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Mechanism and Selectivity of Radical Alkylation of 3,4-Dichloro-2,5-dihydrofuran-2,5-dione

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Abstract—The mechanism of radical alkylation of 3,4-dichloro-2,5-dihydrofuran-2,5-dione with cyclohexane and 2,3-dimethylbutane follows an addition–elimination pattern with reversible formation of alkyl radicals. The proposed kinetic scheme takes into account the possibility for isomerization of primary 2,3-dimethylbutane radicals into tertiary and is consistent with the experimental data. The regioselectivity of the process is linearly related to the concentration of hydrogen chloride, so that the rate constant for the addition of primary 2,3-dimethylbutane radical to 3,4-dichloro-2,5-dihydrofuran-2,5-dione may be estimated. Effective procedures for the synthesis of 3-chloro-4-(2,3-dimethylbut-2-yl)-, 3-chloro-4-cyclohexyl-, and 3,4-dicyclohexyl-2,5-dihydrofuran-2,5-diones have been proposed.

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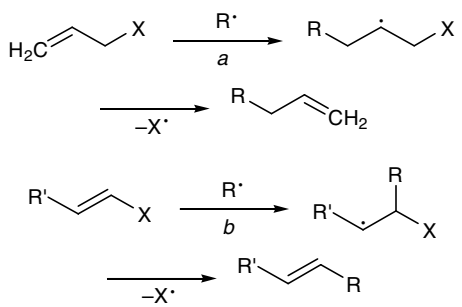
At present, radical reactions attract increased interest from the viewpoint of building up new carbon–carbon bonds, and they are extensively used in synthetic organic chemistry [1]. Widely used reagents for radical reactions are organotin compounds; examples are radical addition or allylation (Scheme 1, reaction *a*, X = $SnBu_3$) [2]. However, toxicity and high cost of organotin compounds, difficulties in their preparation and purification, and complex procedures for treatment of reaction mixtures strongly restrict application of such procedures on an enlarged scale [3]. Therefore, approaches that are free from the above disadvantages are extensively developed in the recent years. Among these, the most promising are based on the known radical addition–elimination sequence (Scheme 1).

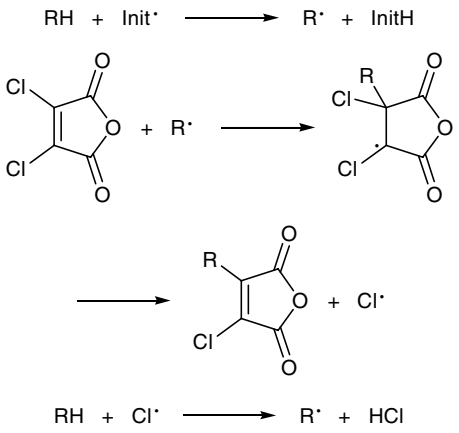
For example, synthetic procedures for radical alkylation of allyl sulfones (Scheme 1, reaction *a*, X = SO_2R) [4, 5], vinyl sulfones (reaction *b*, X = SO_2Alk) [6], and nitrostyrenes (reaction *b*, R′ = Ar, X = NO_2) [7, 8] and addition of *S*,*O*-dialkyl dithiocarbonates to olefins [9, 10] have been proposed, and mechanisms of these reactions have been studied in detail. Addition–elimination processes involving 2,3-dichloro-2,5-dihydrofuran-2,5-dione [11–13], tetrachloroethylene [14, 15], trichloroethylene [11, 14, 15], 1,2-dichloroethylene [14–16], chloranil, and 2,4,6-trichloro-1,3,5-triazine [11] as chlorovinyl substrates were also studied (reaction *b*, X = Cl). However, these studies were concerned with synthetic aspects of reactions of chlorovinyl compounds, while we were aimed at elucidating detailed mechanism of the radical addition–elimination process. As model substrate we selected 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**), taking into account that potential reaction products, 3,4-dialkyl-2,5-dihydrofuran-2,5-diones, are important intermediate compounds in the synthesis of biologically active furan-2(5*H*)-ones (e.g., maculalactones) [17]. In addition, alkylchlorofurandiones are readily converted into the corresponding alkylchloropyrrolediones that are convenient intermediate products in the synthesis of various disubstituted pyrrole-2,5-diones [18].

Scheme 1.



Scheme 2 shows the mechanism proposed by Araneo et al. [11] for alkylation of compound **I** in the presence of calcium carbonate. It was presumed that the process is chain-like and that alkyl radicals R˙ are

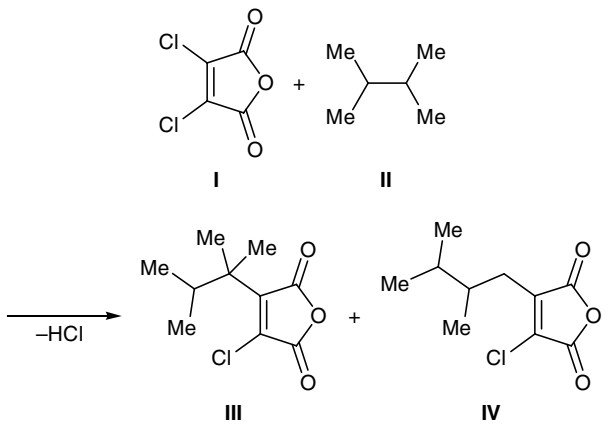
Scheme 2.



InitH is initiator.

generated by abstraction of hydrogen from the RH hydrocarbon with chlorine atom. The last chain propagation step is the same as in the radical chlorination of alkanes. Therefore, the regioselectivity in the alkylation of furandione **I** should coincide with that observed in the chlorination of the corresponding alkane RH. According to the data of [11], the reaction of **I** with 2,3-dimethylbutane (**II**) in the presence of calcium carbonate gives a mixture of 3-chloro-4-(1,1,2-trimethylpropyl)- and 3-chloro-4-(2,3-dimethylbutyl)-2,5-dihydrofuran-2,5-diones **III** and **IV** at a ratio of about 1:1 (Scheme 3), whereas the regioselectivity in the chlorination of 2,3-dimethylbutane (**II**) with molecular chlorine is equal to 0.66 (ratio of 2-chloro-2,3-dimethylbutane to 1-chloro-2,3-dimethylbutane) [19].

Scheme 3.



With a view to examine the mechanism of radical alkylation of dichloride **I** in more detail, first of all we tried various initiation versions using the reaction of **I** with cyclohexane as an example (Table 1). The reactions were carried out at room temperature or under reflux in the presence of the most commonly used chemical initiators and initiating systems. The progress of reactions was monitored by GLC following accumulation of 3-chloro-4-cyclohexyl-2,5-dihydrofuran-2,5-dione; the latter was preliminarily isolated in the reaction initiated by benzoyl peroxide. The kinetic chain length was estimated as the yield of the alkylation product per mole of initiator, taking into account

Table 1. Reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with cyclohexane under different initiation modes

Run no.	**I**, mmol	Substrate (ml)–solvent (ml)	Initiator (mol %)[a]	Temperature, °C (irradiation)	Time, h	Yield,[b] %
1	2.0	C_6H_{12} (10)	$(BzO)_2$ (10)	80	1	59
2	1.5	C_6H_{12} (4)	AIBN[c] (10)	80	1	27
3	1.5	C_6H_{12} (7)	$[(CH_3)_2NCS_2]_2$ (5)	80	1	0.042
4	1.5	C_6H_{12} (3)–$CHCl_3$ (3)–CH_3CN (4)	[*c*-HexCo(dmgH)$_2$Py] (5)	20 (*hν*)	1.5	12
5	1.0	C_6H_{12} (3)–$CHCl_3$ (3)	$PhICl_2$ (10)[d]	20 (*hν*)	1	7.5
6	1.0	C_6H_{12} (3)–$CHCl_3$ (3)	$PhICl_2$ (5×2)[d]	20 (*hν*)	5×0.3	23
7	1.0	C_6H_{12} (3)–$CHCl_3$ (3)	$PhICl_2$ (20×0.5)[d]	20 (*hν*)	20×0.25	23
8	2.0	C_6H_{12} (4)–$CHCl_3$ (4)	Cl_2 (250)[e]	20 (*hν*)	2.5	65

[a] Relative to compound **I**.

[b] Calculated on the initial compound **I** from the GLC data.

[c] AIBN is 2,2′-azobis(isobutyronitrile).

[d] (Dichloro-λ^3-iodanyl)benzene was added in 10, 2, and 0.5% portions, respectively.

[e] Chlorine was slowly passed through the reaction mixture in a stream of argon (the latter was bubbled through a saturated solution of chlorine in carbon tetrachloride).

that the half-decomposition period of benzoyl peroxide is 3.03 h in cyclohexane at 80°C [20], and of azobis(isobutyronitrile) (AIBN) in toluene at 80°C, 1.20 h [20]. We found that, despite chain character of the alkylation of **I**, the chains are rather short: their length is ~10. The most effective thermal initiators were benzoyl peroxide and AIBN, in keeping with published data [11, 12]. For comparison, the kinetic chain length in the radical addition–elimination reaction of cyclohexane with cyanogen chloride, initiated by benzoyl peroxide (98°C), is ~11 [21]. Published data on the alkylation of **I** under photochemical initiation are very scanty: only biacetyl was used as photosensitizer, and the reaction time varied from 24 to 120 h. Our experiments showed (Table 1, run nos. 4–8) that photoinitiation may be effective in the presence of both bis(dimethylglyoximato)(pyridine)cyclohexylcobalt(III) [*c*-HexCo(DmgH)$_2$Py] and chlorinating agents [(dichloro-λ^3-iodanyl)benzene or molecular chlorine]. In the latter case, the concentration of the chlorinating agent should be maintained at a low level to minimize side transfer of chlorine to alkyl radical R. This is achieved by as slow as possible addition of the chlorinating agent to the reaction mixture (Table 1, run nos. 5–7).

Important results were obtained while studying factors affecting the selectivity in the alkylation of compound **I** with 2,3-dimethylbutane (**II**). All reactions with alkane **II** were carried out in sealed ampules in the presence of an internal standard. The selectivity was calculated as the product ratio determined from the GLC data; the products were preliminarily identified by NMR spectroscopy. Compound **III** was isolated as individual substance. We revealed an important relation: in the absence of potassium carbonate, the selectivity in the alkylation of **I** increases in parallel with its conversion (Table 2). Therefore, we concluded that the selectivity depends on the concentration of hydrogen chloride in the reaction system and that rise in the HCl concentration favors formation of tertiary radical addition product **III**. It is known that, in the general case, the existence of a dependence of selectivity on the conversion indicates complex mechanism of the process (some parameters of the reaction system, affecting the selectivity, are not fixed). An analogous effect of HCl on the regioselectivity of radical addition–elimination was described in [21] for the reaction of cyanogen chloride with alkanes (Scheme 4) [21]. For example, the selectivity in the reaction of cyanogen chloride with hexane (ratio of the secondary and primary alkyl cyanides) attained a value of more than 150. The authors proved that increase in the regioselectivity with rise in HCl concentration is related to reversibility of hydrogen transfer from alkane to chlorine.

Table 2. Effect of the conversion on the selectivity of the reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with 2,3-dimethylbutane (**II**)[a]

Solvent	Additive	Reaction time, h	Conversion,[b] %	Selectivity
$CHCl_3$	–	1	11	1.9
		2	19	2.6
		3[c]	29	3.2
		4	36	4.0
$CHCl_3$	K_2CO_3[d]	1	14	1.1
		2	22	1.1
		3[c]	34	1.1
		4	43	1.2
$(CH_2Cl)_2$–CH_3CN[e]	HCl (0.47 M)	0.25	1.85	10.8
		0.5	3.3	10.0
		1	6.3	10.5
		2	11.6	10.4
		3	16.1	10.9

[a] Reactant concentrations, M: **I**, 0.25, **II**, 2.88, $(BzO)_2$, 0.02 (8%); $CHCl_3$, 1 ml; 80°C.

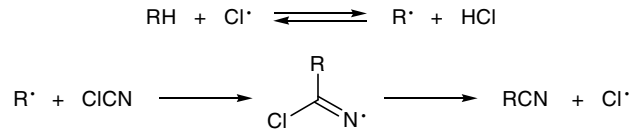
[b] Hereinafter, the conversion is defined as the overall amount of alkylation products (primary and tertiary) in mol % relative to dichloride **I**.

[c] An additional 0.1 mmol of $(BzO)_2$ was added.

[d] 200 mg.

[e] $[(CH_2Cl)_2] = 3.17$, $[CH_3CN] = 7.19$ M.

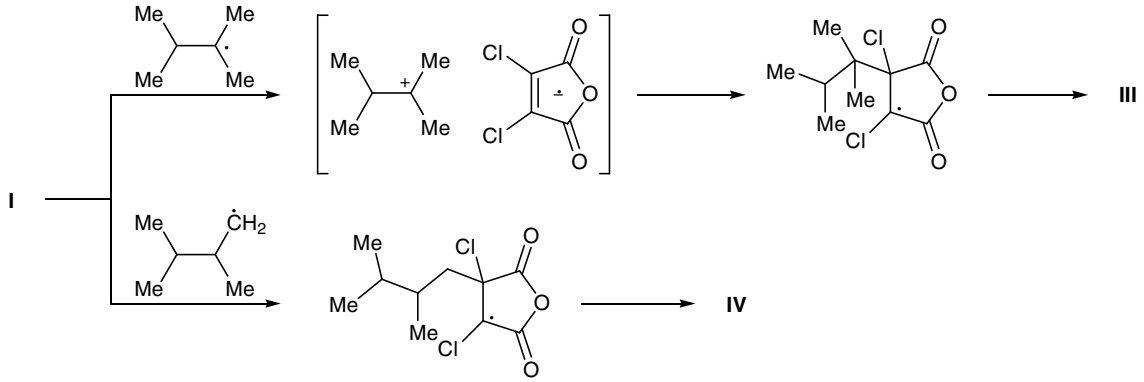
Scheme 4.



We analyzed the dependence of the regioselectivity in the alkylation of compound **I** on the concentration of HCl in two ways: (1) in terms of a radical ion mechanism and (2) in terms of reversibility of elementary steps in the assumed radical mechanism.

It is known that dichloride **I** is a strong one-electron oxidant (*EA* = 1.90 eV [22]). Therefore, it is quite probable that the addition of nucleophilic tertiary alkyl radical to molecule **I** involves a polar transition state (radical ion intermediate in the limiting case); by con-

Scheme 5.



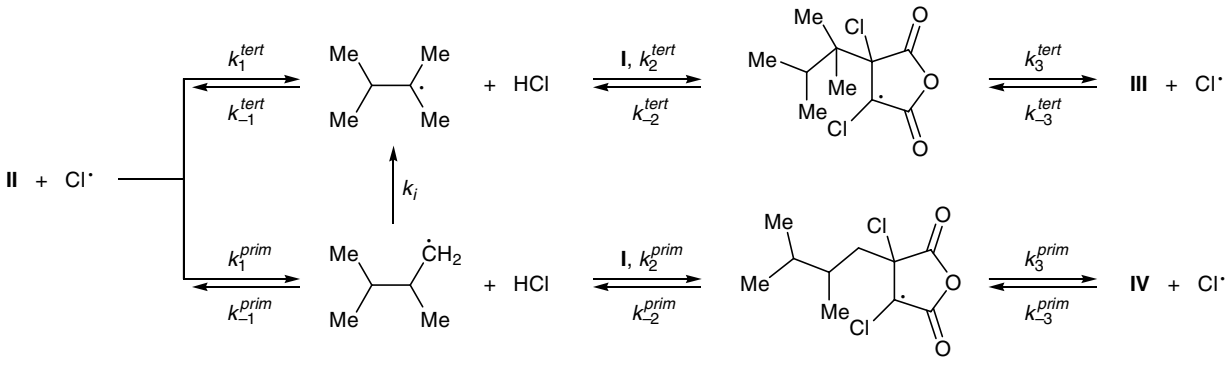
trast, primary radical reacts with **I** following a common radical addition pattern through a relatively weakly polar transition state (Scheme 5). Then, added acid should solvate more polar transition state in a specific mode, and polar solvents, in a nonspecific mode; i.e., addition of tertiary radical to compound **I** should be accelerated, and the selectivity of the alkylation should increase.

We examined the effect of acids and polar solvent (CH_3CN) on the selectivity in the reaction of dichloride **I** with alkane **II** (Table 3). The results showed that addition of acetonitrile or trifluoroacetic acid only slightly affects the selectivity (cf. the data in Table 2). These data are not consistent with the radical ion mechanism of addition of alkyl radicals to compound **I**. Another interpretation of the dependence of the selectivity on the HCl concentration is based on the kinetic scheme shown in Scheme 6, which assumes both reversibility of all steps of the process and possible isomerization of primary radicals into tertiary. Taking into account published data, the step of addition of nucleophilic alkyl radicals to electrophilic double carbon–carbon bond at moderate temperatures can be regarded as irreversible [23]; therefore, $k_3^{\text{tret}} >> k_{-2}^{\text{tert}}$ and $k_3^{\text{prim}} >> k_{-2}^{\text{prim}}$. The low reactivity of electrophilic chlorine atom toward C=C bond [24, 25] in combination with the high rate of the subsequent reaction of chlorine atom with alkane molecule **II** suggests that the β-decomposition step is also irreversible (k_3^{tert}, k_3^{prim}).

The isomerization of primary alkyl radicals into tertiary ($R^{\cdot}_{\text{prim}} + RH \rightarrow R^{\cdot}_{\text{tert}} + RH$) was included in Scheme 6, for in some rare cases this process affects the kinetics of radical transformations of alkane **II**. The absolute rate constant k_i of the isomerization step was measured by ESR spectroscopy using decomposition of pentanoyl peroxide in 2,3-dimethylbutane (**II**) as model system; it is 4×10^3 l mol^{-1} s^{-1} at 353 K (calculated on a single hydrogen atom) [26]. If [**II**] >> [**I**], the contribution of the isomerization process may become quite appreciable.

There are no published data on absolute rate constants (k_{-1}) and equilibrium constants for liquid-phase reactions of alkyl radicals with HCl. The use of the corresponding data for gas-phase reactions is inappropriate because of considerable disagreement between the experimental and calculated constants obtained by different authors [27]. We estimated the absolute rate constants k_{-1}^{tert} and k_{-1}^{prim} on the basis of the H–Cl and C–H bond dissociation energies: E_{dis}(H–Cl) = 432,

Scheme 6.



$E_{dis}(R_{prim}–H)$ = 417.2 (propane), $E_{dis}(R_{tert}–H)$ = 390.2 kJ/mol (2-methylpropane) [28]. Then, the heat effects of hydrogen abstraction from the primary and tertiary carbon atoms in molecule **II** by chlorine atom are ΔH_{tert} = –41.8 and ΔH_{prim} = –14.8 kJ/mol. Assuming (as a rough approximation) that the main contribution to ΔG for the step of hydrogen transfer by chlorine is given by the enthalpy factor, $\Delta G \approx \Delta H = -RT\ln K$ (R = 8.314 J mol^{-1} K^{-1}, T = 353.15 K), we calculated the equilibrium constants $K_{tert} = 1.52\times10^6$ and $K_{prim} = 1.55\times10^2$ (353.15 K). The absolute rate constants for chlorination of alkane **II** were measured in [19] by laser flash photolysis at 300 K: $k_1^{tert} = 6.5\times10^8$, $k_1^{prim} = 1.67\times10^8$ l mol^{-1} s^{-1} (calculated on a single hydrogen atom). On the basis of these data we estimated the rate constants $k_{-1}^{tert} = 4.3\times10^2$ and $k_{-1}^{prim} = 1.1\times10^6$ l mol^{-1} s^{-1} (on a single hydrogen atom). Comparison of the above estimates of k_{-1} with k_2 values (10^4–10^8 l mol^{-1} s^{-1} [11]) shows that the reaction of primary alkyl radical with HCl, leading to regeneration of initial alkane **II** and chlorine atom, should successfully compete with the addition to compound **I**; on the other hand, the reaction of tertiary alkyl radical with HCl may be neglected. This means that addition of hydrogen chloride to the reaction mixture will favor more effective back transformation of primary radicals into compound **II**, the concentration of tertiary radicals remaining unchanged; as a result, the selectivity in the alkylation of dichloride **I** should increase.

$$\frac{\partial[R^{\cdot}_{prim}]}{\partial\tau} = 12k_1^{prim}[RH][Cl^{\cdot}] - k_{-1}^{prim}[R^{\cdot}_{prim}][HCl] - k_2^{prim}[R^{\cdot}_{prim}][\mathbf{I}] - 2k_i[R^{\cdot}_{prim}][RH] = 0; \quad (1)$$

$$\frac{\partial[R^{\cdot}_{tert}]}{\partial\tau} = 2k_1^{tert}[RH][Cl^{\cdot}] - k_{-1}^{tert}[R^{\cdot}_{tert}][HCl] - k_2^{tert}[R^{\cdot}_{tert}][\mathbf{I}] + 2k_i[R^{\cdot}_{prim}][RH] = 0; \quad (2)$$

$$[R^{\cdot}_{prim}] = \frac{12k_1^{prim}[RH][Cl^{\cdot}]}{k_{-1}^{prim}[HCl] + k_2^{prim}[\mathbf{I}] + 2k_i[RH]}; \quad (3)$$

$$[R^{\cdot}_{prim}] = \left(\frac{12k_1^{prim}[RH]}{k_{-1}^{prim}[HCl] + k_2^{prim}[\mathbf{I}] + 2k_i[RH]} + \frac{k_1^{tert}}{k_i}\right) \times \frac{2k_i[RH][Cl^{\cdot}]}{k_{-1}^{tert}[HCl] + k_2^{tert}[\mathbf{I}]}; \quad (4)$$

$$S_{app} = \frac{[\mathbf{III}]}{[\mathbf{IV}]} = \frac{k_2^{tert}[R^{\cdot}_{tert}][\mathbf{I}]}{k_2^{prim}[R^{\cdot}_{prim}][\mathbf{I}]} = \frac{1}{6}\frac{k_2^{tert}k_1^{tert}}{k_2^{prim}k_1^{prim}} \times \frac{k_{-1}^{prim}[HCl] + k_2^{prim}[\mathbf{I}] + 2k_i[RH] + 12(k_1^{prim}k_i/k_1^{tert})[RH]}{k_{-1}^{tert}[HCl] + k_2^{tert}[\mathbf{I}]}. \quad (5)$$

Let us analyze the selectivity in the reaction between compounds **I** and **II** on a quantitative level. Application of the quasistationary concentration principle [Eqs. (1), (2)] gives expressions (3) and (4) for the stationary concentrations of alkyl radicals. Substituting [R] into the expression for the apparent selectivity (S_{app}) gives (after algebraic transformations) formula (5). If the reaction system contains hydrogen chloride traps ([HCl] = 0) or inequalities $k_2^{prim}[\mathbf{I}] + 2k_i[RH] + 12(k_1^{prim}k_i/k_1^{tert})[RH] >> k_{-1}^{prim}[HCl]$ and $k_2^{tert}[\mathbf{I}] >> k_{-1}^{tert}[HCl]$ are fulfilled, the apparent selectivity should tend to

$$S_{app} = \frac{1}{6}\frac{k_1^{tert}}{k_1^{prim}} + \frac{k_i[RH]}{k_2^{prim}[\mathbf{I}]}\left(2 + \frac{k_1^{tert}}{3k_1^{prim}}\right). \quad (6)$$

Under the additional constraint $[RH]\to 0$ or $k_i[RH] << k_2^{prim}[I]$ it attains its minimal value:

$$S_{app} = \frac{1}{6}\frac{k_1^{tert}}{k_1^{prim}}. \quad (7)$$

This limiting expression is similar to the formula reflecting the selectivity of radical chlorination of alkane **II** with molecular chlorine. Thus at early steps of the reaction of compound **I** with alkane **II** (i.e., at a low conversion), as well as in the presence of hydrogen chloride acceptor (potassium carbonate), the apparent selectivity should be similar to the selectivity in the photochemical chlorination of alkane **II** with molecular chlorine in an open system, where the hydrogen abstraction step is irreversible (S_{app} = 0.66 at 300 K) [19]. The real selectivity in the alkylation of **I** in the presence of HCl acceptor is 0.9–1.2, according to both our data (Table 2) and those given in [11]. In

Table 3. Effect of acids on the selectivity of the reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with 2,3-dimethylbutane (**II**)[a]

Solvent	Additive	Reaction time, h	Conversion, %	Selectivity
CH_3CN–$(CH_2Cl)_2$	–	1	24	2.6
CH_3CN–$(CH_2Cl)_2$	K_2CO_3[b]	3	26	0.94
CH_3CN– $(CH_2Cl)_2$	HCl[c]	1	22	6.0
Alkane **II**	CF_3COOH[d]	2	11	2.3

[a] Amounts of the reactants: **I**, 1 mmol; benzoyl peroxide, 0.1–0.2 mmol; K_2CO_3, 200 mg; compound **II**, 1 ml; solvent, 2 ml; temperature 80°C.
[b] 200 mg.
[c] [HCl] = 0.4 M.
[d] [CF_3COOH] = 0.6 M.

Table 4. Effect of the concentration of compound **I** on the selectivity of its reaction with 2,3-dimethylbutane (**II**) in the absence of hydrogen chloride

[**I**], M	[**II**], M	Conversion, %	Selectivity
0.3	6.9	12.5	0.9
0.01	6.9	40	1.1
0.0025	6.9	15	1.9

[a] $(BzO)_2$, 10 mol % relative to **I**; 80°C, 1 h at [**I**] = 0.3 M or 6 h at [**I**] = 0.01 and 0.0025 M; $CaCO_3$ was used as HCl acceptor, and acetonitrile was added.

addition, we found that S_{app} does not depend on the concentration of alkane **II** over a wide range (Table 4) at a typical concentration of **I** (0.25–0.3 M) in the presence of calcium carbonate. This means that the inequality $k_i[RH] << k_2^{prim}[\mathbf{I}]$ is valid within the above concentration range of dichloride **I** and that the reaction selectivity in the presence of $CaCO_3$ (K_2CO_3) is described by Eq. (7); i.e., the mechanism of alkylation of compound **I** corresponds to simplified Scheme 2 [11]. Slightly increased selectivity compared to the chlorination of alkane **II** is likely to be related to participation of phenyl radicals arising from decomposition of the initiator at the hydrogen abstraction step. The selectivity S_{app} for the reaction of phenyl radicals with compound **II** is equal to 7.6 (318 K) [29]. As noted above, the kinetic chain length in the examined process is about 10; therefore, a 5–10% contribution of phenyl radicals at the hydrogen abstraction step should give rise to an overestimated value of S_{app} (~1) which corresponds to the experimental data. Increased selectivity in the alkylation of **I** can also result from limited efficiency of carbonates as heterogeneous HCl acceptor.

As follows from Eq. (6), the selectivity depends on the concentration of alkane **II**, and this dependence should be given by a straight line with a slope described by Eq. (8):

$$\tan\alpha = \frac{k_i}{k_2^{prim}[\mathbf{I}]}\left(2 + \frac{k_1^{tert}}{3k_1^{prim}}\right). \quad (8)$$

In order to determine $\tan\alpha$, we performed experiments at reduced concentrations of dichlorde **I**. The data in Table 4 show that decrease in [**I**] leads to increased selectivity. However, when the concentration of **I** is smaller than 0.01 M, the error in the determination of selectivity (and hence of $\tan\alpha$) is large; therefore, the obtained data cannot be used to calculate k_2^{prim}.

Another limiting case of Eq. (5) is achieved when the inequalities $k_2^{prim}[\mathbf{I}] + 2k_i[RH] + 12(k_1^{prim}k_i/k_1^{tert}) \times [RH] << k_{-1}^{prim}[HCl]$ and $k_2^{tert}[\mathbf{I}] << k_{-1}^{tert}[HCl]$ are fulfilled. Then, the expression for the selectivity is simplified to formula (9):

$$S_{app} = \frac{1}{6}\frac{K_1^{tert}k_2^{tert}}{K_1^{prim}k_2^{prim}}. \quad (9)$$

Equation (9) characterizes the highest possible (or equilibrium) selectivity. On the basis of our estimates of the equilibrium and rate constants, the maximal selectivity should be ~1.6×10^3 (at $k_2^{tert} \approx k_2^{prim}$). However, such a high selectivity is unattainable because of limited solubility of hydrogen chloride in the reaction mixture.

Analysis of Eq. (5) in the hydrogen chloride concentration range from 0 to 0.7 M makes it possible to estimate k_2^{prim} in an alternative mode. Formula (5) can be simplified as follows. Insofar as k_{-1}^{tert} (4.28×10^2 l mol^{-1} s^{-1}) << k_2^{tert} (10^4–10^8 l mol^{-1} s^{-1}) and the concentrations of HCl and compound **I** are comparable, the inequality $k_2^{tert}[\mathbf{I}] >> k_{-1}^{tert}[HCl]$ is valid, and the reaction of tertiary radical with HCl can be neglected. Additional exclusion of the contribution of isomerization of alkyl radicals at [**I**] = 0.25 M (in this case, the selectivity does not depend on [**II**]; see Table 4) leads (after some transformations) to Eq. (10).

$$S_{app} = \frac{1}{6}\frac{k_1^{tert}(k_{-1}^{prim}[HCl] + k_2^{prim}[\mathbf{I}])}{k_2^{prim}k_1^{prim}[\mathbf{I}]} = \frac{1}{6}\frac{k_1^{tert}}{k_1^{prim}} + \frac{1}{6}\frac{k_1^{tert}k_{-1}^{prim}[HCl]}{k_2^{prim}k_1^{prim}[\mathbf{I}]}. \quad (10)$$

Thus the selectivity should be linearly related to the concentration of HCl at a fixed concentration of **I** (i.e., at low conversions). Figure shows the plot of selectivity versus HCl concentration over a wide range of the latter. From the good linear correlation between S_{app} and [HCl] ($S_{app} = a[HCl] + b$, $a = 21.1\pm1.2$, $b = 0.74\pm0.43$, $R = 0.98$) and $k_1^{tert} = 6.5\times10^8$, $k_1^{prim} = 1.67\times10^8$, $k_{-1}^{prim} = 1.1\times10^6$ l mol^{-1} s^{-1}, and [**I**] = 0.25 M we obtained the rate constant of the addition of primary alkyl radicals to molecule **I**: $k_2^{prim} = 1.4\times10^5$ l mol^{-1} s^{-1}. This value well fits the range of rate constants for addition of alkyl radicals to electron-deficient double bonds, given in [11]: k_2^{prim} ~10^4–10^8 l mol^{-1} s^{-1}. However, the k_2^{prim} value obtained by us should be regarded only as a rough estimate, for the k_{-1}^{prim} value was determined on the assumption that the entropy in the corresponding elementary step of the process does not change.

According to Eq. (10), increase in the concentration of **I** should lead to reduced selectivity. In fact, as follows from the data in Table 5, the selectivity sharply decreases as the concentration of **I** rises, the concentration of HCl being constant. At a fixed concentration of hydrogen chloride, [HCl] = 0.51 M, Eq. (11) should be fulfilled:

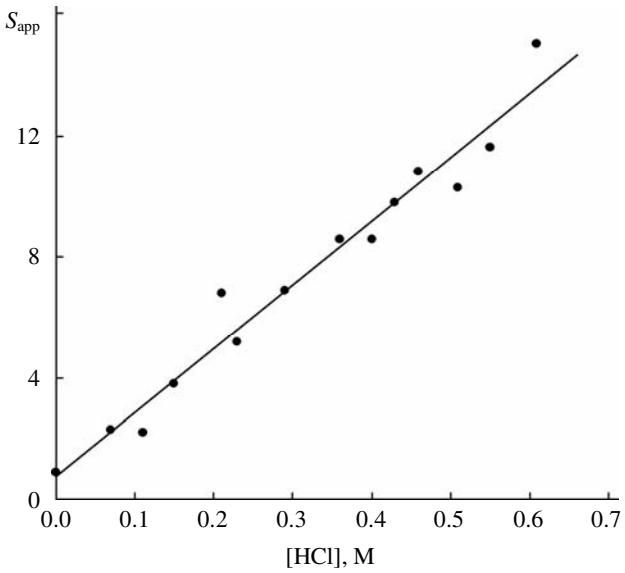
$$\frac{1}{6}\frac{k_1^{tert}k_{-1}^{prim}[HCl]}{k_2^{prim}k_1^{prim}[\mathbf{I}]} = 2.7. \qquad (11)$$

Therefore, the selectivity should be related to the concentration of **I** through the equation $S_{app} = 0.66 + 2.7/[\mathbf{I}]$. We showed that the experimental selectivities (Table 5) well fit the above dependence. Thus our results are fully consistent with Scheme 6 which includes reversible transfer of hydrogen from primary carbon atom in alkane **II** and isomerization of primary radicals into tertiary.

An important tool for controlling the regioselectivity in radical chlorination of alkenes is proper choice of a solvent capable of forming complexes with chlorine atoms. Such solvents are simple homologs of aromatic hydrocarbons [30], carbon disulfide [31], pyridine [32], alkyl halides [33], etc. As shown in [11], the use of benzene as solvent increases the regioselectivity in the reaction of compound **I** with alkane **II** in the presence of calcium carbonate from ~1 to ~6. We found conditions which ensured advantages of the effects of a complex-forming solvent and hydrogen chloride to be combined. In the alkylation of compound **I** with 2,3-dimethylbutane in benzene in the presence of HCl, the selectivity of the process attained a value of 40 (Table 6), which is very important from the viewpoint of synthetic applications.

While studying the alkylation of **I** we also examined the effect of phenyl iodide and ethyl iodide on the selectivity. According to Russell [30], no interpretable results on the effect of iodine-containing solvents on the selectivity of radical chlorination of alkanes with molecular chlorine were obtained because of concurrent oxidation of iodides [30]. We have found that both ethyl iodide and phenyl iodide considerably increase the selectivity in the reaction of compound **I** with alkane **II** (Table 6) and that no appreciable oxidation of the iodides occurs (when the reaction was complete, iodine color did not appear). We were the first to observe increased selectivity in ethyl iodide.

Apart from 2,3-dimethylbutane (**II**), the alkylation of **I** with hexane was studied. Our interest in this reaction was aroused by the data of [12], according to which the reaction of hexane with dichloride **I** in the presence of biacetyl as photosensitizer gave a mixture of 3-chloro-4-hexyl-, 3-chloro-4-(1-methylpentyl)-, and 3-chloro-4-(1-ethylbutyl)-2,5-dihydrofuran-2,5-diones **V**–**VII** at a ratio of ~5:3:1. The regioselectivity observed in [12] sharply differs from that found for the chlorination of hexane with molecular chlorine, where the ratio of 1-, 2-, and 3-chlorohexanes was ~1.0:1.6:1.7 (20°C) [34]. We examined the reaction of **I** with hexane (Scheme 7) under the conditions most typical for the reaction of **I** with 2,3-dimethylbutane (**II**) (Table 7). The progress of the reaction was monitored by GLC, and the products were identified by comparing the GLC and NMR data. The results showed that the ratio of the primary and secondary hexyl-substituted products follows the same relations as those observed in the alkylation with 2,3-dimethylbutane (**II**). The selectivity values obtained by us dis-



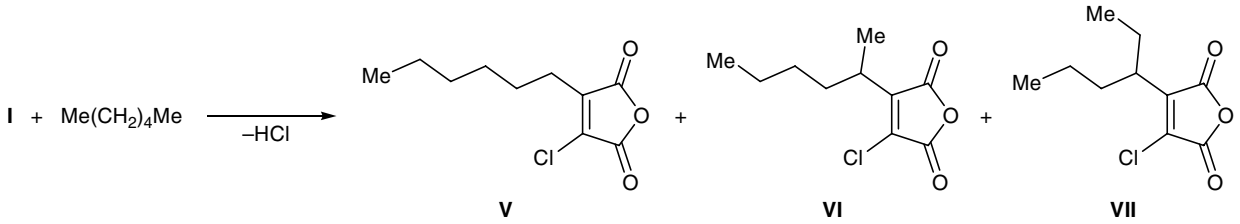
Plot of the selectivity in the reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with 2,3-dimethylbutane (**II**) versus HCl concentration. The conversion of **I** is 0.6–14%.

Table 5. Effect of the concentration of compound **I** on the selectivity of its reaction with 2,3-dimethylbutane (**II**) at a fixed concentration of hydrogen chloride[a]

[**I**], M	Conversion,[b] %	Selectivity
0.05	60.0	35.3
0.25	18.0	12.6
1.25	5.7	3.6

[a] Reactant concentrations, M: $(BzO)_2$, 0.02; **II**, 2.88; $(CH_2Cl)_2$, 3.17; CH_3CN, 7.19; HCl, 0.51; 80°C, 1 h.

Scheme 7.



prove the data of [12] indicating preferential formation of compound **V**.

While studying factors affecting the selectivity in the alkylation of **I**, initiated by benzoyl peroxide, we also detected formation of up to 20% of the corresponding alkyl chlorides together with alkyl-substituted furandiones. In the reaction with 2,3-dimethylbutane (**II**), regardless of the **III**-to-**IV** ratio, tertiary 2-chloro-2,3-dimethylbutane was always formed, while no primary chloride was detected. Presumably, the source of chlorine for the formation of 2-chloro-2,3-dimethylbutane is benzoyl hypochlorite arising from the reaction of benzoyl peroxide with HCl [35]. At high HCl concentrations (>0.7 M), the fraction of the tertiary chloride exceeded 50%. Therefore, while studying the dependence of the selectivity upon HCl concentration (see figure), the latter was lower than 0.7 M to avoid errors in the determination of selectivity owing to side processes.

Table 6. Effect of the solvent on the selectivity of the reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with 2,3-dimethylbutane (**II**)[a]

Solvent (additive)	Conversion, %	Selectivity
$CHCl_3$	22	1.1
Benzene	50[b]	5.4
Benzene–HCl[c]	6.9	40
Phenyl iodide	3.1	45
Ethyl iodide	9	25

[a] Amounts of the reactants: **I**, 1 mmol; $(BzO)_2$, 0.1 mmol; K_2CO_3, 200 mg; **II**, 1 ml; solvent, 2 ml; 80°C, 2 h.
[b] $(BzO)_2$, 0.2 mmol.
[c] The same as in [a], but without potassium carbonate; 0.5 ml of CH_3CN and HCl (0.4 M) were added.

Table 7. Selectivity in the reaction of 3,4-dichloro-2,5-dihydrofuran-2,5-dione (**I**) with hexane[a]

Solvent (additive)	Conversion, %	Selectivity	
		([**VI**]+[**VII**])/[**V**]	[**VI**]/[**VII**]
Hexane ($CaCO_3$)[b]	14	3.9	1.1
Hexane–benzene ($CaCO_3$)[b]	8	8.0	0.94
Hexane (HCl, 0.5 M)[c]	17	20	1.2
Hexane (HCl, 1 M)[c]	16	33	1.3
Hexane–benzene (HCl, 0.5 M)[c]	32	86	1.3

[a] Amounts of the reactants: **I**, 1 mmol; $(BzO)_2$, 0.1 mmol; hexane, 1 ml; solvent, 2 ml; 80°C, 2 h.
[b] $CaCO_3$, 200 mg.
[c] The same as in [a], and a required amount of a saturated solution of HCl in CH_3CN was added.

The information obtained in the present work on the alkylation of dichloride **I** was used to develop preparative procedures for the synthesis of some 3-alkyl-4-chloro- and 3,4-dialkyl-2,5-dihydrofuran-2,5-diones (Table 8). The syntheses of 3-chloro-4-cyclohexyl- and 3,4-dicyclohexylfurandiones **VIII** and **IX** were described previously; however, our procedures are characterized by considerably shorter reaction time, the product yield being comparable. 3-Chloro-4-(1,1,2-trimethylpropyl)-2,5-dihydrofuran-2,5-dione (**III**) was isolated by us for the first time. Studies on possible synthetic extensions of the alkylation of compound **I** will be the main line of our research activity.

EXPERIMENTAL

Thermal radical reactions were initiated with the aid of an MLW U15[C] flow thermostat. Photochemical initiation was performed using a DRL-400 high-pressure mercury lamp (400 W). GLC analysis was performed on a Model 3700 gas chromatograph (manufactured by *Khromatograf*, Moscow, Russia) equipped with a flame ionization detector and an HP-1 30-m capillary column (polydimethylsiloxane); carrier gas nitrogen. The chromatograms were quantitated using a CI-100 integrator. The calibration coefficients of isomeric chloro(alkyl)furandiones were assumed to be equal. Column chromatography was performed on a column (2.5 cm i.d.) charged with 10 g of silica gel

(0.035–0.070 mm; from Acros Organics). The ^1H and ^{13}C NMR spectra were recorded at 20°C from solutions in $CDCl_3$ on a Bruker DPX-300 spectrometer at 300.130 and 75.468 MHz, respectively.

1,2-Dichloroethane, 2,3-dimethylbutane (from Lancaster Synthesis), and cyclohexane were used without additional purification. Hexane was purified by washing with concentrated sulfuric acid, followed by distillation. Acetonitrile was freed from traces of water by distillation over phosphoric anhydride. A saturated solution of hydrogen chloride in acetonitrile was prepared by passing dry hydrogen chloride until the latter no longer absorbed. Hydrogen chloride was generated by heating of concentrated hydrochloric acid and was dried by passing through a layer of concentrated sulfuric acid. The concentration of hydrogen chloride was determined by titration with a standard solution of sodium hydroxide (a portion of acetonitrile solution of HCl was preliminarily diluted with water). The concentration of hydrogen chloride was on the average 2.7–3.0 M.

3,4-Dichloro-2,5-dihydrofuran-2,5-dione (**I**) was synthesized by reaction of maleic anhydride with thionyl chloride in the presence of pyridine according to the procedure described in [36]. Yield 75%. The product was purified by recrystallization from hexane and was stored in a tightly capped vessel in a refrigerator (~0°C). Compound **I** decomposes on prolonged storage, and even small amounts of impurities strongly inhibit radical reactions. If the yield of the radical alkylation products decreased appreciably, dichloride **I** was subjected to repeated recrystallization.

All kinetic experiments were performed at least in triplicate, and the relative error in the given selectivity values did not exceed 15%.

General procedure for kinetic experiments in the presence of hydrogen chloride. A ~2-ml ampule was charged with 50 mg (0.3 mmol) of dichloride **I**, 6.2 mg (0.03 mmol) of benzoyl peroxide (as a 10% solution in 1,2-dichloroethane), and 5.2 mg (0.03 mmol) of 2,4-dichlorobenzonitrile (as a 20% solution in 1,2-dichloroethane; internal standard for GLC). A saturated solution of HCl in acetonitrile with a required concentration, 1 ml, in a mixture with alkane–acetonitrile–1,2-dichloroethane (3:3:2, by volume; 0.375 ml of alkane, 0.375 ml of acetonitrile, and 0.25 ml of 1,2-dichloroethane) was then added; the solvent volume ratio was maintained by adding anhydrous acetonitrile. In studies on the joint effect of HCl and benzene, 1 ml of a solution of HCl with a required concentration in an alkane–acetonitrile–benzene mixture (1:1:3, by volume) was added. The ampule was sealed in such a way that the ratio between the volumes of the liquid and gas phases was about 1:1 and heated for 1 h at 80°C (on a water bath). The ampule was then opened, and the mixture was analyzed by GLC.

Table 8. Preparative syntheses of some 3-alkyl-4-chloro- and 3,4-dialkyl-2,5-dihydrofuran-2,5-diones by alkylation of compound **I**

Hydrocarbon (reaction time, h)[a]	Product	Yield,[b] %	Yield, % (reaction time, h) [12][c]
C_6H_{12} (1.3)	**VIII**	80	91 (20)
C_6H_{12} (6)	**IX**	74 (55)[d]	76 (120)
II (3)[e]	**III**	78	–

[a] $(BzO)_2$, 80°C.
[b] Isolated product.
[c] Biacetyl, 80°C, *hν*.
[d] In parentheses is given the yield after recrystallization.
[e] HCl in benzene.

General procedure for kinetic experiments in the presence of hydrogen chloride acceptors. The corresponding alkane, 2 ml (if necessary, as a mixture with added solvent), was added to a mixture of 100 mg (0.6 mmol) of compound **I**, 12.5 mg (0.06 mmol) of benzoyl peroxide (as a 10% solution in 1,2-dichloroethane), 10.4 mg (0.06 mmol) of 2,4-dichlorobenzonitrile (as a 20% solution in 1,2-dichloroethane; internal standard for GLC), and 200 mg of calcined K_2CO_3 or $CaCO_3$. The reaction vessel was tightly capped with a glass stopper and heated for 1 h at 80°C under stirring using a magnetic stirrer. The mixture was then filtered and analyzed by GLC.

3-Chloro-4-cyclohexyl-2,5-dihydrofuran-2,5-dione (VIII). A mixture of 500 mg (3 mmol) of compound **I**, 37 mg (0.15 mmol) of benzoyl peroxide, and 5 ml of cyclohexane was heated for 80 min at 80°C in a flask equipped with an air-cooled reflux condenser. The progress of the reaction was monitored by GLC. The product was isolated by column chromatography using hexane–1,2-dichloroethane (5:1) as eluent. A 70 to 350-ml fraction was collected, and removal of the solvent gave 520 mg (80%) of compound **VIII** as a transparent liquid. Purity 95% (GLC). ^1H NMR spectrum, δ, ppm: 1.20–1.45 m (2H, CH_2), 1.65–1.95 m (8H, CH_2), 2.65–2.85 m (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 25.7 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 36.7 (CH), 134.7 (C=C), 147.6 (C=C), 160.4 (C=O), 162.6 (C=O).

3,4-Dicyclohexyl-2,5-dihydrofuran-2,5-dione (IX). A mixture of 1 g (6 mmol) of compound **I**, 300 mg (1.2 mmol) of benzoyl peroxide, and 10 ml of cyclohexane was heated for 3 h at 80°C in a flask equipped with an air-cooled reflux condenser, an additional portion of benzoyl peroxide, 300 mg (1.2 mmol) was added, and the mixture was heated for an additional 3 h. The progress of the reaction was monitored by GLC. The product was isolated by column chromatography using hexane–chloroform (4:1). A 70 to 350-ml fraction was collected, and removal of the solvent gave 1.16 g (74%) of compound **IX** as colorless crystals. The product was additionally purified by recrystallization from 5 ml of cyclohexane by slowly evaporating the solvent (for one week). Yield 870 mg (55%), large transparent crystals with mp 117–119°C; published data [12]: mp 123–124°C; purity 99% (GLC). ^{1}H NMR spectrum, δ, ppm: 1.20–1.45 m (4H, CH_2), 1.55–2.00 m (16H, CH_2), 2.60–2.75 t.t (2H, CH). ^{13}C NMR spectrum, δ_C, ppm: 25.7 (CH_2), 26.4 (CH_2), 30.4 (CH_2), 36.7 (CH), 147.4 (C=C), 165.4 (C=O).

3-Chloro-4-(1,2,2-trimethylpropyl)-2,5-dihydrofuran-2,5-dione (III). A mixture of 500 mg (3 mmol) of compound **I**, 150 mg (0.6 mmol) of benzoyl peroxide, 2 ml of 2,3-dimethylbutane (**II**), 2 ml of an acetonitrile solution of HCl (c_{HCl} = 2.7 M), and 6 ml of benzene was heated for 2 h at 80°C, an additional portion of benzoyl peroxide, 75 mg (0.3 mmol), was added, and the mixture was heated for 1 h more. The progress of the reaction was monitored by GLC. The product was isolated by column chromatography using hexane–1,2-dichloroethane (5:1) as eluent. A 50 to 300-ml fraction was collected, and removal of the solvent gave 510 mg (78%) of compound **III** as a colorless liquid with a purity of 97% (GLC). ^{1}H NMR spectrum, δ, ppm: 0.90 d (6H, CH_3), 1.40 s (6H, CH_3), 2.34 sept (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 17.9 (CH_3), 22.9 (CH_3), 34.9 (CH), 42.3 (C), 135.2 (C=C), 149.5 (C=C), 160.6 (C=O), 162.4 (C=O).

REFERENCES

1. Giese, B., *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Oxford: Pergamon, 1986.
2. Curran, D.P., *Comprehensive Organic Synthesis*, Trost, B.M. and Fleming, I., Eds., Oxford: Pergamon, 1991, vol. 4, p. 715.
3. Curran, D.P. and Chang, C.-T., *J. Org. Chem.*, 1989, vol. 54, p. 3140.
4. Quiclet-Sire, B. and Zard, S.Z., *J. Am. Chem. Soc.*, 1996, vol. 118, p. 1209.
5. Le Guyader, F., Quiclet-Sire, B., Seguin, S., and Zard, S.Z., *J. Am. Chem. Soc.*, 1997, vol. 119, p. 7410.
6. Xiang, J., Jiang, W., Gong, J., and Fuchs, P.L., *J. Am. Chem. Soc.*, 1997, vol. 119, p. 4123.
7. Liu, J.-T., Jang, Y.-J., Shih, Y.-K., Hu, S.-R., Chu, C.-M., and Yao, C.-F., *J. Org. Chem.*, 2001, vol. 66, p. 6021.
8. Jang, Y.-J., Shih, Y.-K., Liu, J.-Y., Kuo, W.-Y., and Yao, C.-F., *Chem. Eur. J.*, 2003, vol. 9, p. 2123.
9. Gagosz, F. and Zard, S.Z., *Org. Lett.*, 2003, vol. 5, p. 2655.
10. Bertrand, F., Pevere, V., Quiclet-Sire, B., and Zard, S.Z., *Org. Lett.*, 2001, vol. 3, p. 1069.
11. Araneo, S., Arrigoni, R., Bjorsvik, H.-R., Fontana, F., Liguori, L., Minisci, F., and Recupero, F., *Tetrahedron Lett.*, 1996, vol. 37, p. 6897.
12. Stahlke, K.-R. and Willy, H., FRG Patent Appl. no. 2352216, 1975; *Chem. Abstr.*, 1975, vol. 83, no. 79950e.
13. Schmerling, L., US Patent no. 3780066, 1973; *Chem. Abstr.*, 1974, vol. 80, no. 70349w.
14. Schmerling, L. and West, J.P., *J. Am. Chem. Soc.*, 1953, vol. 75, p. 6216.
15. Rust, F.F. and Bell, C.S., *J. Am. Chem. Soc.*, 1970, vol. 92, p. 5530.
16. Horowitz, A. and Rajbenbach, L.A., *J. Am. Chem. Soc.*, 1970, vol. 92, p. 1634.
17. Kar, A., Gogoi, S., and Argade, N.P., *Tetrahedron*, 2005, vol. 61, p. 5297.
18. Augustin, M., Faust, J., and Koehler, M., *J. Prakt. Chem.*, 1983, vol. 325, p. 293.
19. Bunce, N.J., Ingold, K.U., Landers, J.P., Lusztyk, J., and Scaiano, J.C., *J. Am. Chem. Soc.*, 1985, vol. 107, p. 5464.
20. Walling, Ch., *Free Radicals in Solution*, New York: Wiley, 1957; translated under the title *Svobodnye radikaly v rastvore*, Moscow: Inostrannaya Literatura, 1960, pp. 380, 405.
21. Tanner, D.D. and Bunce, N.J., *J. Am. Chem. Soc.*, 1969, vol. 91, p. 3028.
22. Paul, G. and Kebarle, P., *J. Am. Chem. Soc.*, 1989, vol. 111, p. 464.
23. Nonhebel, D.C. and Walton, J.C., *Free-Radical Chemistry; Structure and Mechanism*, Cambridge: Cambridge Univ., 1974; translated under the title *Khimiya svobodnykh radikalov. Struktura i mekhanizm reaktsii*, Moscow: Mir, 1977, p. 503.
24. Skell, P.S., Baxter, H.N., Tanko, J.M., and Chebolu, V., *J. Am. Chem. Soc.*, 1986, vol. 108, p. 6300.
25. Poutsma, M.L., *J. Am. Chem. Soc.*, 1964, vol. 86, p. 3807.

26. Raner, K.D., Lusztyk, J., and Ingold, K.U., *J. Org. Chem.*, 1988, vol. 53, p. 5220.
27. Bell, T.N., Perkins, K.A., and Perkins, P.G., *J. Phys. Chem.*, 1979, vol. 83, p. 2321.
28. *Handbook of Chemistry and Physics*, Lide, D.R., Ed., Boca Raton: CRC, 2000, 81st ed.
29. Kopinke, F.-D., Zimmermann, G., and Anders, K., *J. Org. Chem.*, 1989, vol. 54, p. 3571.
30. Russell, G., *J. Am. Chem. Soc.*, 1958, vol. 80, p. 4987.
31. Chateauneuf, J.E., *J. Am. Chem. Soc.*, 1993, vol. 115, p. 1915.
32. Breslow, R., Brandl, M., Hunger, J., Turro, N., Cassidy, K., Krogh-Jespersen, K., and Westbrook, J.D., *J. Am. Chem. Soc.*, 1987, vol. 109, p. 7204.
33. Dneprovskii, A.S., Kuznetsov, D.V., Eliseenkov, E.V., Fletcher, B., and Tanko, J.M., *J. Org. Chem.*, 1998, vol. 63, p. 8860.
34. Colebourne, N. and Stern, E.S., *J. Chem. Soc.*, 1965, p. 3599.
35. Bunce, N.J. and Tanner, D.D., *J. Am. Chem. Soc.*, 1969, vol. 91, p. 6096.
36. Relles, H.M., *J. Org. Chem.*, 1972, vol. 37, p. 3630.