Reaction of Enol Ethers with the I_2–H_2O_2 System: Synthesis of 2-Iodo-1-methoxy Hydroperoxides and Their Deperoxidation and Demethoxylation to 2-Iodo Ketones

Alexander O. Terent'ev,* Alexander M. Borisov, Maxim M. Platonov, Zoya A. Starikova, Vladimir V. Chernyshev, Gennady I. Nikishin

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
Leninsky Prospect 47, 119991 Moscow, Russian Federation
Fax +7(499)1355328; E-mail: terentev@ioc.ac.ru

Received 23 July 2009

Abstract: The reaction of enol ethers with the I_2–H_2O_2 system in diethyl ether affords 2-iodo ketones and the previously unknown 2-iodo-1-methoxy hydroperoxides. In the presence of the I_2–H_2O_2 system, the latter compounds undergo deperoxidation and demethoxylation to form 2-iodo ketones. The reaction conditions were found for the synthesis of 2-iodo ketones from enol ethers in 67–94% yields.

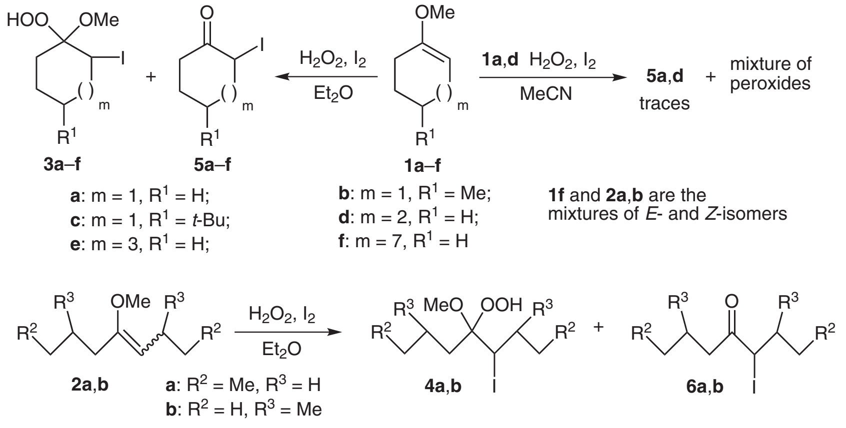
Key words: enol ethers, hydrogen peroxide, iodine, peroxides, peroxidation

In the last two decades, synthetic routes to organic peroxides have attracted much research interest because these compounds have potent antimalarial activity.[1] Compounds with activity comparable or even superior to that of the natural peroxide artemisinin, which is widely used in the therapy, were synthesized.[2] A search for natural and synthetic compounds with antitumor activity is a rather new and promising field of application of organic peroxides.[3]

In the industry, peroxides are widely used as radical polymerization initiators and cross-linking agents. The above-listed practical applications of peroxides stimulated the development of new methods for the synthesis of these compounds.

The present study contributes to the research on the use of the I_2–H_2O_2 system for the peroxidation and halogenation of organic compounds. In recent years, the idea of the combined use of iodine and hydroperoxides or hydrogen peroxide has been applied to the synthesis of peroxides from carbonyl compounds[4] and alkenes,[5] as well as to the synthesis of compounds with the monoperoxy ketal moiety[6] and cyclic triperoxides.[7] The I_2–H_2O_2 system shows versatile reactivity. In this system, hydrogen peroxide acts not only as the reagent for the formation of the O–O group but also as the iodine activator in the iodoalkoxylation of alkenes[8] and the iodination of arenes,[9] ketones,[10] and alkynes.[11] This system was used for the Baeyer–Villiger oxidation of ketones to lactones[12] and the ring contraction in 1,2-quinones to form cyclopentenones.[13] Results of studies on the electrophilic iodination of organic compounds, including those with hydrogen peroxide, were surveyed in the review.[14]

In the present study, we have examined the reactions of cyclic enol ethers **1a**–**f** and linear enol ethers **2a**,**b** with the I_2–H_2O_2 system in diethyl ether and acetonitrile (Scheme 1). It was found that the nature of the solvent has a decisive effect on the reaction pathway. Thus, the reactions in diethyl ether afford 2-iodo ketones and 2-iodo-1-methoxy hydroperoxides, whereas the reactions in aceto-



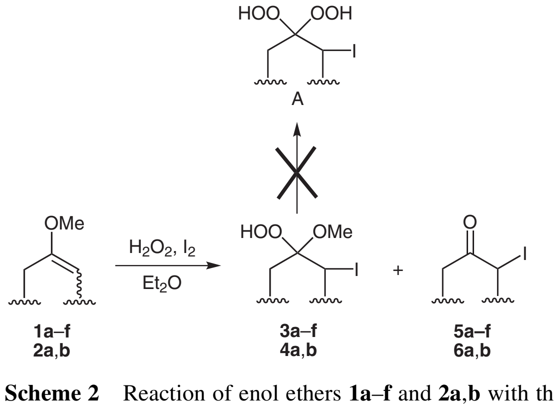
Scheme 1 Reaction of enol ethers **1a**–**f** and **2a**,**b** with the I_2–H_2O_2 system in Et_2O and MeCN

SYNTHESIS 2009, No. 24, pp 4159–4166
Advanced online publication: 19.10.2009
DOI: 10.1055/s-0029-1217062; Art ID: P10509SS

nitrile give complex mixtures of peroxides and trace amounts of 2-iodo ketones.

Reactions of Enol Ethers with the I_2–H_2O_2 System in Diethyl Ether

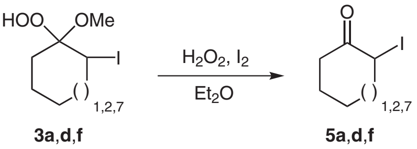
The reactions of enol ethers with the I_2–H_2O_2 system in Et_2O were carried out with the use of a five-fold molar excess of H_2O_2 (according to the stoichiometry, a two-fold molar excess of H_2O_2 is sufficient for the synthesis of iodo dihydroperoxide **A**) and a stoichiometric amount of iodine (0.5 mole per mole of enol ether). However, the expected 1,1-dihydroperoxy-2-iodoalkanes **A** (products of the addition hydrogen peroxide and the iodine-catalyzed replacement of the methoxy group) were not obtained at all; instead, the reaction afforded the previously unknown 2-iodo-1-methoxy hydroperoxides **3a–f** and **4a**,**b** (in 32–41% yields) and 2-iodo ketones **5a–f** and **6a**,**b** (in 40–57% yields) (Table 1, Scheme 2).



Scheme 2 Reaction of enol ethers **1a–f** and **2a**,**b** with the I_2–H_2O_2 system in Et_2O

2-Iodo-1-methoxy hydroperoxides **3a–f** are stable compounds. Under ambient conditions, these compounds remain stable overnight, and they can be stored without decomposition for months at temperatures below –10 °C. These compounds can easily be isolated in the pure state by silica gel column chromatography. The synthesis of iodo peroxides **3c**,**f** was scaled up by a factor of 20 to prepare gram amounts of the compounds in yields given in Table 1.

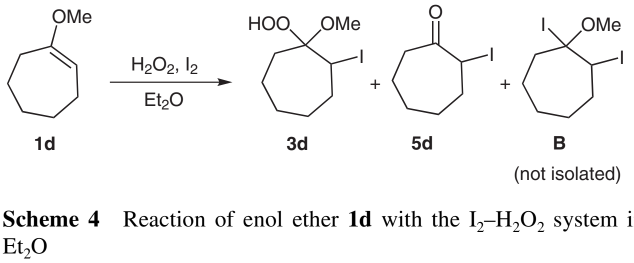
When studying the behavior of peroxides **3** in the reaction medium under the synthesis conditions (in contact with hydrogen peroxide and iodine), we found that peroxides undergo deperoxidation and demethoxylation to form 2-iodo ketones **5** (Scheme 3).



Scheme 3 Reaction of enol ethers **3a**,**d**,**f** with the I_2–H_2O_2 system in Et_2O

In diethyl ether, authentic samples of 2-iodo-1-methoxy cycloalkylhydroperoxides **3a**,**d**,**f** are transformed into 2-iodo cycloalkanones **5a**,**d**,**f** in 93–96% yields in the presence of a two-fold molar excess of hydrogen peroxide and iodine (1 mole per mole of **3**).

Taking into accounts the above results, we developed a procedure for the preparative synthesis of iodo ketones from enol ethers. As exemplified by iodo ketone **5d**, the use of an excess amount of iodine is the key factor determining the selective synthesis from enol ether **1d**. In this case, iodomethoxy hydroperoxide **3d** was obtained as a by-product. The formation of diiodide **B** expected in the presence of a large excess of iodine was not observed (Scheme 4, Table 2).



Scheme 4 Reaction of enol ether **1d** with the I_2–H_2O_2 system in Et_2O

An increase in the amount of iodine from 1 to 2.5 mole(s) per mole of **1d** increases the selectivity of the reaction and the yield of iodo ketone **5d**; iodo hydroperoxide **3d** is generated in trace amounts. The addition of water in an amount equivalent to enol ether has no effect on the yield of iodo ketone **5d**.

A series of experiments was carried out with the use of 2 moles of I_2 per mole of **1d** (see Experimental section) with varying the reaction time (3, 6, and 12 h) and the amount of hydrogen peroxide (3 and 6 moles per mole of **1d**). Under these reaction conditions, iodo ketone **5d** was obtained in 75–80% yield.

Table 1 Yields of 2-Iodo-1-methoxy Hydroperoxides **3a–f** and **4a**,**b** and 2-Iodo Ketones **5a–f** and **6a**,**b** in the Reaction of Enol Ethers **1a–f** and **2a**,**b** with I_2 and H_2O_2 in Et_2O[a]

Enol ether	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**2a**	**2b**
Yield of **3a–f**,**4a**,**b** (%)	**3a**: 33	**3b**: 38	**3c**: 35	**3d**: 34	**3e**: 35	**3f**: 41	**4a**: 33	**4b**: 32
Yield of **5a–f**,**6a**,**b** (%)	**5a**: 40	**5b**: 45	**5c**: 54	**5d**: 41	**5e**: 43	**5f**: 44	**6a**: 57	**6b**: 49

[a] Reaction conditions: an ethereal solution of H_2O_2 (2.53 mL, 6.15 mmol, c = 2.43 mol/L) was added to a solution of enol ether (1.23 mmol) in Et_2O (6 mL), and then I_2 (0.16 g, 0.62 mmol) was added. The reaction mixture was kept at 18–22 °C for 6 h.

Table 2 Influence of the Amount of I_2 on the yields of Iodo Ketone **5d** and Hydroperoxide **3d** in the Reaction of Enol Ether **1d** with the I_2–H_2O_2 System[a]

Mole of I_2 per mole of **1d**	Yield (%) of 2-iodo-1-methoxy-cycloheptyl hydroperoxide **3d**	Yield (%) of iodo ketone **5d**
1	25	54
1.5	17	61
2	~2	78
2[b]	~2	80
2.5	~2	79

[a] Reaction conditions: An ethereal solution of H_2O_2 (2.45 mL, 5.95 mmol, c = 2.43 mol/L) was added to a solution of 1-methoxycycloheptene (**1d**; 0.15 g, 1.19 mmol) in Et_2O (6 mL), then I_2 (0.30–0.76 g, 1.19–2.98 mmol) was added, and the reaction mixture was kept at 18–22 °C for 6 h.

[b] Experiment conducted with the addition of H_2O (0.022 g, 1.2 mmol).

The possibility of the formation of iodo ketones by iodination of ketones, which can be generated in small amounts through aqueous hydrolysis of enol ethers, was discarded by experiments, in which the reactions of cyclohexanone and cycloheptanone were carried out with a three-fold molar excess of H_2O_2 and a two-fold molar excess of I_2. After storage of the reaction mixture at 18–22 °C for 6 hours, 2-iodocyclohexanone and 2-iodocycloheptanone were isolated in 6% and 5% yield, respectively. In this case, the iodine-catalyzed peroxidation of ketones proceeds as the major reaction. This is consistent with the results of the study,[4b] in which iodine catalyzed the peroxidation of ketones in acetonitrile and methanol under similar conditions. Under the optimized conditions of the synthesis of iodo ketone **5d**, iodo ketones **5a–f** and **6a**,**b** were generated in good yields and with good selectivity from enol ethers **1a–f** and **2a**,**b**, respectively (Table 3).

Table 3 Synthesis of Iodo Ketones **5a–f** and **6a**,**b** from Enol Ethers **1a–f** and **2a**,**b** Under Optimized Conditions[a]

Iodo ketone	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**6a**	**6b**
Yield (%)	71	67	68	79	79	88	94	91

[a] General reaction conditions: an ethereal solution of H_2O_2 (2.45 mL, 5.95 mmol, c = 2.43 mol/L) was added to a solution of enol ether **1a–f** or **2a**,**b** (1.19 mmol) in Et_2O (6 mL), and then I_2 (0.61 g, 2.4 mmol) was added; the reaction time was 3 h at 18–22 °C.

The yield of iodo ketones **5** from cyclic enol ethers increases with increasing ring size. The reaction of linear enol ethers **2a**,**b** affords iodo ketones **6a**,**b** in the maximum yield (94 and 91%, respectively). An increase in the yield is apparently associated with a decrease in the influence of the iodine-induced polymerization, whose contribution decreases with increasing ring size and in the case of linear structures containing the internal double bond. This conclusion is consistent with the experimental observations, according to which the addition of iodine to ethereal solutions of enol ethers (in the absence of hydrogen peroxide) results in the rapid resinification.

Reactions of Enol Ethers with the I_2–H_2O_2 System in Acetonitrile

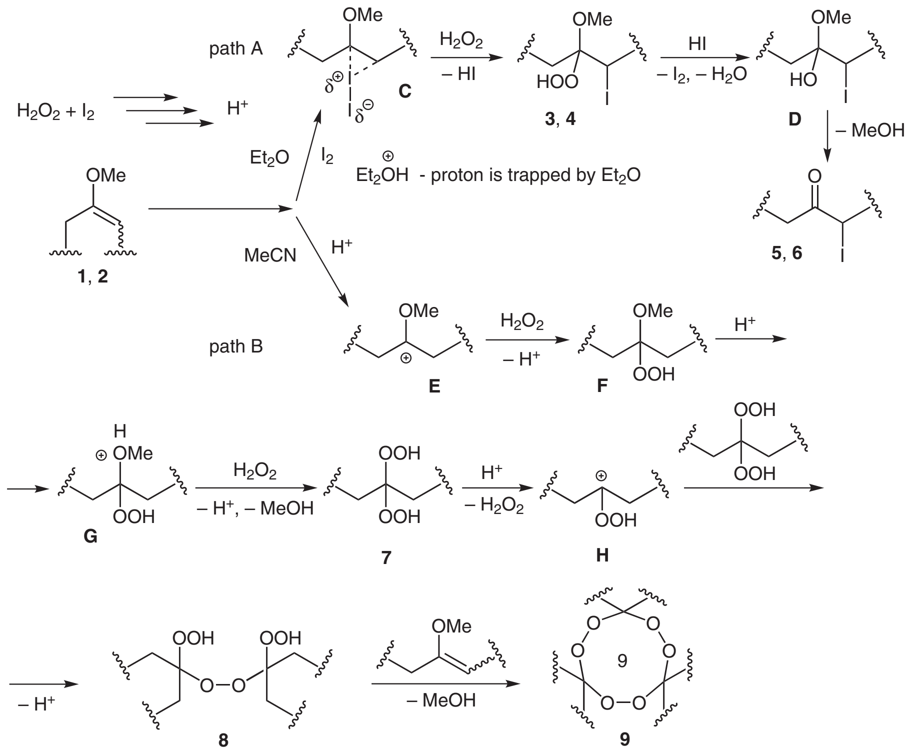
In acetonitrile, which has found use as the solvent in the peroxidation of organic compounds,[4] the results of the reactions of enol ethers with the I_2–H_2O_2 system are substantially different from those obtained in diethyl ether. Under the conditions used for the synthesis of 2-iodo-1-methoxy hydroperoxides (Table 1), the reaction in acetonitrile affords a mixture of peroxides. According to the TLC analysis (by comparing with authentic samples) and based on the characteristic signals of the OOCOO fragments in the ^{13}C NMR spectra,[4–6,15] the following products of the reactions of 1-methoxycyclohexene **1a** and 1-methoxycycloheptene (**1d**) with the I_2–H_2O_2 system were identified: geminal dihydroperoxycyclohexane (**7a**) (110.4 ppm) and dihydroperoxycycloheptane (**7d**) (115.7 ppm), 1,1′-dihydroperoxydi(cyclohexyl)peroxide **8a** (111.0 ppm) and 1,1′-dihydroperoxydi(cycloheptyl)peroxide (**8d**) (116.3 ppm), and cyclohexane triperoxide (**9a**) (107.6 ppm) and cycloheptane triperoxide (**9d**) (112.7 ppm), respectively.

Influence of the Nature of the Reaction Medium on the Composition of the Reaction Products of Enol Ethers with the I_2–H_2O_2 System

It is known that iodine is oxidized by hydrogen peroxide according to a multistep procedure (Bray–Liebhafsky reaction[16]) through the intermediate formation of H^+. The reactions of enol ethers with the I_2–H_2O_2 system in diethyl ether and acetonitrile occur by different paths **A** and **B**, which is apparently attributed to the different basicity of these solvents (Scheme 5).

Path **A**: In diethyl ether, the proton of hydroiodic acid is accepted by the ethereal oxygen atom and is removed from the reaction. Iodine and hydrogen peroxide are successively added to enol ether **C** to form iodomethoxy peroxides **3** and **4**, which are reduced with HI (with formation of **D**) under the reaction conditions and then, after elimination of methanol, are transformed into 2-iodo ketones **5** and **6**.

Path **B**: In acetonitrile, the proton, which is not accepted by the solvent, catalyzes the reaction. The addition of the proton to enol ether **E** followed by the reaction with hydrogen peroxide afford methoxy hydroperoxide **F**. After protonation, elimination of methanol, and the addition of hydrogen peroxide, compound **F** is transformed into geminal dihydroperoxide **7**. Then the elimination of hydrogen peroxide **H** followed by homocondensation afford 1,1′-dihydroperoxydi(alkyl)peroxide **8**, which reacts with the starting enol ether to form triperoxide **9**. Hence, the higher



Scheme 5 Mechanism of the reaction of enol ethers with the I_2–H_2O_2 system in Et_2O and MeCN

basicity of diethyl ether compared to acetonitrile is a key factor determining the reaction pathway.

Structure Determination

The structures of iodo ketones **5** and **6** were established by ^1H and ^{13}C NMR spectroscopy based on the characteristic signals for the C=O (^{13}C, 203.9–209.7 ppm) and CHI (^{13}C, 28.1–33.9 ppm; ^1H, 4.1–4.4 ppm) groups.[10]

2-Iodo-1-methoxy hydroperoxides **3** and **4** are novel unusual structures containing the oxidizing (OOH), reducing (I), and highly reactive (methoxy hydroperoxide) moieties. The structures of these compounds were proved by ^1H and ^{13}C NMR spectroscopy. Thus, the ^{13}C NMR spectra show signals characteristic of the OCOO (104.7–108.4 ppm),[6] CI (29.1–36.3 ppm),[10] and OCH_3 (48.3–51.9 ppm)[6] groups corresponding to the known values. The ^1H NMR spectrum shows the signal at 7.8–8.4 ppm characteristic of the OOH group.[6,11] Peroxides **3e**,**f** and **4a**,**b** were obtained as mixtures of diastereomers, as evidenced from the doubled number of the signals in the ^{13}C NMR spectra (the isomers are virtually inseparable by TLC); the starting enol ethers **1f** and **2a**,**f** are mixtures of *cis*-, *trans*, and *E*-, *Z*-isomers.

The 2D NOESY experiment on the establishment of the configuration of iodoperoxide **3a** showed the presence of the nuclear Overhauser effect between the proton of the CHI group and the methyl protons, which suggests that they are in equatorial positions, whereas the hydroperoxide group and iodine are in axial positions (Figure 1).

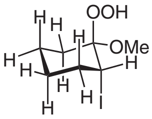


Figure 1 Conformation of iodoperoxide **3a**

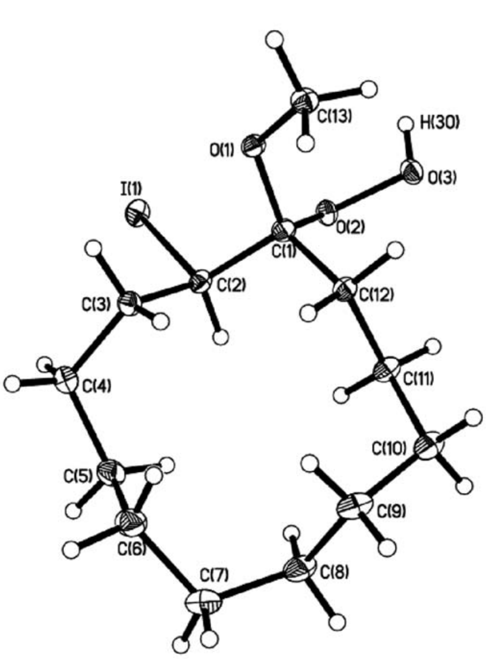


Figure 2 Molecular structure of 2-iodo-1-methoxycyclododecyl hydroperoxide (**3f**) with thermal ellipsoids drawn at 50% probability level

The problem of determining the structures of new peroxides is often difficult to solve based only on the NMR spectroscopic and elemental analysis data. In the present investigation, the structures of 2-iodo-1-methoxy hydroperoxides were unambiguously established by the X-ray diffraction study of the peroxide **3f** (Figure 2).

Molecule **3f** has standard bond lengths and bond angles. The ring adopts the [4.4.4.4] conformation; the iodine atom and the O(2) atom of the peroxide group are in nearly axial positions and are in the *trans* arrangement, which in agreement with the establishment of the configuration of iodoperoxide **3a** by NMR spectroscopy. The O(1) atom of the methoxy group deviates from the mean plane of the ring in the same direction as the iodine atom.

In the crystal structure, the molecules form dimers through the O(3)–H(3O).O(1)′ hydrogen bonds [O···O′, 2.832(3) Å; H(3O)···O(1)′, 2.06(4) Å; the angle at the H(3O) atom is 163.0(9)°]. The dimers are linked into layers parallel to the xy0 plane by the weak I1···(12a)′ hydrogen bonds [I1···H(12a)′, 3.04 Å].

Conclusions

In solvents of strongly different basicity, the reactions of enol ethers with the I_2–H_2O_2 system were found to occur by different paths. Thus, the reactions in diethyl ether afford 2-iodo ketones and the previously unknown 2-iodo-1-methoxy hydroperoxides, whereas the reactions in acetonitrile give mixtures of geminal diperoxides. The synthesis of 2-iodo-1-methoxy hydroperoxides from enol ethers, which are generated based on ketones or alkynes, can be scaled up to prepare gram amounts of the target compounds. It was found that the same reagents that are used for the synthesis of 2-iodo-1-methoxy hydroperoxides cause the deperoxidation and demethoxylation of the latter compounds to form 2-iodo ketones. The selective method was developed for the synthesis of 2-iodo ketones in 67–94% yields.

NMR spectra were recorded on Bruker OC-200 and Bruker AM-300 spectrometers ($CDCl_3$ as the solvent). TLC analyses were carried out on Silufol UV-254 plates. Column chromatography was performed with silica gel 63–200 mesh (Acros). Melting points were measured on a Kofler hot-stage apparatus. The solvents Et_2O, MeCN, CH_2Cl_2, hexane, and EtOAc (high-purity grade) were distilled before use over the corresponding drying agents. The reagents I_2, $Na_2S_2O_3·5H_2O$, and Na_2SO_4 were of high-purity grade. A H_2O_2 solution was prepared by extraction with Et_2O from the corresponding aqueous solutions followed by drying over $MgSO_4$. The concentrations of peroxides were determined by iodometric titration. Enol ethers were synthesized according to a known procedure.[17] 1,1-Dihydroperoxycyclohexane (**7a**), 1,1-dihydroperoxycycloheptane (**7d**), 1,1′-dihydroperoxydi(cyclohexyl)peroxide (**8a**), 1,1′-dihydroperoxydi(cycloheptyl)peroxide (**8d**), cyclohexane triperoxide (**9a**), and cycloheptane triperoxide (**9d**) were prepared according to methods described earlier.[11,15]

Reaction of Enol Ethers 1a–f and 2a,b with Iodine and Hydrogen Peroxide in Et_2O; 1-Hydroperoxy-2-iodo-1-methoxycyclohexane (3a) and 2-Iodocyclohexanone (5a); Typical Procedure (Table 1)

An ethereal solution of H_2O_2 (2.53 mL, 6.15 mmol, *c* = 2.43 mol/L) was added to a solution of 1-methoxycyclohexene (**1a**; 0.14 g, 1.23 mmol) in Et_2O (6 mL). Then I_2 (0.16 g, 0.62 mmol) was added to the reaction mixture with vigorous stirring, and the mixture was kept at 18–22 °C for 6 h. CH_2Cl_2 (10 mL) and finely dispersed $Na_2S_2O_3·5H_2O$ (1 g) were added, and the suspension was vigorously stirred until the formation of a pale-yellow solution. The solution was filtered through a thin layer of silica gel (1 cm) and the solvent was evaporated. The residue was separated by silica gel column chromatography using a hexane–EtOAc mixture as the eluent with an EtOAc gradient from 2 to 20% (v/v). 1-Hydroperoxy-2-iodo-1-methoxycyclohexane (**3a**) was obtained in 33% yield (0.11 g, 0.40 mmol) and 2-iodocyclohexanone (**5a**) was obtained in 40% yield (0.11 g, 0.39 mmol).

In addition, iodo peroxides **3c**,**f** were synthesized from enol ethers **1c**,**f** using the starting reagents in 20 times higher amounts.

2-Iodocycloalkanones 5a,d,f from 1-Hydroperoxy-2-iodo-1-methoxycycloalkanones 3a,d,f; 2-Iodocyclohexanone (5a); Typical Procedure

An ethereal solution of H_2O_2 (0.60 mL, 1.47 mmol, *c* = 2.43 mol/L) was added to a solution of **3a** (0.2 g, 0.74 mmol) in Et_2O (6 mL). Then I_2 (0.19 g, 0.74 mmol) was added to the reaction mixture with vigorous stirring, and the mixture was kept at 18–22 °C for 6 h. Then CH_2Cl_2 (10 mL) and finely dispersed $Na_2S_2O_3·5H_2O$ (1 g) were added, the suspension was vigorously stirred until the formation of a pale-yellow solution. The solution was filtered through a thin layer of silica gel (1 cm) and the solvent was evaporated. The residue was separated by silica gel column chromatography using a hexane–EtOAc mixture as the eluent with an EtOAc gradient from 2 to 20% (v/v). 2-Iodocyclohexanone (**5a**) was obtained in 94% yield (0.16 g, 0.70 mmol).

Influence of the Amount of Iodine on the Yields of Iodo Ketone 5d and Hydroperoxide 3d in the Reaction of Enol Ether 1d with the I_2–H_2O_2 System; 2-Iodo-1-methoxycycloheptyl Hydroperoxide (3d) and 2-Iodocyclohexanone (5d) (Table 2)

An ethereal solution of H_2O_2 (2.45 mL, 5.95 mmol, *c* = 2.43 mol/L) was added to a solution of 1-methoxycycloheptene (**1d**; 0.15 g, 1.19 mol) in Et_2O (6 mL). Then I_2 (0.30–0.76 g, 1.19–2.98 mmol) was added to the reaction mixture with vigorous stirring. In one experiment, H_2O (0.022 g, 1.2 mmol) was added. The mixture was kept at 18–22 °C for 6 h. Then, CH_2Cl_2 (10 mL) and finely dispersed $Na_2S_2O_3·5H_2O$ (1 g) were added, and the suspension was vigorously stirred until the formation of a pale-yellow solution. The solution was filtered through a thin layer of silica gel (1 cm), and the solvent was evaporated. The residue was separated by silica gel column chromatography using a hexane–EtOAc mixture as the eluent with an EtOAc gradient from 2 to 20% (v/v). 2-Iodo-1-methoxycycloheptyl hydroperoxide (**3d**) was obtained in 25–2% yield (0.07–0.005 g, 0.30–0.02 mmol); 2-iodocyclohexanone (**5d**) was obtained in 54–79% yield (0.18–0.27 g, 0.64–0.94 mmol).

2-Iodocycloheptanone (5d); Variations of the Reaction Time and the Amount of Hydrogen Peroxide (Table 2)

An ethereal solution of H_2O_2 (1.47 or 2.94 mL, 3.57 or 7.14 mmol, 3 and 6 mol per mol of **1d**, *c* = 2.43 mol/L) was added to a solution of 1-methoxycycloheptene (**1d**; 0.15 g, 1.19 mmol) in Et_2O (6 mL). Then I_2 (0.60 g, 2.38 mmol) was added to the reaction mixture with vigorous stirring. The mixture was kept at 18–22 °C for 3, 6, and 12 h. 2-Iodocycloheptanone (**5d**) was isolated according to the above-described procedure (see the experimental conditions to Table 2).

Reactions of Cyclohexanone and Cyclopentanone with Iodine and Hydrogen Peroxide

An ethereal solution of H_2O_2 (1.47 g, 3.57 mmol, 3 mol per mol of **1d**, *c* = 2.43 mol/L) was added to a solution of cyclohexanone (0.116 g, 1.19 mmol) or cycloheptanone (0.133 g, 1.19 mmol) in Et_2O (6 mL). Then I_2 (0.60 g, 2.38 mmol) was added to the reaction mixture with vigorous stirring, and the mixture was kept at 18–22 °C for 6 h. The isolation of 2-iodocyclohexanone (**5a**; 6%, 0.016 g, 0.071 mmol) and 2-iodocycloheptanone (**5d**; 5%, 0.014 g, 0.06 mmol) was carried out according to the above-described procedure (see the experimental conditions to Table 2).

Iodo Ketones 5a–f and 6a,b from Enol Ethers 1a–f and 2a,b Under Optimized Conditions; 2-Iodocycloheptanone (5d); Typical Procedure (Table 3)

An ethereal solution of H_2O_2 (2.45 mL, 5.95 mmol, *c* = 2.43 mol/L) was added to a solution of 1-methoxycycloheptene (**1d**; 0.15 g, 1.19 mmol) in Et_2O (6 mL). Then I_2 (0.61 g, 2.4 mmol) was added to the reaction mixture with vigorous stirring. The reaction time was 3 h at 18–22 °C. 2-Iodocycloheptanone (**5d**; 224 mg, 79%, 0.94 mmol) was isolated according to the above-described procedure (see the experimental conditions to Table 2).

Reactions of 1-Methoxycyclohexene (1a) and 1-Methoxycycloheptene (1d) with the I_2–H_2O_2 System in MeCN

To a solution of H_2O_2 (0.2 g, 5.9 mmol) in MeCN (8 mL) was added 1-methoxycyclohexene (**1a**; 0.13 g, 1.16 mmol) or 1-methoxycycloheptene (**1d**; 0.15 g, 1.19 mmol), and then I_2 (0.15 g, 0.60 mmol) was added with vigorous stirring. The reaction mixture was kept at 18–22 °C for 6 h and then concentrated to 1/5 of the initial volume at 10–20 mmHg. CH_2Cl_2 (25 mL) and finely dispersed $Na_2S_2O_3 \cdot 5H_2O$ (1 g) were added to the residue. The suspension was vigorously stirred until the formation of a pale-yellow solution. The solution was filtered through a thin layer of silica gel (1 cm), and the solvent was evaporated. The residue was analyzed by TLC by comparing with authentic samples of 1,1-dihydroperoxycyclohexane (**7a**), 1,1-dihydroperoxycycloheptane (**7d**), 1,1′-dihydroperoxydi(cyclohexyl)peroxide (**8a**), 1,1′-dihydroperoxydi(cycloheptyl)peroxide (**8d**), cyclohexane triperoxide (**9a**), and cycloheptane triperoxide (**9d**), and also by ^{1}H and ^{13}C NMR spectroscopy.

2-Iodo-1-methoxycyclohexyl Hydroperoxide (3a)

White or light-yellow crystals; mp 49–51 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07–2.39 [m, 8 H, $(CH_2)_4$], 3.31 (s, 3 H, CH_3O), 4.60–4.73 (m, 1 H, CHI), 8.07 (br s, 1 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 27.6, 29.6 [CI(CH$_2$)$_3$], 32.3 (CI), 33.5 (CH$_2$CO), 48.4 (CH_3O), 104.9 (COOH).

Anal. Calcd for $C_7H_{13}IO_3$: C, 30.90; H, 4.82; I, 46.64. Found: C, 30.67; H, 5.13; I, 46.17.

2-Iodo-1-methoxy-4-methylcyclohexyl Hydroperoxide (3b)

Yellow oil.

IR (CCl_4): 3366 cm^{-1} (OOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.76–2.14 (m, 10 H, $CHCH_3$, CH_2), 3.29 (s, 3 H, CH_3O), 4.61–4.67 (m, 1 H, CHI), 8.19 (br s, 1 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9, 27.5, 27.9, 30.6 (CH, CH_2, CH_3), 31.3 (CHI), 41.2 (CH$_2$COOH), 48.3 (OCH_3), 105.0 (COOH).

Anal. Calcd for $C_8H_{15}IO_3$: C, 33.58; H, 5.28; I, 44.36. Found: C, 33.41; H, 5.19; I, 44.21.

4-*tert*-Butyl-2-iodo-1-methoxycyclohexyl Hydroperoxide (3c)

White or light-yellow crystals; mp 101–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 9 H, CH_3C), 1.19–1.38 [m, 1 H, CHC$(CH_3)_3$], 1.54–2.16 (m, 6 H, CH_2), 3.30 (s, 3 H, CH_3O), 4.71–4.76 (m, 1 H, CHI), 7.93 (br s, 1 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1, 27.6, 27.8, 31.8, 32.6, 34.3 (CH, CH_2, CH_3), 42.9 [CHC$(CH_3)_3$], 48.4 (CH_3O), 105.0 (COOH).

Anal. Calcd for $C_{11}H_{21}IO_3$: C, 40.26; H, 6.45; I, 38.67. Found: C, 40.37; H, 6.20; I, 38.33.

2-Iodo-1-methoxycycloheptyl Hydroperoxide (3d)

White or light-yellow crystals; mp 41–42 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44–2.22 (m, 10 H, CH_2), 3.31 (s, 3 H, CH_3O), 4.69–4.80 (m, 1 H, CHI), 7.91 (s, 1 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 25.5, 26.6, 31.9, 32.2, 36.4 (CH, CH_2), 49.1 (CH_3O), 108.4 (COOH).

Anal. Calcd for $C_8H_{15}IO_3$: C, 33.58; H, 5.28; I, 44.36. Found: C, 33.61; H, 5.36; I, 44.07.

2-Iodo-1-methoxycyclooctyl Hydroperoxide (3e)

Diastereomeric mixture. Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–2.33 (m, 12 H, CH_2), 3.32 (s, 1.2 H, CH_3O), 3.36 (s, 1.8 H, CH_3O), 4.61–4.68 (m, 0.6 H, CHI), 4.86–4.93 (m, 0.4 H, CHI), 8.08 (br s, 0.4 H, OOH), 8.34 (br s, 0.6 H, OOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.6, 25.6, 25.8, 27.2, 27.4, 27.83, 27.89, 29.6, 29.7 (CH_2), 33.8, 36.0 (CHI), 49.8, 50.8 (CH_3O), 106.7, 106.9 (COOH).

Anal. Calcd for $C_9H_{17}IO_3$: C, 36.02; H, 5.71; I, 42.28. Found: C, 36.41; H, 5.35; I, 42.67.

2-Iodo-1-methoxycyclododecyl Hydroperoxide (3f)

Diastereomeric mixture. White or light-yellow crystals; mp 79–81 °C.

IR (CCl_4): 3416 cm^{-1} (OOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–2.17 (m, 20 H, CH_2), 3.42 (s, 1.2 H, CH_3O), 3.63 (s, 1.8 H, CH_3O), 4.22 (d, *J* = 11.0 Hz, 0.6 H, CHI), 4.35 (d, *J* = 11.0 Hz, 0.4 H, CHI), 7.91 (br s, 0.4 H, OOH), 8.41 (br s, 0.6 H, OOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.6, 21.7, 21.8, 21.9, 22.0, 22.5, 22.6, 24.5, 25.2, 25.47, 25.52, 25.91, 25.96, 25.98, 29.1, 31.5, 31.7 (CH_2), 30.4, 33.5 (CHI), 50.4, 51.9 (CH_3O), 104.7, 105.6 (COOH).

Anal. Calcd for $C_{13}H_{25}IO_3$: C, 43.83; H, 7.07; I, 35.62. Found: C, 43.27; H, 6.54; I, 35.25.

1-Butyl-2-iodo-1-methoxypentyl Hydroperoxide (4a)

Diastereomeric mixture. Yellow oil.

IR (CCl_4): 3399 cm^{-1} (OOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74–2.07 (m, 16 H, CH_3, CH_2), 3.39 (s, 2.25 H, CH_3O), 3.40 (s, 0.75 H, CH_3O), 4.27 (dd, *J* = 13.9, 2.9 Hz, 0.75 H, CHI), 4.37–4.48 (m, 0.25 H, CHI), 7.85 (br s, 1 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.1, 13.8 (CH_3), 23.1, 23.2, 23.4, 25.6, 25.9, 29.6, 31.8, 32.2, 36.6, 36.8 (CH_2), 37.6, 38.9 (CHI), 50.3, 51.1 (CH_3O), 106.6 (COOH).

Anal. Calcd for $C_{10}H_{21}IO_3$: C, 37.99; H, 6.69; I, 40.14. Found: C, 38.27; H, 6.43; I, 40.27.

2-Iodo-1-isobutyl-1-methoxy-3-methylbutyl Hydroperoxide (4b)

Diastereomeric mixture. Yellow oil.

IR (CCl_4): 3404 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.73–2.13 [m, 18 H, CH_3, $(CH_3)_2CHCH_2$, CH_2], 3.42 (s, 0.45 H, CH_3O), 3.45 (s, 2.55 H, CH_3O), 4.37 (d, *J* = 2.4 Hz, 0.85 H, CHI), 4.51 (d, *J* = 2.9 Hz, 0.15 H, CHI), 7.91 (br s, 0.15 H, OOH), 8.04 (br s, 0.85 H, OOH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 22.6, 23.8, 23.9, 24.1, 24.6, 24.7, 29.1 [$CH(CH_3)_2$, CH_3, CHI], 40.8, 41.9 (CH_2), 49.5, 51.1 (CH_3O), 107.0 (COOH).

Anal. Calcd for $C_{10}H_{21}IO_3$: C, 37.99; H, 6.69; I, 40.14. Found: C, 37.84; H, 6.47; I, 40.32.

2-Iodocyclohexanone (5a)[18]
Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–2.46 (m, 7 H, CH_2, *H*CHCO), 3.02–3.33 (m, 1 H, HC*H*CO), 4.55–4.81 (m, 1 H, CHI).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 26.6, 32.4, 36.3, 37.2, 204.6.

2-Iodo-4-methylcyclohexanone (5b)[19]
Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92–2.39 (m, 9 H, CH_3, CH_2, *H*CHCO, CH_3CH), 3.26–3.40 (m, 1 H, HC*H*CO), 4.54–4.59 (m, 1 H, CHI).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 27.4, 29.9, 34.5, 34.6, 43.6, 205.5.

4-*tert*-Butyl-2-iodocyclohexanone (5c)[20]
Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (s, 9 H, CH_3C), 1.16–2.36 (m, 6 H, CH_2, CHC, *H*CHCO), 3.10–3.40 (m, 1 H, HC*H*CO), 4.61–4.67 (m, 1 H, CHI).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.3, 27.5, 29.6, 31.1, 34.8, 36.8, 42.1, 205.7.

2-Iodocycloheptanone (5d)[10b]
Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–2.48 (m, 9 H, CH_2, *H*CHCO), 2.84–2.98 (m, 1 H, HC*H*CO), 4.54 (dd, *J* = 16.1, 5.9 Hz, 1 H, CHI).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 28.3, 29.3, 32.21, 35.5, 38.2, 207.4.

2-Iodocyclooctanone (5e)[10b]
Yellow oil.

IR (CCl_4): 1692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–2.02 (m, 9 H, CH_2, *H*CHCO), 2.22–2.59 (m, 2 H, CH_2CH_2CO), 2.89–3.04 (m, 1 H, HC*H*CO), 4.68 (dd, *J* = 16.1, 3.7 Hz, 1 H, CHI).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 25.3, 29.4, 29.7, 33.9, 34.1, 35.0, 209.7.

2-Iodocyclododecanone (5f)[18]
White or pale-yellow crystals; mp 48–50 °C (Lit.[18] mp 52–52.5 °C).

IR (CCl_4): 1702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–2.03 (m, 17 H, CH_2, *H*CHCO), 2.37–2.58 (m, 2 H, CH_2CH_2CO), 2.90–3.02 (m, 1 H, HC*H*CO), 4.68 (dd, *J* = 16.1, 3.7 Hz, 1 H, CHI).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.3, 24.20, 24.24, 24.4, 25.05, 25.12, 25.7, 28.1, 35.0, 36.4, 205.9.

4-Iodononan-5-one (6a)[21]
Yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78–0.99 (m, 6 H, CH_3), 1.13–1.98 (m, 8 H, $CH_2CH_2CH_3$), 2.47–2.88 (m, 2 H, CH_2CO), 4.42 (t, *J* = 14.7, 7.3 Hz, 1 H, CHI).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.2, 13.8, 22.1, 22.6, 26.4, 32.6, 36.3, 38.5, 204.8.

3-Iodo-2,6-dimethylheptan-4-one (6b)
Yellow oil.

IR (CCl_4): 1706 (C=O) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.76–1.24 (m, 12 H, CH_3), 1.89–2.28 [m, 2 H, $CH(CH_3)_2$], 2.49–2.61 (m, 2 H, CH_2), 4.20 (d, *J* = 8.79 Hz, 1 H, CHI).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1, 22.1, 22.4, 23.5, 24.3, 30.8, 44.7, 48.4, 204.0.

Anal. Calcd for $C_9H_{17}IO$: C, 40.31; H, 6.39; I 47.33. Found: C, 40.54; H, 6.15; I, 47.80.

Acknowledgment

This work was supported by the Program for Support of Leading Scientific Schools of the Russian Federation (Grant NSh 2942.2008.3) and an RFBR grant (project No. 10-03-91220-CT).

References

(1) (a) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487. (b) Borstnik, K.; Paik, I.-H.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661. (c) Dussault, P. H.; Lee, I. Q.; Lee, H. J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. *J. Org. Chem.* **2000**, *65*, 8407. (d) Jin, H.-X.; Liu, H.-H.; Zhang, Q.; Wu, Y. *Tetrahedron Lett.* **2005**, *46*, 5767. (e) McCullough, K. J.; Wood, J. K.; Bhattacharjee, A. K.; Dong, Y.; Kyle, D. E.; Milhous, W. K.; Vennerstrom, J. L. *J. Med. Chem.* **2000**, *43*, 1246. (f) Wu, Y.-L.; Li, Y. *Med. Chem. Res.* **1995**, *5*, 569. (g) Jin, H.-X.; Zhang, Q.; Kim, H.-S.; Wataya, Y.; Liu, H.-H.; Wu, Y. *Tetrahedron* **2006**, *62*, 7699. (h) Bernat, V.; André-Barrès, C.; Baltas, M.; Saffon, N.; Vial, H. *Tetrahedron* **2008**, *64*, 9216. (i) Šolaja, B. A.; Terzić, N.; Pocsfalvi, G.; Gerena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. *J. Med. Chem.* **2002**, *45*, 3331. (j) Atheaya, H.; Khan, S. I.; Mamgain, R.; Rawat, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1446. (k) Sabbani, S.; Stocks, P. A.; Ellis, G. L.; Davies, J.; Hedenstrom, E.; Ward, S. A.; O'Neill, P. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5804.

(2) (a) Amewu, R.; Stachulski, A. V.; Ward, S. A.; Berry, N. G.; Bray, P. G.; Davies, J.; Labat, G.; Vivas, L.; O'Neill, P. M. *Org. Biomol. Chem.* **2006**, *4*, 4431. (b) Dong, Y.; Tang, Y.; Chollet, J.; Matile, H.; Wittlin, S.; Charman, S. A.; Charman, W. N.; Tomas, J. S.; Scheurer, C.; Snyder, C.; Scorneaux, B.; Bajpai, S.; Alexander, S. A.; Wang, X.; Padmanilayam, M.; Cheruku, S. R.; Brun, R.; Vennerstrom, J. L. *Bioorg. Med. Chem.* **2006**, *14*, 6368. (c) Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 459.

(3) (a) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Mini-Rev. Med. Chem.* **2007**, *7*, 571. (b) Jung, M.; Kim, H.; Lee, K.; Park, M. *Mini-Rev. Med. Chem.* **2003**, *3*, 159. (c) Kim, J.; Park, E. J. *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 485. (d) Dembitsky, V. M. *Eur. J. Med. Chem.* **2008**, *43*, 223. (e) Terzić, N.; Opsenica, D.; Milić, D.; Tinant, B.; Smith, K. S.; Milhous, W. K.; Šolaja, B. A. *J. Med. Chem.* **2007**, *50*, 5118.

(4) (a) Žmitek, K.; Zupan, M.; Iskra, J. *Org. Biomol. Chem.* **2007**, *5*, 3895. (b) Žmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *J. Org. Chem.* **2007**, *72*, 6534. (c) Kumar, N.; Khan, S. I.; Sharma, M.; Atheaya, H.; Rawat, D. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1675.

(5) Terent'ev, A. O.; Krylov, I. B.; Borisov, D. A.; Nikishin, G. I. *Synthesis* **2007**, 2979.

(6) Terent'ev, A. O.; Platonov, M. M.; Krylov, I. B.; Chernyshev, V. V.; Nikishin, G. I. *Org. Biomol. Chem.* **2008**, *6*, 4435.

(7) Terent'ev, A. O.; Platonov, M. M.; Krylov, I. B.; Nikishin, G. I. *Russ. Chem. Bull.* **2009**, in press; *Izv. Akad. Nauk, Ser. Chim.* **2009**, 333 (in Russian).

(8) Jereb, M.; Zupan, M.; Stavber, S. *Green Chem.* **2005**, *7*, 100.

(9) (a) Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* **2004**, 1869. (b) Kim, M. M.; Ruck, R. T.; Zhao, D.; Huffman, M. A. *Tetrahedron Lett.* **2008**, *49*, 4026. (c) Pavlinac, J.; Zupan, M.; Stavber, S. *Synthesis* **2006**, 2603.

(10) (a) Jereb, M.; Zupan, M.; Stavber, S. *Chem. Commun.* **2004**, 2614. (b) Barluenga, J.; Marco-Arias, M.; G onzález-Bobes, F.; Ballesteros, A.; González, J. M. *Chem. Commun.* **2004**, 2616. (c) Jereb, M.; Iskra, J.; Zupan, M.; Stavber, S. *Lett. Org. Chem.* **2005**, *2*, 465.

(11) Terent'ev, A. O.; Borisov, D. A.; Krylov, I. B.; Nikishin, G. I. *Synth. Commun.* **2007**, *37*, 3151.

(12) Gaikwad, D. D.; Dake, S. A.; Kulkarni, R. S.; Jadhav, W. N.; Kakde, S. B.; Pawar, R. P. *Synth. Commun.* **2007**, *37*, 4093.

(13) Ferreira, S. B.; Kaiser, C. R.; Ferreira, V. F. *Synlett* **2008**, 2625.

(14) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

(15) Terent'ev, A. O.; Platonov, M. M.; Sonneveld, E. J.; Peschar, R.; Chernyshev, V. V.; Starikova, Z. A.; Nikishin, G. I. *J. Org. Chem.* **2007**, *72*, 7237.

(16) (a) Bray, W. C.; Liebhafsky, H. A. *J. Am. Chem. Soc.* **1931**, *53*, 38. (b) Liebhafsky, H. A.; Wu, L. S. *J. Am. Chem. Soc.* **1974**, *96*, 7180. (c) Schmitz, G. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4741.

(17) (a) Terent'ev, A. O.; Chodykin, S. V. *Centr. Eur. J. Chem.* **2005**, *3*, 417. (b) *Dictionary of Organic Compounds*; Chapman & Hall: New York, **1982**. (c) *Dictionary of Organic Compounds*, Suppl.; Chapman & Hall: New York, **1983-1988**, 1–6.

(18) Ruhottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731.

(19) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.

(20) Dolenc, D. *Synth. Commun.* **2003**, *33*, 2917.

(21) Horiuchi, C. A.; Ji, S.-J.; Matsushita, M.; Chai, W. *Synthesis* **2004**, 202.