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FACILE CONVERSION OF 1,3-DISUBSTITUTED THIOUREAS TO THE CORRESPONDING UREAS BY SUPEROXIDE RADICAL ANION ($O_2^{\cdot -}$) IN DIMETHYL SULFOXIDE

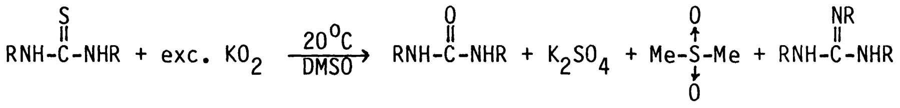
Yong Hae KIM,* Gyu Hwan YON, and Hyung Jin KIM

Department of Chemistry, Korea Advanced Institute of Science and Technology,
P.O. Box 150 Chong-Yang-ni, Seoul, Korea

Treatment of 1,3-disubstituted thioureas with superoxide radical anion ($O_2^{\cdot -}$) at 20 °C in dimethyl sulfoxide resulted in the formation of 1,3-disubstituted ureas in excellent yields. The desulfurization appears to proceed by the formation of peroxy-sulfur intermediates such as peroxy-sulfenate, -sulfinate and/or -sulfonate.

Since superoxide dismutase was discovered in 1969 to be a respiratory intermediate in aerobic organisms,$^{1)}$ biological researches of superoxide ($O_2^{\cdot -}$) have been intensively studied over the past two decades. But only a few reports have appeared on the reactivity of $O_2^{\cdot -}$ with simple organic compounds.$^{2)}$ Recently, numerous groups have shown interests$^{3)}$ in the physical and chemical properties of $O_2^{\cdot -}$ and stimulated its use in development of organic synthesis. With regard to the use of superoxide in the reactions of organic sulfur compounds, there have been only a few reports on the oxidation of thiol,$^{4)}$ thiouracil,$^{5)}$ disulfide related oxidation compounds,$^{6)}$ and aromatic sulfur halides,$^{7)}$ in which the initial step is presumed to involve the nucleophilic attack of superoxide anion on the sulfenyl sulfur of disulfides, thiolsulfinates, thiolsulfonate, and sulfonyl halides.

Our previous work on the oxidation of diaryl disulfides,$^{6)}$ heterocyclic thioureas,$^{8)}$ and arylsulfonyl halides$^{7)}$ to the corresponding sulfonates suggests that if peroxysulfur intermediates or sulfonates are formed, they may be useful intermediates in organic syntheses owing to their lability under mild conditions. Recently, we reported that 1,3-disubstituted thioureas reacted with $O_2^{\cdot -}$ in acetonitrile or in tetrahydrofuran to give the 1,2,3-trisubstituted guanidines as the main product.$^{9)}$ We have now found that 1,3-disubstituted thioureas reacted readily with potassium superoxide at 20 °C in anhydrous dimethyl sulfoxide to afford 1,3-disubstituted ureas (**9**) in excellent yields together with dimethyl sulfone (**11**), potassium sulfate (**10**) and trace amount of 1,2,3-trisubstituted guanidine (**12**).$^{10)}$



$$\mathrm{RNH\text{-}\overset{\overset{S}{\|}}{C}\text{-}NHR} + \text{exc. } \mathrm{KO_2} \xrightarrow[\text{DMSO}]{20\,^{\circ}\mathrm{C}} \underset{\mathbf{9}}{\mathrm{RNH\text{-}\overset{\overset{O}{\|}}{C}\text{-}NHR}} + \underset{\mathbf{10}}{\mathrm{K_2SO_4}} + \underset{\mathbf{11}}{\mathrm{Me\text{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{O}{\uparrow}}{S}}\text{-}Me}} + \underset{\mathbf{12}}{\mathrm{RNH\text{-}\overset{\overset{NR}{\|}}{C}\text{-}NHR}}$$

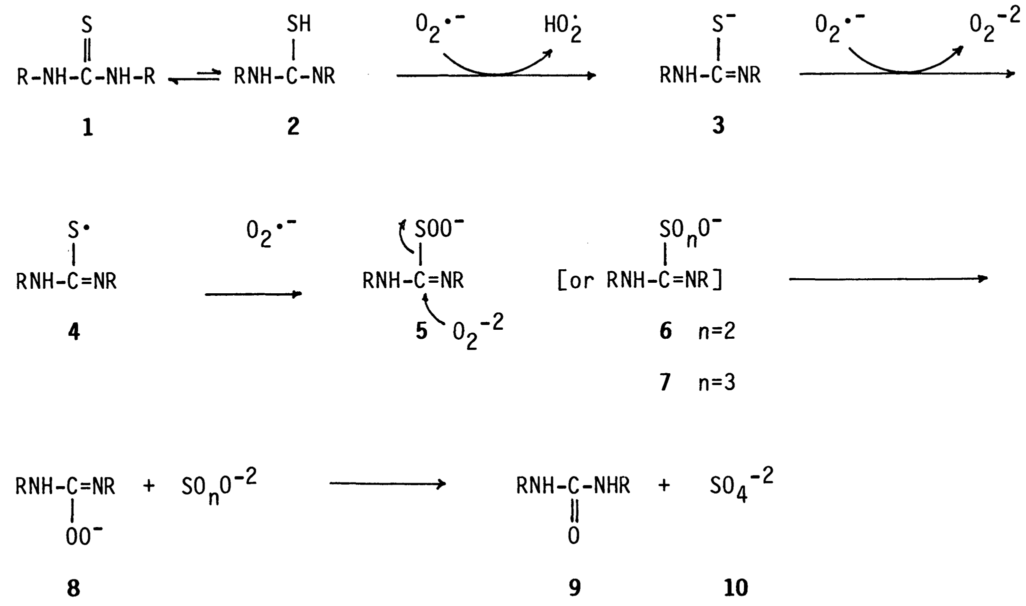
9 10 11 12

In a typical experiment, a mixture of 1,3-diphenylthiourea (228 mg, 1 mmol) and powdered potassium superoxide (296 mg, 4 mmol) in anhydrous dimethyl sulfoxide (4 ml) was stirred well for 8 h at 20 °C under nitrogen atmosphere, then poured into cold water, and extracted with chloroform. Potassium sulfate (ca. 80%) was obtained from the water layer. The chloroform solution was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The yield of dimethyl sulfone was determined by gas chromatographic analysis. The residues were separated by low pressure liquid column chromatography (eluent: CH_2Cl_2) to give 1,3-diphenyl urea (85%) and a trace amount of 1,2,3-trisubstituted guanidine.10) The products obtained were identified by comparing their IR, ^{1}H NMR, and mass spectra with those of authentic samples. The results obtained are summarized in Table 1.

Table 1. Conversion of Thiourea Derivatives ($R^1R^2N(C{=}S)NR^3R^4$) to the Urea Derivatives by Superoxide($^{\overline{\cdot}}O_2$)a) in DMSO.b)

Run	Substrates R^1	R^2	R^3	R^4	Reaction time/h	Yield/%c)	Recovery
1	$4\text{-}O_2N\text{-}C_6H_4\text{-}$	H	$4\text{-}O_2N\text{-}C_6H_4\text{-}$	H	3	95	-
2	$4\text{-}O_2N\text{-}C_6H_4\text{-}$	H	$C_6H_5\text{-}$	H	8	93	-
3	$4\text{-}O_2N\text{-}C_6H_4\text{-}$	H	$4\text{-MeO-}C_6H_4\text{-}$	H	10	86	-
4	$C_6H_5\text{-}$	H	$C_6H_5\text{-}$	H	8	85	-
5	$4\text{-Cl-}C_6H_4\text{-}$	H	$4\text{-Cl-}C_6H_4\text{-}$	H	16	55	40
6	$2\text{-Me-}C_6H_4\text{-}$	H	$2\text{-Me-}C_6H_4\text{-}$	H	24	72	10
7	$4\text{-Me-}C_6H_4\text{-}$	H	$4\text{-Me-}C_6H_4\text{-}$	H	24	80	
8	$4\text{-MeO-}C_6H_4\text{-}$	H	$4\text{-MeO-}C_6H_4\text{-}$	H	30	50	44
9	Cyclohexyl-	H	Cyclohexyl-	H	36	95d)	-
10	$C_2H_5\text{-}$	$C_6H_5\text{-}$	$C_6H_5\text{-}$	H	72	35	60
11	$C_2H_5\text{-}$	$C_6H_5\text{-}$	$C_6H_5\text{-}$	$C_6H_5\text{-}$	72	0	100
12	$C_6H_5\text{-}$	$C_6H_5\text{-}$	$C_6H_5\text{-}$	$C_6H_5\text{-}$	72	0	100

a) Molar ratio ; substrates : KO_2 = 1:4. b) K_2SO_4 was isolated in yields of 55-80%.
c) Isolated yield. d) 1,3-Dicyclohexylthiourea : KO_2 : 18-crown-6-ether = 1:4:0.4.



Scheme 1.

1-Ethyl-1,3-diphenylthiourea was converted with $O_2^{\bullet -}$ to the corresponding urea (35%) in DMSO (Table 1, Run 10), but no oxidation occurred with 1,1,3,3-tetraphenyl- and 1,3-diethyl-1,3-diphenylthiourea which have no proton on the nitrogen atom: the starting material was recovered quantitatively under the same reaction conditions (Table 1, Runs 11 and 12). The possibility of the formation of a tetrahedral intermediate formed by a direct nucleophilic attack of $O_2^{\bullet -}$ on the thiocarbonyl carbon like the nucleophilic attack of $O_2^{\bullet -}$ to phenylacetate or ethylacetate[11)] can be ruled out because tetraphenyl thiourea, whose more electrophilic thiocarbonyl carbon is expected to be more readily attacked by $O_2^{\bullet -}$ than 1,3-diphenyl thiourea, was not observed to react with $O_2^{\bullet -}$ under the same conditions. Thus, the oxidation reaction of thiourea derivatives appears to require, at least, one proton which is neccessary for the tautomeric change from thioureas (**1**) to the thiol form (**2**). Using more than three equiv. of $O_2^{\bullet -}$ with thioureas (**1**) gave higher yields of ureas (**9**).[12)] The thiolate anion (**3**) in basic $O_2^{\bullet -}$ may be converted to the thiyl radical (**4**) by one electron transfer for $O_2^{\bullet -}$. A behavior of $O_2^{\bullet -}$ as an oxidizing agent to accept one electron has been reported.[2)] The thiyl radical, **4** then couples with $O_2^{\bullet -}$ to form peroxysulfenate (**5**). The reaction of peroxysulfur intermediates (**5**, **6**, or **7**) or peroxyintermediate (**8**) with the oxygen trapping reagent such as DMSO led to dimethyl sulfone (50-80%). A nucleophilic attack[13)] by O_2^{-2} or $O_2^{\bullet -}$ on the formamidine carbon may form the urea together with SO_2^{-2} or SO_3^{-2} which is further oxidized[14] to SO_4^{-2}. A key step appears to be oxidation of 1,3-disubstituted thioureas to the sulfinates or sulfonates, since the heterocyclic thioureas such as benzimidazole-2-thione or naphth[2,3-d]imidazole-2-thione were shown to be readily oxidized to the corresponding sulfonate respectively in quantitative yields.$^{8)}$ Actually, stable 1,3-dicyclohexylthiourea -S,S-dioxide and -trioxide were found to react with various amounts of $O_2^{\cdot -}$ (1-3 equiv.) at 20 °C to give the corresponding urea in quantitative yields respectively.

Although considerable interest has been focused on the oxidation of thioureas using alkali halides,$^{15)}$ sodium peroxide,$^{16)}$ and alkaline hydrogen peroxide,$^{17)}$ all the oxidations are carried out in aqueous solvents and inferior to our method in comparison with the yields of urea products. Usually, the reactions using KO_2 needs 18-crown-6-ether, but our method does not require the crown ether for the desulfurization reactions at room temperature though the reactions in the presence of 18-crown-6-ether were observed to be accelerated, and is simple for work up and considered to be widely available for the desulfurization of thiourea derivatives.

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10) Usually, the yields of 1,2,3-trisubstituted guanidines are less than 5%: Runs 1,2,3, and 9(0%), Runs 4,5,6, and 8(ca. 1-5%).
11) M.J. Gibian, D.T. Sawyer, R. Tanpoonpholivivat, T. Ungermann, and M.M. Morrison, *J. Am. Chem. Soc.*, **101**, 640 (1979).
12) The yield of **9** (R=Ph) increased as the amount of KO_2 used increased (KO_2/**1**, reaction time (h), yield of **9**; 1, 24 h, 32 %; 2, 24 h, 45 %, 3, 24 h, 60 %; 4, 8 h, 85 %).
13) $O_2^{\cdot -}$ is known to be less basic but more nucleophilic than hydroxide anion: S. Oae and Y. Kadoma, *Chemistry*, **27**, 1045 (1973).
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