Oxidation of 2-(thiazol-2-yl)acrylonitrile derivatives with an H_2O_2—KOH system: convenient route to new oxirane-2-carboxamides

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An efficient procedure was developed for the synthesis of previously unknown 3-aryl(styryl)-2-(4-arylthiazol-2-yl)oxirane-2-carboxamides and 2-(4-arylthiazol-2-yl)-1-oxaspiro[2.5]octane-2-carboxamides based on treatment of (*E*)-3-aryl-2-(4-arylthiazol-2-yl)acrylonitriles and cyclohexylidene(4-arylthiazol-2-yl)acetonitriles with an H_2O_2—KOH system in EtOH. Oxidation of (*E*)-3-(4-chlorophenyl)-2-(4-phenylthiazol-2-yl)acrylonitrile with an H_2O_2—AcOH system affords 3-(4-chlorophenyl)-2-(4-phenylthiazol-2-yl)oxirane-2-carbonitrile in 55% yield.

Key words: α,β-unsaturated nitriles, oxidation, hydrogen peroxide, Radziszewski reaction, oxirane-2-carboxamides, 1-oxaspiro[2.5]octane-2-carboxamides, oxirane-2-carbonitriles.

Oxidative hydrolysis of nitriles with hydrogen peroxide in an alkaline medium, which is known as the Radziszewski reaction, is recognized as one of the most efficient and convenient procedures for chemoselective transformations of nitriles into the corresponding amides, and it has found wide application in the routine syntheses.[1—4] More recently, peroxide oxidation of α,β-unsaturated nitriles in an alkaline medium has been found[4] to be accompanied by a competitive process, *viz.*, epoxidation of an activated double bond, to give finally oxirane-2-carboxamide derivatives. The procedure for the synthesis of α,β-epoxyamides from unsaturated nitriles has been further developed in the studies.[5—7] This transformation is of considerable interest, particularly, in the light of recent advantages in the use of various epoxy compounds in organic synthesis and great prospects for application of these compounds,[8—10] on the one hand, and data on biological activities of oxiranes, in particular, of 2,3-epoxy derivatives of carboxylic acid amides and esters,[11] on the other hand. In continuation of studies on the chemistry of cyanothioacetamide,[12] we examined the behavior of its derivatives, *viz.*, (*E*)-3-aryl-2-(4-arylthiazol-2-yl)acrylonitriles **1**, which were prepared according to a procedure described in our earlier publication,[13] under conditions of the Radziszewski reaction.

Heating of unsaturated nitriles **1a—d** with an excess of 35% H_2O_2 in the presence of an equimolar amount of KOH for a short period of time was demonstrated to be a convenient and highly efficient procedure for the synthesis of previously unknown 3-aryl-2-(4-arylthiazol-2-yl)oxirane-2-carboxamides **2a—d**. These compounds are of interest as precursors of various oxygen-functionalized building blocks (Scheme 1). The reaction proceeds also at room temperature to give products in comparable yields (70—90%). However, a substantially longer period of time (4—24 h) is required in the latter case to achieve the complete conversion of the starting reagents. Unsaturated nitrile **1e** (Ar = 4-$Me_2NC_6H_4$, Ar´ = Ph) was quantitatively recovered from the reaction mixture even after refluxing for 5 min. Evidently, inertness of this compound is attributed to the strong electron-donating effect of the Me_2N group, which hinders the attack of the hydroperoxide anion on the electrophilic centers of the conjugated chain due to deactivation of the latter. By contrast, cyclohexylidene(4-arylthiazol-2-yl)acetonitriles **3a,b** [14] are easily oxidized to give previously unknown 1-oxaspiro[2.5]octane derivatives **4a,b** in high yields (84—91%). The latter are promising polyfunctional reagents for fine organic synthesis[8] (see Scheme 1).

The reaction of penta-2,4-dienonitrile derivative **5** proceeds with great difficulty. The corresponding oxirane-2-carboxamide **6** can be prepared in only 46% yield under more drastic conditions. It should also be noted that oxidation of unsaturated nitrile **1c** with peracetic acid (H_2O_2—AcOH system) differs from the alkali-catalyzed process in that the cyano group in the former reaction

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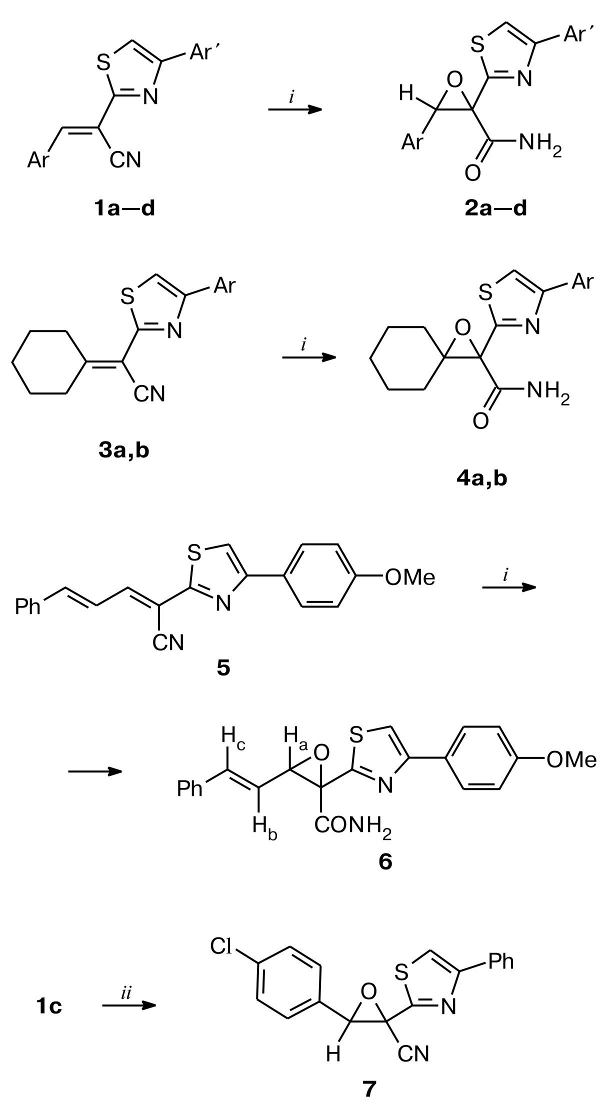
Scheme 1



Reagents and conditions: *i.* 35% H_2O_2, EtOH, 10% aqueous KOH solution, Δ; *ii.* 35% H_2O_2, AcOH, Δ.

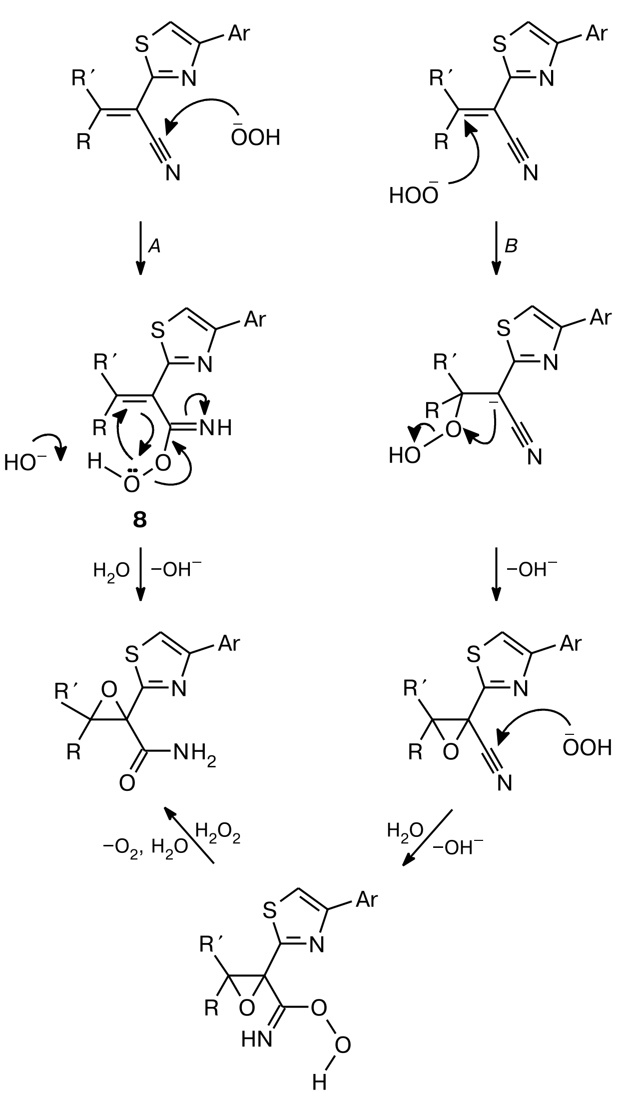
1, 2	a	b	c	d
Ar	$2\text{-ClC}_6\text{H}_4$	Ph	$4\text{-ClC}_6\text{H}_4$	$4\text{-ClC}_6\text{H}_4$
Ar′	Ph	$4\text{-ClC}_6\text{H}_4$	Ph	$4\text{-BrC}_6\text{H}_4$

3, 4	a	b
Ar	$4\text{-ClC}_6\text{H}_4$	$4\text{-BrC}_6\text{H}_4$

remains intact and the reaction gives the epoxidation product, *viz.*, oxirane-2-carbonitrile **7**, in 55% yield (see Scheme 1).

By analogy with the published data,[5] one of the most probable reaction mechanisms presumably involves the formation of peroxycarbimic acid **8** followed by its intramolecular rearrangement (Scheme 2, path *A*). However, in view of the ambiguity of the results obtained for epoxidation of isoproylidenemalononitrile,[7] the possibility of the initial attack of the hydroperoxide anion on the electrophilic carbon atom of the double bond cannot be ruled out. This attack occurs in an analogous process, *viz.*, in Weitz—Scheffer epoxidation of polar olefins[11] (path *B*). Contrary to oxidation with peroxy acids, epoxidation of alkenes with an H_2O_2—KOH system more likely proceeds stereoselectively than stereospecifically.[15] Conclusions about the general features of stereoregularity of this reaction are difficult to draw from the available experimental data. Hence, the reaction mechanism requires additional investigation.

Scheme 2



The structures of compounds **2a—d**, **4a,b**, **6**, and **7** were confirmed by spectroscopic studies and elemental analysis. The IR spectra of oxirane-2-carboxamides **2**, **4**, and **6** have no absorption bands characteristic of the nitrile function; instead, the spectra show absorption bands corresponding to stretching vibrations of the amide group with maxima at 3375—3330 (NH) and 1686—1630 cm^{-1} (C=O). The ^1H NMR spectra of amides **2a—d** are characterized by the presence of a narrow singlet for the only proton of the oxirane ring at δ 4.72—4.81. The corresponding signal in the spectrum of amide **6** appears as a doublet at δ 4.23, whereas the proton of the oxirane ring in the spectrum of oxirane-2-carbonitrile **7** resonates at δ 4.98. It should be noted that these chemical shifts agree well with the chemical shifts published in the literature for the protons of 2-alkoxycarbonyl-2-cyanooxiranes and 2,2-dicyanooxiranes (δ 4.48—4.66 [16] and 4.73—4.95,[17] respectively). At the same time, these chemical shifts differ substantially from δ for the methine protons in the spectra of the starting compounds **1** (δ 8.10—8.45).[13] The signal for the amide group in the ^1H NMR spectra of compounds **2**, **4**, and **6** is resolved, as a rule, as two broadened peaks at δ 7.35—7.71, and a singlet for the proton of the thiazole ring is observed at δ 7.78—8.03. It is known[18] that thiazole derivatives can be transformed into the corresponding *N*-oxides with the use of an H_2O_2—AcOH system or peroxy acids. However, a comparison of the ^1H NMR spectra of epoxynitrile **7** and unsaturated nitriles **1** showed that the chemical shift of the thiazole proton in the spectrum of compound **7** (δ 8.12) is typical of this class of compounds (δ 7.91—8.30),[13] which is additional evidence for the proposed structure. The presence of a weak band with a maximum at 2254 cm^{-1} (the unconjugated CN group) and the absence of characteristic absorption bands of the amide fragment in the IR spectrum of epoxynitrile **7** confirm the fact that the cyano group remains unoxidized in the presence of an H_2O_2—AcOH system.

To summarize, investigation of oxidation of 2-(4-arylthiazol-2-yl)acrylonitriles with an H_2O_2—KOH system allowed us to develop simple and efficient procedures for the synthesis of previously unknown 2-(4-arylthiazol-2-yl)oxirane-2-carboxamides.

Experimental

The ^1H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The IR spectra were measured on an IKS-29 spectrophotometer in Nujol mulls. Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyzer. The course of the reactions was monitored and the purities of the reaction products were checked by TLC on Silufol UV 254 plates using a 1 : 1 acetone—heptane system; spots were visualized with iodine vapor and UV irradiation. The melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Synthesis of oxirane-2-carboxamides 2a—d, 4a,b, and 6 (general procedure). A 10% aqueous KOH solution (1.6 mL, 3 mmol) was added in one portion to a mixture of the corresponding unsaturated nitrile (**1a—d**, **3a,b**, or **5**) (3 mmol), which has been thoroughly ground to a fine powder, and 35% H_2O_2 (d = 1.1 g cm^{-3}) (2.7 mL, 0.03 mol) in EtOH (15—20 mL). The reaction mixture was brought to reflux with vigorous stirring and allowed to stand, after which a vigorous exothermic reaction started, the process being accompanied by liberation of oxygen and the formation of a finely crystalline precipitate. The mixture was stirred at ~20 °C for 1.5 h until the color of the starting nitrile was completely disappeared. The colorless precipitate of the corresponding amide **2a—d** or **4a,b** was filtered off and washed three times with EtOH. In the case of amide **6**, the reaction mixture was refluxed with stirring for 3 min, after which the solution was filtered through a paper filter and stirred at ~20 °C for 24 h. The resulting precipitate was treated analogously.

3-(2-Chlorophenyl)-2-(4-phenyl-1,3-thiazol-2-yl)oxirane-2-carboxamide (2a). The yield was 88%, m.p. 218—219 °C (Me_2CO). Found (%): C, 60.99; H, 3.71; N, 7.95. $C_{18}H_{13}ClN_2O_2S$. Calculated (%): C, 60.59; H, 3.67; N, 7.85. IR, ν/cm^{-1}: 3345 (NH_2); 1685 (C=O). ^1H NMR, δ: 4.81 (s, 1 H, CH of oxirane); 7.30—7.62 (m, 9 H, 7 H arom. + $CONH_2$); 7.92 (s, 1 H, CH of thiazole); 7.97 (d, 2 H, Ph, ^3J = 7.6 Hz).

2-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-3-phenyloxirane-2-carboxamide (2b). The yield was 89%, m.p. 222—224 °C (Me_2CO—DMF, 4 : 1). Found (%): C, 60.83; H, 3.70; N, 8.00. $C_{18}H_{13}ClN_2O_2S$. Calculated (%): C, 60.59; H, 3.67; N, 7.85. IR, ν/cm^{-1}: 3370 (NH_2); 1686 (C=O). ^1H NMR, δ: 4.74 (s, 1 H, CH of oxirane); 7.36—7.58 (m, 8 H, 7 H arom. + 1 H $CONH_2$); 7.68 (br.s, 1 H, $CONH_2$); 7.98 (d, 2 H, H arom., ^3J = 8.6 Hz); 8.03 (s, 1 H, CH of thiazole).

3-(4-Chlorophenyl)-2-(4-phenyl-1,3-thiazol-2-yl)oxirane-2-carboxamide (2c). The yield was 80%, m.p. 201—203 °C. Found (%): C, 61.06; H, 3.69; N, 7.94. $C_{18}H_{13}ClN_2O_2S$. Calculated (%): C, 60.59; H, 3.67; N, 7.85. IR, ν/cm^{-1}: 3330 (NH_2); 1682 (C=O). ^1H NMR, δ: 4.73 (s, 1 H, CH of oxirane); 7.38 (m, 5 H, H arom.); 7.51 (m, 3 H, overlap of signals: d, 2 H, H arom., ^3J = 8.7 Hz, + s, 1 H, $CONH_2$); 7.71 (br.s, 1 H, $CONH_2$); 7.92 (s, 1 H, CH of thiazole); 7.96 (d, 2 H, H arom., ^3J = 7.0 Hz).

2-[4-(4-Bromophenyl)-1,3-thiazol-2-yl]-3-(4-chlorophenyl)oxirane-2-carboxamide (2d). The yield was 88%, m.p. 223—225 °C (decomp.). Found (%): C, 50.21; H, 2.80; N, 6.38. $C_{18}H_{12}BrClN_2O_2S$. Calculated (%): C, 49.62; H, 2.78; N, 6.43. IR, ν/cm^{-1}: 3350 (NH_2); 1678 (C=O). ^1H NMR, δ: 4.72 (s, 1 H, CH of oxirane); 7.36 (d, 2 H, 4-BrC_6H_4, ^3J = 8.6 Hz); 7.52 (m, 5 H, 4 H arom. + 1 H $CONH_2$); 7.71 (br.s, 1 H, $CONH_2$); 7.90 (d, 2 H, 4-BrC_6H_4, ^3J = 8.6 Hz); 8.03 (s, 1 H, CH of thiazole).

2-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-1-oxaspiro[2.5]octane-2-carboxamide (4a). The yield was 84%, m.p. 180—182 °C. Found (%): C, 59.12; H, 4.86; N, 8.16. $C_{17}H_{17}ClN_2O_2S$. Calculated (%): C, 58.53; H, 4.91; N, 8.03. IR, ν/cm^{-1}: 3365 (NH_2); 1645 (C=O). ^1H NMR, δ: 1.51 (m, 6 H, $(CH_2)_3$); 1.75 (m, 4 H, 2 CH_2); 7.39 (m, 3 H, overlap of signals: d, 2 H, H arom., ^3J = 8.5 Hz, + s, 1 H, $CONH_2$); 7.60 (br.s, 1 H, $CONH_2$); 7.96 (m, 3 H, overlap of signals: d, 2 H, H arom., ^3J = 8.5 Hz, + s, 1 H, CH of thiazole).

2-[4-(4-Bromophenyl)-1,3-thiazol-2-yl]-1-oxaspiro[2.5]octane-2-carboxamide (4b). The yield was 91%, m.p. 211—213 °C. Found (%): C, 52.52; H, 4.31; N, 7.11. $C_{17}H_{17}BrN_2O_2S$. Calculated (%): C, 51.92; H, 4.36; N, 7.12. IR, ν/cm^{-1}: 3375 (NH_2); 1630 (C=O). ^1H NMR, δ: 1.50 (m, 6 H, $(CH_2)_3$); 1.74 (m, 4 H, 2 CH_2); 7.35 (br.s, 1 H, $CONH_2$); 7.52 (d, 2 H, H arom., ^3J = 8.5 Hz); 7.58 (br.s, 1 H, $CONH_2$); 7.89 (d, 2 H, H arom., ^3J = 8.5 Hz); 7.95 (s, 1 H, CH of thiazole).

2-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]-3-((*E*)-styryl)oxirane-2-carboxamide (6). The yield was 46%, m.p. 162—163 °C. Found (%): C, 65.92; H, 4.83; N, 7.33. $C_{21}H_{18}N_2O_3S$. Calculated (%): C, 66.65; H, 4.79; N, 7.40. IR, ν/cm^{-1}: 3360 (NH_2); 1660 (C=O). ^{1}H NMR, δ: 3.79 (s, 3 H, MeO); 4.23 (d, 1 H, CH_a, J_{H_a,H_b} = 8.5 Hz); 6.18 (dd, 1 H, CH_b, J_{H_a,H_b} = 8.5 Hz, J_{H_b,H_c} = 16.0 Hz); 6.89 (d, 2 H, H arom., ^3J = 8.4 Hz); 7.03 (d, 1 H, CH_c, J_{H_b,H_c} = 16.0 Hz); 7.23—7.42 (m, 6 H, Ph + C(O)NH); 7.69 (br.s, 1 H, $CONH_2$); 7.78 (s, 1 H, CH of thiazole); 7.83 (d, 2 H, H arom., ^3J = 8.4 Hz).

3-(4-Chlorophenyl)-2-(4-phenyl-1,3-thiazol-2-yl)oxirane-2-carbonitrile (7). A mixture of unsaturated nitrile **1c** (0.5 g, 1.55 mmol) and 35% H_2O_2 (1.4 mL, 15.5 mmol) in AcOH (10 mL) was refluxed for 1 min, stirred at ~50 °C for 1 h, and kept at ~20 °C for 4 days. The finely crystalline pale-yellow precipitate was filtered off and washed with ethanol to prepare nitrile **7** in a yield of 0.29 g (55%), m.p. 148—149 °C. Found (%): C, 64.51; H, 3.30; N, 8.20. $C_{18}H_{11}ClN_2OS$. Calculated (%): C, 63.81; H, 3.27; N, 8.27. IR, ν/cm^{-1}: 2254 (CN). ^{1}H NMR, δ: 4.98 (s, 1 H, CH of oxirane); 7.37 (m, 3 H, Ph); 7.53 (q, 4 H, 4-ClC_6H_4, ^3J = 8.7 Hz); 7.97 (d, 2 H, Ph, ^3J = 7.2 Hz); 8.12 (s, 1 H, CH of thiazole).

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References

1. B. Radziszewski, *Ber. Deutsch. Chem. Ges.*, 1885, **18**, 355.
2. J. Deinert, *J. Prakt. Chem.*, 1895, **63**, 431.
3. J. V. Dubsky, *J. Prakt. Chem.*, 1916, **93**, 137.
4. J. V. Murray and J. B. Cloke, *J. Am. Chem. Soc.*, 1934, **56**, 2749.
5. J. B. Payne and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 651.
6. J. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 659.
7. J. B. Payne, *J. Org. Chem.*, 1961, **26**, 663.
8. L. I. Kas´yan, A. O. Kas´yan, and I. N. Tarabara, *Zh. Org. Khim.*, 2001, **37**, 1431 [*Russ. J. Org. Chem.*, 2001, **37**, 1361 (Engl. Transl.)].
9. L. I. Kas´yan, S. I. Okovityi, and A. O. Kas´yan, *Zh. Org. Khim.*, 2004, **40**, 1 [*Russ. J. Org. Chem.*, 2004, **40**, 1 (Engl. Transl.)].
10. W. Adam and A. Zhang, *Synlett*, 2005, 1041.
11. V. G. Dryuk, V. G. Kartsev, and M. A. Voitsekhovskaya, *Oksirany — sintez i biologicheskaya aktivnost´. Mekhanizm, assotsiativnye i stericheskie effekty peroksidnogo epoksidirovaniya alkenov* [*Oxiranes: Synthesis and Biological Activity. Mechanism, Associative and Steric Effects of Peroxide Epoxidation of Alkenes*], Bogorodskii Pechatnik, Moscow, 1999, 528 pp. (in Russian).
12. V. P. Litvinov, *Usp. Khim.*, 1999, **68**, 817 [*Russ. Chem. Rev.*, 1999, **68**, 737 (Engl. Transl.)]; V. V. Dotsenko, Ph. D. (Chem.) Thesis, N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 2004, 167 pp. (in Russian).
13. V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Mendeleev Commun.*, 1998, 23; S. G. Krivokolysko, V. D. Dyachenko, V. N. Nesterov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 2001, 929 [*Chem. Heterocycl. Compd.*, 2001, **37**, 855 (Engl. Transl.)].
14. A. D. Dyachenko, Ph. D. (Chem.) Thesis, V. N. Karazin Kharkov National University, Kharkov, 2003, 196 pp. (in Russian); A. D. Dyachenko, V. D. Dyachenko, and S. M. Desenko, *Ukr. Khim. Zh.* [*Ukr. Chem. J.*], 2003, **69**, 115 (in Russian).
15. A. H. Haines, *Methods for the Oxidation of Organic Compounds. Alkanes, Alkenes, Alkynes and Arenes*, Academic Press, London, 1985.
16. A. Foucaud and M. Bakouetila, *Synthesis*, 1987, 854.
17. J. Volmajer, R. Toplak, S. Bittner, and A. Majcen Le Marechal, *ARKIVOK*, 2003 (xiv), 49; http://arkat-usa.org./ark/journal/2003/I14_Stanovnik/BS-862A/862A.pdf.
18. *Thiazole and its Derivatives. The Chemistry of Heterocyclic Compounds*, Ed. J. V. Metzger, J. Wiley and Sons, New York, 1979, Vol. **34**, Part 1, 612 pp.

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