1165 cm^{-1} for **4**) and the acyl chloride group (1790 cm^{-1} for **3** or 1742 cm^{-1} for **4**) and the appearance of new absorption bands of the anhydride groups for intermediates **9** and **10**, *viz.*, exocyclic AcO and endocyclic CO—O groups at 1750—1760 cm^{-1} and 1800—1820 cm^{-1}, respectively. In the ^1H NMR spectra of the reaction mixtures, singlet signals for the Ac group at δ 1.94—2.27 (for **9a—e**) or δ 1.57—1.73 (for **10**) are observed.

The target products **1a—e** and **2** are isolated by distillation *in vacuo* (methods *A—D*) or by crystallization (method *E*) following removal of sodium chloride and the solvent from the reaction mixtures. The yields and physicochemical characteristics of compounds are presented in Table 1, and spectral characteristics and titration data are presented in Table 2. The neutralization equivalent (NaOH) and oxidimetric equivalent (with $KMnO_4$) of

Table 1. Physicochemical characteristics of synthesized compounds

Starting sulfinyl chloride	Synthetic procedure	Anhydride obtained	Yield[a] (%)	B.p./°C (*p*/Torr) [m.p./°C (solvent)]	n_D (*T*/°C)	Found / Calculated (%)			Molecular formula
						C	H	S	
3a	*A*	**1a**	61	60—65 (0.03) [49—52 ($CHCl_3$—light petroleum)][b,c]	1.5092 (22)	—	—	—	—
3b	*A*	**1b**	69	50—53 (0.06)[c]	1.4909 (25)	—	—	—	—
	B	**1b**	67	45 (0.017)[c]					
3c	*A*	**1c**	78	56—58 (0.05)[c]	1.4950 (20)	35.71	4.20	24.14	$C_4H_6O_3S$
	B	**1c**	74	84—87 (0.08)[c]		35.82	4.48	23.88	
3d	*C*	**1d**	73	97—98 (0.08)	1.5358 (21)	22.90	2.15	20.39	$C_3H_3ClO_3S$
	D	**1d**	94	64—66 (0.03)	1.5359 (24)	23.30	1.94	20.71	
3e	*C*	**1e**	60	70—75 (0.04)[d] [83—86][b,d]	—	28.35	2.98	18.85	$C_4H_5ClO_3S$[e]
						28.49	2.97	18.99	
4	*E*	**2**	70	90 (0.05) [91—96 ($CHCl_3$—light petroleum)][c,f]	—	—	—	—	—

[a] After purification by distillation or recrystallization.
[b] In a sealed capillary.
[c] *cf.* Ref. 2.
[d] *cf.* Ref. 1.
[e] Found: Cl, 20.96%. Calculated: Cl, 21.07%.
[f] *cf.* Ref. 11: m.p. 81—82 °C.

Table 2. Spectral characteristics of the synthesized compounds and titration data (NaOH or $KMnO_4$) of anhydrides **1a—e** and **2**

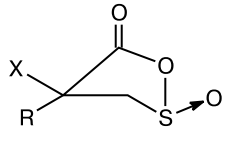
Compound	^{1}H NMR, δ (*J*/Hz)[a]	IR, ν/cm^{-1}		Equivalent, found/calculated	
		C=O	S=O	neutralization, NaOH	oxidimetric, $KMnO_4$
1a	2.67—3.50 (m, 4 H, CH_2CH_2)	1813	1100, 1167	61/60	61/60
1b	1.42 (d, 3 H, Me, *J* = 6.9); 2.42—3.77 (m, 3 H, $CHCH_2$)	1805—1810	1115, 1170	67.4/67	68.5/67
1c	1.39 (d, 3 H, Me, *J* = 6.7, 81%)[b]; 1.55 (d, 3 H, Me, *J* = 7.7, 19%)[c]; 2.84—3.79 (m, 3 H, CH_2CH)	1800 1820[d]	1120, 1160 1110, 1160[d]	66.4/67	—
1d	3.37—4.15 (m, 2 H, CH_2); 4.74—4.95 (m, 1 H, CH, 50%)[b]; 5.13—5.27 (m, 1 H, CH, 50%)[c]	1815	1110—1160	52/51.5[e]	52.5/51.5[e]
1e	1.93 (s, 3 H, Me, 50%)[b]; 2.09 (s, 3 H, Me, 50%)[c]; 3.38—4.07 (m, 2 H, CH_2)	1800	1135, 1155	55/56[e]	54/56[e]
2	7.51—8.12 (m, 4 H, C_6H_4)	1785	1135, 1160	84.2/84	81/84

[a] In CH_2Cl_2 for **1a—c**, in $CHCl_3$ for **1d**, in $CDCl_3$ for **1e**, and in DMSO-d_6 for **2**.
[b] *trans*-Isomer.
[c] *cis*-Isomer.
[d] In C_6D_6 or in $CDCl_3$.
[e] M/3.

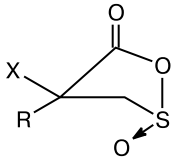
compounds **1a—c** and **2** are equal to a half of the molecular mass, whereas these equivalents for chlorosubstituted anhydrides **1d**,**e** are equal to one third of the molecular mass, which additionally confirms the increased CH acidity of the $CH_2S(O)$ group in compounds **1d**,**e**. The IR spectra of aliphatic anhydrides **1a—e** show absoption bands of the CO group at 1800—1815 cm^{-1} and at 1785 cm^{-1} for aromatic anhydride **2**. The sulfinyl groups in all compounds **1** and **2** appear as two absorption bands at 1110—1135 and 1155—1170 cm^{-1} area, which agreed with the known data.[2]

The existence of diastereomers that differ in *cis* or *trans* arrangement of the S=O group and the substituent

relative to the ring plane[13] was demonstrated by the example of 5-aryl-1,2-oxathiolane 2-oxides (γ-sulthines) by ^{1}H NMR spectroscopy. Similar results were observed for mono- and disubstituted 1,2-oxathiolan-5-one 2-oxides **1**. In the case of 4-methyl-substituted anhydride **1c**, one should expect that different cyclization methods would afford different stereoisomers (see Schemes 1 and 2). However, analysis of the ^{1}H NMR spectra (recorded on the same instrument and in the same solvent)* of samples of **1c**, obtained by different methods showed that in both cases mixtures of *cis* and *trans* isomers formed with the prevalence of the latter. The share of *cis* **1c** was ~16—22% in the product obtained according to the method described earlier[2] and ~19% in the case of the new method *A* (with AcONa). In the product obtained using of $Hg(OAc)_2$ (method *B*), the share of *cis* isomer in anhydride **1c** was within 19-35%.



trans-**1c—e**



cis-**1c—e**

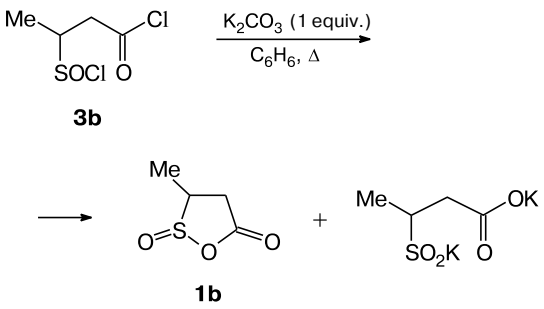
Compound	R	X	Percentage (%)	
			trans	*cis*
1c	Me	H	81	19
1d	H	Cl	50	50
1e	Me	Cl	50	50

4-Chloro- (**1d**) and 4-methyl-4-chlorooxathiolanone oxide (**1e**) according to the data from ^{1}H NMR spectra (see Table 2) are mixtures of two stereoisomers in a 1 : 1 ratio (see above). Due to structural features (proximity of Me and S=O groups), 3-methyl-substituted anhydride **1b** synthesized by both the oxalyl-chloride method (see Scheme 1)[2] and the new method (see Scheme 2) apparently has *trans* configuration because only one signal for the Me group was observed in the ^{1}H NMR spectrum (see Table 2).

In addition, attempts of selective synthesis of anhydride **1b** were undertaken using other O-nucleophiles. However, in the absence of a catalyst sulfinyl chloride **3b** reacted with neither oxalic acid nor $(COONa)_2$, and the addition of Et_4NBr resulted in polymerization. The reaction of **3b** with potash (pK_B 3.7), which is a stronger base than AcONa, afforded a mixture of anhydride **1b** and the starting compound **3b** (~1 : 1) due to the competitive reaction of complete saponification (see Scheme 4).

Thus, we have established that the most appropriate reagent with regard of basicity for selective cyclization is the acetate anion (pK_B 9.3). A new synthetic procedure for the synthesis of 1,2-oxathiolan-5-one 2-oxides **1** and 3*H*-2,1-benzoxathiol-3-one 1-oxide **2** consisted in cyclization of 3-chlorosulfinylalkanoyl chlorides **3** and **4** under the action of AcONa or $Hg(OAc)_2$ is proposed. The method allows one to obtain carboxylic-sulfinic anhydrides containing various substituents in the heterocycle, including chloro-substituted ones, under mild conditions.

Scheme 4



* The values for δ and *J* of **1c** corresponded to those presented in Table 2, but not to those reported earlier.[2]

Experimental

The IR spectra were recorded on a UR-20 spectrophotometer in a liquid film and in KBr pellets (for solids). The ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer using HMDS as the internal standard. Anhydrous reagents and solvents purified according to known procedures[14] were used in all experiments.

The starting sulfinyl chlorides **3a—e** and **4** were synthesized as described earlier.[1,3] Silufol UV-254 plates were used for TLC (visualization with iodine vapor). The purity of carboxylic-sulfinic anhydrides was also checked by titration (with NaOH or $KMnO_4$). Oxidimetry was carried out according to a known procedure.[2] The amount of the starting sulfinyl chlorides as admixtures in various fractions of the obtained anhydrides was determined by chlorine content in the sample (the Vollhardt titration) and by ^{1}H NMR spectra. The yields and the properties of synthesized compounds **1a—e** and **2** are listed in Table 1, spectral (IR, ^{1}H NMR) and titration data are listed in Table 2.

1,2-Oxathiolan-5-one 2-oxides (1a—c). Method *A*. A solution of 3-(chlorosulfinyl)alkanoyl chloride **3a—c** (0.1 mol) in $CHCl_3$ (60 mL) was added with stirring and cooling with cold water (≤15 °C) to a suspension of freshly fused ground sodium acetate (9.02 g, 0.11 mol) in $CHCl_3$ (75 mL). After stirring for 1.5—2 h at 20 °C, the reaction mixture was heated on stirring for 2 h at 65—70 °C (in a water bath) and cooled to 20 °C. The precipitate of NaCl was filtered off and washed with chloroform. The filtrate was concentrated *in vacuo*, the residue was distilled.

Method *B*. 1,2-Oxathiolan-5-one 2-oxides **1b,c** were obtained from the corresponding chlorides **3b,c** (0.1 mol) analogously to method *A*, $Hg(OAc)_2$ (35.06 g, 0.11 mol) being used instead of sodium actate; the reaction is exothermic.

4-Chloro-1,2-oxathiolan-5-one 2-oxide (1d). Method *C*. Ground freshly fused sodium acetate (4.92 g, 0.06 mol) was added portionwise with stirring to a solution of 2-chloro-3-(chlorosulfinyl)propionyl chloride **3d** (12.6 g, 0.06 mol) in

$CHCl_3$ (88 mL) at 0 °C. After ~24 h, the precipitate was filtered off, washed with chloroform, the filtrate was distilled *in vacuo*.

Method *D*. Synthesis of **1d** from chloride **3d** (12.6 g, 0.06 mol) was carried out analogously to method *C*, $Hg(OAc)_2$ (19.12 g, 0.06 mol) being used instead of sodium acetate.

4-Methyl-4-chloro-1,2-oxathiolan-5-one 2-oxide (1e) was prepared analogously to **1d** (method *C*) from 2-methyl-2-chloro-3-(chlorosulfinyl)propionyl chloride **3e**.

3*H*-2,1-Benzoxathiol-3-one 1-oxide (2). Method *E*. Synthesis of compound **2** from 2-chlorosulfinylbenzoyl chloride (**4**) was carried out analogously to method *A* (in $CHCl_3$ or C_6H_6), but without distillation. The residue after removal of the solvent and cooling crystallized. Pure product **2** was obtained by precipitation with petroleum ether from hot $CHCl_3$ and drying *in vacuo* over P_2O_5; R_f 0.44 (Me_2CO—$CHCl_3$, 1 : 1), 0.08 (Me_2CO—CCl_4, 1 : 3). If the reaction is carried out in C_6H_6, the yield of compound **2** is higher (75%) than in $CHCl_3$ (67%).

References

1. T. P. Vasil´eva, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2153 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.* (*Engl. Transl.*), 1992, **41**, 1685].
2. M. G. Lin´kova, T. P. Vasil´eva, V. M. Bystrova, N. V. Kalyuzhnaya, O. V. Kil´disheva, I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 617 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1984, **33**, 570].
3. T. P. Vasil´eva, M. G. Lin´kova, O. V. Kil´disheva, I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 159 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1981, **30**, 570].
4. T. P. Vasil´eva, V. M. Bystrova, O. V. Kil´disheva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 1633 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1988, **37**, 1448].
5. V. V. Znamensky, A. D. Efremov, V. M. Bystrova, T. P. Vasil´eva, O. V. Kil´disheva, *Khim.-pharm. Zh.*, 1986, **20**, No 7, 843 [*Pharm. Chem. J.* (*Engl. Transl.*), 1986, **20**, No. 7, 496].
6. T. P. Vasil´eva, V. V. Znamensky, *Khim.-pharm. Zh.*, 1994, **28**, No. 1, 33 [*Pharm. Chem. J.* (*Engl. Transl.*), 1994, **28**, No. 1, 47].
7. T. P. Vasil´eva, N. I. Lisina, V. V. Znamensky, *Khim.-pharm. Zh.*, 1997, **31**, No. 5, 40 [*Pharm. Chem. J.* (*Engl. Transl.*), 1997, **31**, No. 5, 258].
8. J. Stawinski, M. Thelin, *Tetrahedron Lett.*, 1992, **33**, 3189.
9. J. Stawinski, M. Thelin, *J. Org. Chem.*, 1991, **56**, 5169.
10. H. Kohn, P. Charumilind, S. Simonsen, *J. Am. Chem.* Soc., 1979, **101**, 5431.
11. R. Iyer, L. Phillips, W. Egan, J. Regan, S. Beaucage, *J. Org. Chem.*, 1990, **55**, 4693.
12. L. Breydo, K. Gates, *Bioorg. Med. Chem.*, 2000, **10**, 885.
13. P. Messinger, *Arch. Pharm.*, 1985, **318**, 950.
14. A. Weissberger, E. Proskauer, J. Riddick, E. Toops, *Organic Solvents*, Interscience Publishers Inc., New York, 1955.

Received April 28, 2009;
in revised form July 8, 2009