REGIOSPECIFIC OXIDATION OF ALKANESULFONAMIDES TO 3-OXOALKANESULFONAMIDES

É. I. Troyanskii, M. I. Lazareva, V. E. Zubarev, A. I. Lutsenko, and G. I. Nikishin

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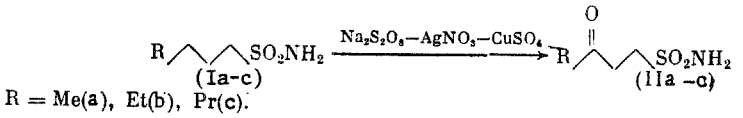
One-step remote oxidative functionalization based on rearrangement of oxygen- and nitrogen-centered radicals with hydrogen migration is an effective method for directed transformation of various classes of organic compounds at an unactivated carbon atom [1-3].

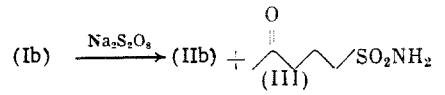
Oxidation of aliphatic sulfonamides in a sodium peroxidisulfate–cupric chloride system is a simple method for generation of nitrogen centered sulfonylamidyl radicals, and their rearrangement with 1,5- or 1,5- and 1,6-hydrogen migration was used for γ-regioselective chlorination of alkanesulfonamides to 3- and 4-chloroalkanesulfonamides [4] and for regiospecific oxidative cyclization of N-mesylalkylamines into N-mesylpyrrolidines [3].

These investigations established that N-unsubstituted alkanesulfonamides (Ia-c) upon oxidation with sodium peroxidisulfate in the presence of catalytic amounts of $CuSO_4$ and $AgNO_3$, an effective catalyst for $S_2O_8^{2-}$ decomposition [5], undergo regiospecific γ-oxidation to form 3-oxoalkanesulfonamides (IIa-c)* (Table 1)



R = Me(a), Et(b), Pr(c).

Actually, $Na_2S_2O_8$ without adding salts of variable valency metals also causes oxidation of (I). Moreover, (Ia) under the action of an equimolar amount of $Na_2S_2O_8$ forms (IIa) [85% yield based on consumed (Ia), conversion of 35%]. For compound (Ib) the regiospecificity of oxidation at the C^3 atom is lost and a mixture of (IIb) and isomeric 4-oxopentanesulfonamide (III) is formed in 1:1 ratio (conversion ~ 10%)



Upon oxidation of (Ia) with $Na_2S_2O_8$ in the presence of catalytic amounts of $AgNO_3$ [(Ia): $Na_2S_2O_8$:$AgNO_3$ = 1:1:0.15] compound (IIa) is formed in 90% yield based on consumed (Ia) and conversion of 30%. The regioselectivity of oxidation of (Ib) at the C^3 atom under the same conditions is significantly greater than with oxidation by only $Na_2S_2O_8$; (IIb) and (III) are formed in 6:1 ratio.

The assumed oxidation mechanism includes one-electron oxidation of (I) to the corresponding nitrogen-centered cation radicals (IV) which are deprotonated into sulfonylamidyl radicals (V). The latter in a $Na_2S_2O_8$–$AgNO_3$–$CuSO_4$ system are isomerized regiospecifically with 1,5-migration of hydrogen to carbon centered radicals (VI) which then are oxidized with ligand (OH from water) transfer to intermediate 3-hydroxylalkanesulfonamides (VII) which are further transformed to (II). The capacity of $Na_2S_2O_8$ and systems based on it to effectively oxidize alcohols into carbonyl compounds is known [7].

In the presence of only $Na_2S_2O_8$ radical (Vb) undergoes 1,6- along with 1,5-hydrogen migration leading to radical $MeCH(CH_2)_3SO_2NH_2$, which is stabilized by coupling with the Me group and is the precursor of 4-oxopentanesulfonamide (III).

*For previous communication see [6].

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.
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TABLE 1. γ-Oxidation of Sulfonamides (Ia-c) in $Na_2S_2O_8$–$AgNO_3$–$CuSO_4$*

Sulfonamide	Conversion, %	Product, yield in % per transformed (I)
(Ia)	46	(IIa), 90
(Ib)	30	(IIb), 90
(Ic)	20	(IIc), 100

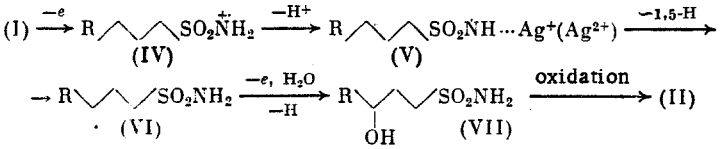
*85-90°C, 5 h, ratio of (I):$Na_2S_2O_8$:$AgNO_3$:$CuSO_4$ = 1:1:0.15:0.2.

TABLE 2. Physicochemical and Spectral Characteristics of Starting Substances and Reaction Products

Substance	Mp, °C	PMR spectra, δ, ppm	^{13}C NMR spectra, δ, ppm	Mass spectra (m/z, rel. intensity)
(Ic)	56	0.99t (3H, CH_3), 1.25–1.86m(8H, $(CH_2)_4$), 3,06t (2H, CH_2SO_2), 5,40 br. s (2H, NH_2)	–	165(M^+) Chemical ionization
(IIa)	Oil *	2,23s (3H, CH_3), 3,22 s (4H, CH_2CH_2), 5,40 br. s (2H, NH_2)	21,72 q., 37,92t, 44,38 t, 183,24 s	151(M^+, 1), 119(11), 117(10), 108(5), 95(4), 85(66), 83(100), 73(12)
(IIb)	Oil*	1,25 t (3H, CH_3), 2,60 q (2H, $CH_3CH_2C(O)$) 3,25s (4H, $CH_2CH_2SO_2$), 5,40 br. s (2H, NH_2)	9,48 q, 29,30 t, 36,68t, 44,37 t, 188,05 s	165(M^+, 5), 164(24), 149(25), 134(40), 121(56), 108(13), 96(18), 94(17), 84(24), 70(30)
(IIc)	Oil*	1,00t (3H, CH_3), 1,67–1,86m(2H, CH_3CH_2), 2,53t (2H, $EtCH_2$), 5,40 br. s (2H, NH_2)		
(III)	–	2,23 s (3H, CH_3), 2,45–2,65m(2H, $CH_2CH_2CH_2$), 3,15–3,25m(4H, $C(O)CH_2$ and $CH_2SO_2NH_2$)		
(VIIIa)	175,5–179 **	–	–	332(M^{++}1) Chemical ionization
(VIIIb)	149–151 ***	–	–	346(M^{++}1) Chemical ionization
(VIIIc)	115–117	–	–	

*IR spectrum: νC=O 1715-1720 cm^{-1}.
**Found, %: C 36.69; H 4.08; N 21.13; S 9.75. $C_{10}N_{13}N_5O_6S$.
Calculated, %: C 36.25; H 3.96; N 21.14; S 9.67.
***Found, %: C 38.40; H 4.32; N 20.23; S 9.35. $C_{11}H_{15}N_5O_6S$.
Calculated, %: C 38.26; H 4.38; N 20.28; S 9.28.

It is most probable that the observed regiospecificity of isomerization of (V) with 1,5-hydrogen migration in a $Na_2S_2O_8$–$AgNO_3$–$CuSO_4$ system (unlike the competitive 1,5- and 1,6-hydrogen shifts in (V) in a $Na_2S_2O_8$–$CuCl_2$ system [4] and also in the presence of $Na_2S_2O_8$ only) is caused mainly by complex formation of (V) with silver ions $Ag^+(Ag^{2+})$



and by effective oxidation of the rearranged radicals (VI) by copper ions. Naturally, complex formation of (V) with $Ag^+(Ag^{2+})$ ought to decrease the reactivity of these radicals and increase the selectivity of their transformations.

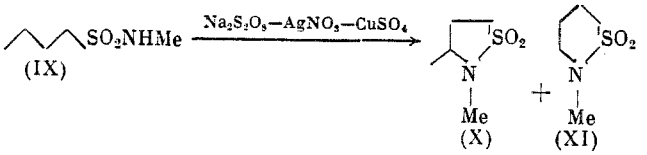
Intermediate formation of sulfonylamidyl radicals (V) and C-centered radicals of (VI) in the systems containing $Na_2S_2O_8$ was confirmed by identification of these radicals by EPR. We studied oxidation of (Ia) by the action of $Na_2S_2O_8$ in the presence of 2-methyl-2-nitroso-

propane (MNP) as a spin trap. Use of spin traps for recording radicals in aqueous $Na_2S_2O_8$ solutions, as shown earlier [8], is complicated by oxidative decomposition of the spin trap, which can be fully suppressed by using a two-phase system containing an aqueous solution of $Na_2S_2O_8$ with sulfonamide (Ia). Under these conditions MNP and (Ia) are in the organic phase. Upon oxidation of (Ia) in the presence of MNP spectra of radical adducts are obtained, among which is a spectrum consisting of a triplet of triplets with a_N = 14.3 Oe and a_{NH} = 1.95 Oe due to the radical formed by addition to MNP of the N-centered radical of (Va) [or, which cannot be excluded completely, of its antecedent cation-radical of (IVa)]. Upon increasing the initiation temperature from 60 to 80-85°C a decrease in the signal intensity of this adduct is observed and the intensity increases in the spectrum of the MNP adduct of a radical of the alkyl (C-centered) type consisting of triplet of doublets with the parameters a_N = 15.85 Oe and a_H^{β} = 1.88 Oe. Since in the preparation of (Ia) by oxidation with $Na_2S_2O_8$ only 3-oxobutanesulfonamide (IIa) is formed and the isomeric 1- and 2-oxobutanesulfonamides were not found, we assign this spectrum to the adduct of MNP with the radical of (IVa), the precursor of (IIa). The adducts of MNP with the radical of $CH_2(CH_2)_3SO_2NH_2$, an intermediate in functionalization of (Ia) at the end Me group, is absent in the reaction mixture according to EPR data.

In order to separate 3-oxosulfonamides (IIa-c) from the unreacted starting materials (Ia-c) the reaction mixtures after oxidation of (Ia-c) by the $Na_2S_2O_8$—$AgNO_3$—$CuSO_4$ system were treated with 2,4-dinitrophenylhydrazine. Individual products (IIa-c) were isolated by cleaveage of the obtained 2,4-dinitrophenylhydrazones (2,4-DNPH's) (VIIIa-c) of 3-oxosulfonamides (IIa-c) with $SnCl_2$ in HCl—AcOH. Physicochemical and spectral characteristics of (IIa-c) and (VIIIa-c) are shown in Table 2.

We note that in the PMR (250 MHz) spectra of (IIa-c) the CH_2CH group signal is one singlet. The observed equivalency of these protons is probably due to the shift of the $CH_2C(O)$ group signal downfield under the influence of the SO_2NH_2 group and by formation of intra- and intermolecular hydrogen bonds with participation of both functional groups in the (IIa) molecule. Analogous PMR spectra were obtained for (IIb, c). For (IIb) the signal of the $C(O)CH_2CH_2SO_2$ fragment is a singlet or multiplet depending on the solution pH.

It was unexpected that γ-oxidation does not occur with N-alkyl alkanesulfonamides. Upon oxidation of N-methyl butanesulfonamide (IX) by $Na_2S_2O_8$—$AgNO_3$—$CuSO_4$ conversion of (IX) is low (<10%) and a mixture of three products is formed, among which five- or six-membered sultams (X) and (XI) were identified from the PMR and ^{13}C NMR spectral data.



EXPERIMENTAL

Gas liquid chromatography was carried out on a LKhM-8MD chromatograph with flame-ionizing detector in an N_2 flow. Columns (stainless steel) 1000 × 3 mm with 5% XE-60 on N-AW chromaton (0.125-0.160 mm) and 1000 × 3 mm with 5% SE-30 on N-AW-DMCS chromaton (0.160-0.200 mm) were used. PMR spectra of $CDCl_3$ solutions were taken on a Bruker WM-250 (250 MHz) or a Bruker AM-300 (300 MHz) instrument. ^{13}C NMR spectra of $CDCl_3$ solutions were obtained on a Bruker WM-250 (62.9 MHz) or a Bruker AM-300 (75.4 MHz) instrument. Chemical shifts are in δ units from TMS as internal standard. EPR spectra were obtained on a PÉ-1307 spectrometer. Mass spectra were taken on a Varian MAT CH-6 spectrometer with direct sample introduction into the ion source. The energy of the ionizing electrons was 70 eV. Chemical ionization was carried out on a Kratos MS-30 mass spectrometer with direct sample introduction into the ion source. The source temperature was 100°C and the reagent gas (isobutane) pressure was 0.2 torr. IR spectra were obtained on a Perkin—Elmer 577 instrument using thin layers.

The oxidant $Na_2S_2O_8$ was chemically pure (ch.p.) and the $AgNO_3$ and $CuSO_4 \cdot 5H_2O$, ch.p., were used without additional purification. Water was distilled once.

Alkanesulfonamides (Ia, b) and (IX) were described in [4]. Compound (Ic) (bp 117-120°C, 0.55 mm; mp 56°C) was synthesized by reaction of hexanesulfony chloride with aqueous ammonia. Spectral characteristics of (Ic) are shown in Table 2.

Oxidation of Alkanesulfonamides (Ia-c) with $Na_2S_2O_8$–$CuSO_4$–$AgNO_3$ (general method). To a suspension of 10 mmoles of (Ia-c) in 20 ml water 0.5 g (2 mmoles) of $CuSO_4 \cdot 5H_2O$ and 0.255 g (1.5 mmoles) of $AgNO_3$ was added and the reaction mixture was heated to 85-90°C, then a solution of 2.38 g (10 mmoles) of $Na_2S_2O_8$ in 20 ml water was added dropwise. The reaction mixture was stirred for 5 h at 85°C, cooled, and extracted with ether (3 times by 30 ml). The extract was dried with Na_2SO_4 and evaporated. In the residue conversion of (Ia-c) and yields of (IIa-c) were determined by GLC and PMR spectroscopy (Table 1). Then the obtained mixtures (Ia-c) and (IIa-c) were treated with 2,4-dinitrophenylhydrazine and (VIIIa-c) was isolated. Physicochemical and spectral characteristics of (VIIIa-c) are shown in Table 2.

Oxidation of (Ia-b) by $Na_2S_2O_8$ and $Na_2S_2O_8$–$AgNO_3$ was carried out analogously.

Oxidation of N-methyl butanesulfonamide (IX) in $Na_2S_2O_8$–$AgNO_3$–$CuSO_4$ was carried out according to the general method of oxidation of (Ia-c). After evaporation of ether from the extract conversion of (IX) (<10%) was determined in the residue by GLC. In order to remove unreacted (IX) the reaction mixture was boiled with NaH in toluene and filtered. The filtrate was evaporated and the organic residue was analyzed by PMR and ^{13}C NMR spectra. In the spectra the following signals were isolated: 2,3-dimethylisothiazolidine-1,1-dioxide (X) – PMR spectrum (δ, ppm): 1.25 d (3H, $C\underline{H}_3CH$), 2.31-2.49 m (2H, $C\underline{H}_2CH$), 2.61 s (3H, CH_3), 3.10-3.25 m (1H, CHN) (this coalesces upon irradiation at the signal frequency of 1.25 ppm), 3.30 t (2H, CH_2SO_2); ^{13}C NMR spectrum (δ, ppm): 19.42 q ($\underline{C}H_3CH$), 32.79 q ($\underline{C}H_3CN$), 27.24 t ($\underline{C}H_2CH$) 51.22 t (CH_2SO_2), 55.29 d (CH) and 2-methylperhydrothiazine-1,1-dioxide (XI) – PMR spectrum (δ, ppm): 1.88-2.03 m and 2.11-2.22 m (4H, CH_2CH_2), 2.91 s (3H, CH_3N), 3.00-3.10 m (2H, CH_2SO_2), 3.41 t (2H, CH_2N); ^{13}C NMR spectrum (δ, ppm): 23.95 t and 25.27 t (CH_2CH_2), 29.35 q (CH_3), 51.09 t (CH_2SO_2), 52.58 t (CH_2N).

Cleavage of 2,4-dinitrophenylhydrazones (VIIIa-c) was carried out according to [9]. Into 25 ml of ice cold AcOH 1.15 g of $SnCl_2$ was added and heated for a few minutes in order to obtain a fine suspension which was then cooled. Then a solution of 0.25 g of (VIIIa-c) in 25 ml of $CHCl_3$ and 1 ml of concentrated HCl was added and the reaction was stirred. The yellow solution obtained after dissolution of (VIII) was stirred for 5 h more and then diluted with water. The organic layer was separated, washed with saturated soda solution, and dried with anhydrous Na_2SO_4. The solvent was distilled off and (IIa-c) were obtained. Spectral characteristics of (IIa-c) are given in Table 2.

EPR Investigation of Butanesulfonamide (Ia) under the Action of $Na_2S_2O_8$. 0.2 ml of 0.05 M $Na_2S_2O_8$ solution in twice-distilled water was placed in a glass ampul. The solution was frozen at –10°C and 0.2 ml of a 0.1 M solution of spin trap [2-methyl-2-nitrosopropane (MNP)] in butanesulfonamide (Ia) was added. The reaction mixture was cooled with liquid nitrogen and carefully evacuated (3 freeze–defrost cycles). The ampul was shaken at 20°C and entirely immersed in a water bath (80°C), kept for 15-30 sec and the EPR spectrum of the organic phase was recorded at 20°C. Together with the spectra of the MNP adducts of radicals (Va) and (VIa) also the spectrum of the $(t\text{-}Bu)_2NO^{\cdot}$ radical, formed by cleavage of MNP (a_N = 16.20 Oe), was recorded. This spectrum (a narrow line of 0.5 Oe width) differs sharply from the spectra of the MNP spin adducts and practically disappears upon repeated evacuation of the samples (the spin adducts are significantly less volatile).

CONCLUSIONS

1. N-nonsubstituted alkanesulfonamides under the action of $Na_2S_2O_8$–$AgNO_3$–$CuSO_4$ are transformed into 3-oxoalkanesulfonamides by regiospecific γ-oxidation with yields of 90-100% based on consumed substrate.

2. The reaction mechanism includes generation of nitrogen-centered sulfonylamidyl radicals and rearrangement with 1,5-hydrogen migration to carbon centered radicals as recorded by EPR. The regiospecificity of the 1,5-hydrogen migration is determined probably by complex formation of the sulfonylamidyl radicals with silver ions.

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SYNTHESIS OF OXYGEN-CONTAINING DERIVATIVES OF OCIMENE BASED ON 4-PHENYLSULFINYLMYRCENE

V. V. Veselovskii, N. A. Shpiro, and A. M. Moiseenkov

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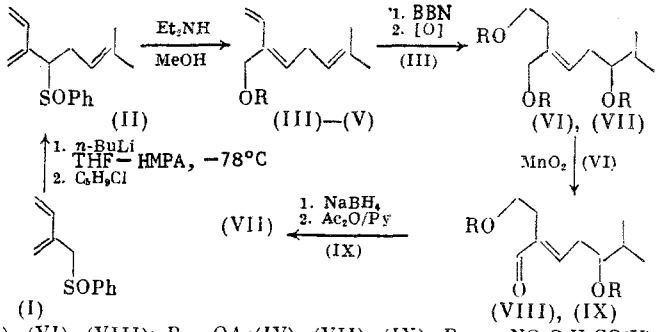
Sulfur-containing isoprenoid synthons have been used successfully for the directed construction of terpenes [1-4]. In the present work we studied the synthesis of the oxygen-containing derivatives of the ocimene series on the basis of the readily obtainable 4-phenylsulfinylmyrcene (I) [5].

The standard prenylation of the sulfoxide (I) takes place without an allylic shift of the C=C bond, giving the myrcene derivative (II) with a yield of ~40% in the form of an oily mixture of diastereomers (~1:1); its structure was confirmed by the data from elemental and physicochemical analyses. In particular, the PMR spectrum of (II) (250 MHz) contains a multiplet for HCS at $\delta \approx 3.5$ ppm and broad signals for the methyl groups at $\delta \approx 1.5$, 1.6, and 1.7 ppm (integral intensity ratios ~1:2:1).

The sulfoxide–sulfenate rearrangement (II) takes place smoothly in the presence of diethylamine, leading preferentially in accordance with the stereochemical result established for this sigmatropic reaction [6] to the E-hydroxy derivative (III) of the relatively difficultly obtainable and little investigated cis-ocimene series. Thus, comparison of the integral intensities of the CH_2O signals (br.s, $\delta \approx 4.2$ ppm) in the PMR spectrum of (III) indicates the presence of ≤10% of the Z stereoisomer as impurity. The structure of the previously undescribed ocimenol (III) was additionally confirmed by spectral and elemental analysis of its acetate (IV) and crystalline p-nitrobenzoate (V).



R = H(III), (VI), (VIII); R = OAc(IV), (VII), (IX); R = *p*-$NO_2C_6H_4CO$(V).

Regioselective hydroboronation of (III) by 9-borabicyclo[3.3.1]nonane (BBN) at the least substituted C=C bond was expected [7]. However, it was found that the isopropylidene

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.
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