

Activation of superoxide: Application of peroxysulphur intermediates to organic synthesis

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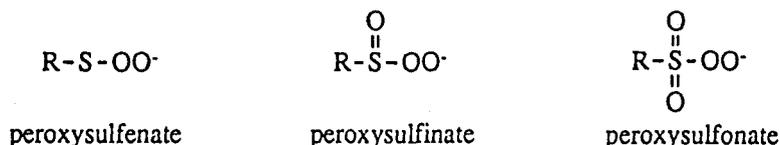
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Abstract : For the activation of superoxide anion radical ($O_2^{\cdot-}$), $O_2^{\cdot-}$ was reacted with arenesulfonyl or arenesulfinyl-chlorides at $-20 - 30\text{ }^\circ\text{C}$ to generate the corresponding new arenesulfonylperoxy- or arenesulfinylperoxy radical intermediates. These peroxysulfur intermediates show excellent oxidizing abilities for the regioselective epoxidations of olefins, oxidative desulfurizations of thiocarbonyls to carbonyls, cleavages of $C=N$ to $C=O$ and conversion of the benzylic methylene groups to ketones under mild conditions at ca. $-20\text{ }^\circ\text{C}$. The formation of these peroxy intermediates have been also confirmed by the spin trapping studies by ESR.

INTRODUCTION

Intensive investigation of the biochemistry and chemistry of superoxide anion radical has been reported since the discovery of superoxide dismutase.¹ Several reviews on organic reactions involving the superoxide has appeared.² Recently, the accumulation of information of the physical and chemical properties of superoxide has promoted the study of organic chemistry using superoxide. It has been amply demonstrated that $O_2^{\cdot-}$ displays four basic modes of action including deprotonation as a base, H-atom abstraction as a radical, nucleophilic attack as an anion, and an electron transfer reagent. However, the oxidizing ability of $O_2^{\cdot-}$ is limited, probably due to its relatively weak reactivity and poor solubility in aprotic organic solvents. Superoxide has been known to act as a moderated reducing agent but a pitifully weak oxidizing agent.³ Thus numerous reports dealing with the activation of superoxide through reactions of various organic substrates with superoxide have appeared within only one decade.

It has been reported that peroxysulfur intermediates such as peroxysulfenate, peroxysulfinate, and peroxysulfonate which are formed from the reaction of organic sulfur compounds with superoxide anion have the ability to oxidize sulfoxides, phosphines, and olefins to the corresponding sulfones, phosphine oxides, and epoxides, respectively.⁴⁻⁶



The peroxy intermediate (Cl_3COO^{\cdot}) was reported to induce the formation of the active species which causes the biological toxicity.⁷ Treatment of diarylthioureas with $O_2^{\cdot-}$ resulted in the formation of triarylguanidines or ureas in good yields. This reaction appears to involve a peroxysulfenate intermediate.⁸

Most of these peroxy intermediates have been studied in connection to the reactivity of superoxide or the biological toxicity but are not sufficiently strong oxidizing agents for use in organic synthesis, probably due to their instability. Thus, it has been attempted to find a more stable peroxy intermediate. The synthetic approach using peroxy intermediates generated from superoxide and some activators was recently achieved in our laboratory. The formation and characterization of peroxysulfur intermediates are reviewed. Various useful organic synthesis using peroxysulfur intermediates formed by activating superoxide are introduced with a special emphasis on the reaction mechanism and character of peroxy intermediates.

Epoxidation of olefins, oxidation of arenes to arene oxides, oxidation of sulfides to sulfoxides, and oxidation of sulfoxides to sulfones occurred smoothly under mild conditions. Oxidative desulfurization of thioamides and thioureas, oxidative cleavage of $C=N$ to $C=O$, and oxidation of active methylene group ($-CH_2-$) to ketones ($C=O$) could be smoothly carried out.

OXIDATION OF THIOUREAS

Treatment of 1,3-disubstituted thioureas with $O_2^{\cdot-}$ at 20 °C in DMSO resulted in formation of 1,3-disubstituted ureas in good yields as shown in Table 1. The desulfurization seems to proceed by the formation of a peroxysulfenate (Scheme 1).⁹

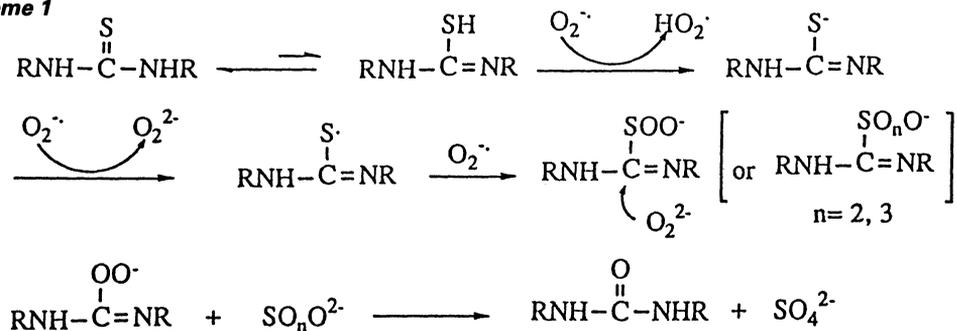
TABLE 1. Conversion of thioureas($R^1R^2N(C=S)NR^3R^4$) to ureas by $O_2^{\cdot-}$ in DMSO.^{a,b}

Run	R ¹	Substrate R ²	R ³	R ⁴	Reaction time/h	Yield/% ^c	Recovery
1	4-O ₂ N-Ph-	H	4-O ₂ N-Ph-	H	3	94	-
2	4-O ₂ N-Ph-	H	Ph-	H	8	93	-
3	4-O ₂ N-Ph-	H	4-MeO-Ph-	H	10	86	-
4	Ph-	H	Ph-	H	8	85	-
5	4-Cl-Ph-	H	4-Cl-Ph-	H	16	55	40
6	2-Me-Ph-	H	2-Me-Ph-	H	24	72	10
7	4-Me-Ph-	H	4-Me-Ph-	H	24	80	-
8	4-MeO-Ph-	H	4-MeO-Ph-	H	30	50	44
9	Cyclohexyl-	H	Cyclohexyl-	H	36	95 ^b	-
10	Et-	Ph-	Ph-	H	72	35	60
11	Et-	Ph-	Ph-	H	72	0	100
12	Ph-	Ph-	Ph-	H	72	0	100

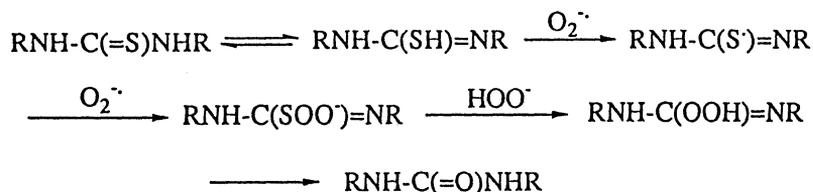
a. Molar ratio; substrate : KO_2 = 1 : 4. b. K_2SO_4 was isolated in yields of 55-80%.

c. Isolated yield. d. 1,3-Dicyclohexylthiourea : KO_2 : 18-crown-6-ether = 1 : 4 : 0.4.

Scheme 1

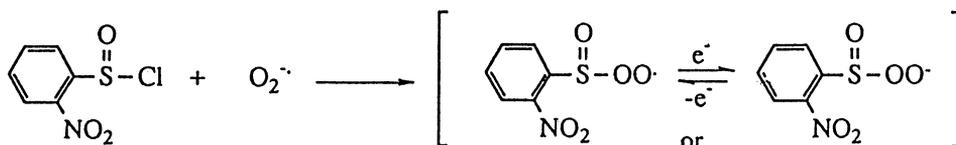
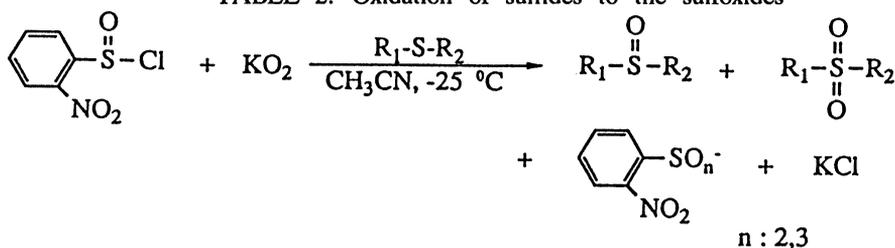


As described in the above reaction of thioureas with superoxide, this reaction probably involves the formation of unstable peroxysulfenate. If an activated oxygen atom of a superoxide anion and such a peroxysulfur intermediate are involved in alkaline autoxidation, the latter may be expected to be a useful intermediate in desulfurization owing to its lability under the strongly alkaline conditions. Thus, key steps would appear to involve the formation of peroxysulfenate intermediate by coupling of the thioyl radical and $O_2^{\cdot-}$ which may occur in alkaline conditions^{10,11} as shown below.



OXIDATION OF SULFIDES

In the oxidation of sulfides to sulfoxides, it is important to avoid the further oxidation of the sulfoxides to sulfones. Various sulfides are readily oxidized to the corresponding sulfoxides in excellent yields under the mild condition by 2-nitrobenzenesulfinyl peroxy intermediate which is generated *in situ* by the treatment of 2-nitrobenzenesulfinyl chloride and potassium superoxide at -25°C in acetonitrile.¹² Only traceable amount of the sulfones were obtained or observed by ^1H NMR spectroscopy. The results obtained are shown in Table 2.

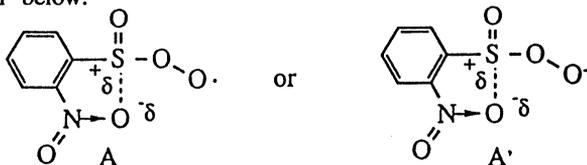
TABLE 2. Oxidation of sulfides to the sulfoxides^a

Run	R ₁	R ₂	Reaction time(h)	-SO-	Yield(%) ^b -SO ₂ -	-S-
1	4-Me-Ph	Me	5	97	trace	
2	4-Me-Ph	Benzyl	4	95	"	
3	4-Me-Ph	Et	4	96	"	
4	Ph	Me	4	92	"	
5	4-Br-Ph	Me	5	95	"	
6	4-Cl-Ph	Me	5	91	"	
7	4-Cl-Ph	Et	4	94	"	
8	4-Cl-Ph	Benzyl	7	94	"	
9	Benzyl	Benzyl	5	97	3 ^c	
10	α -Naphthyl	Me	7	98	2 ^c	
11	4-NO ₂ -Ph	Me	8	62	12	24 ^c

a: Molar ratio ; sulfide : ArSO₂ : KO₂ = 0.5 : 1 : 3

b: Isolated yields. c: Determined by ^1H NMR.

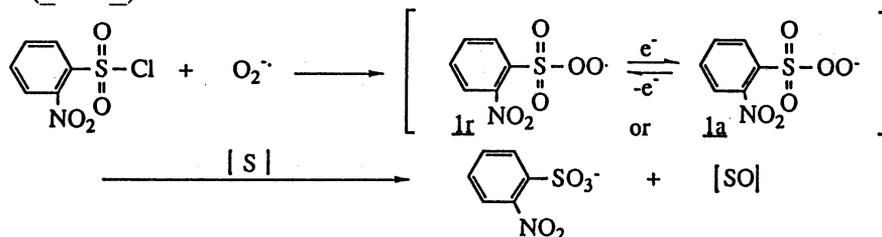
The sulfinylperoxy intermediate seems to be stabilized by a neighboring group effect of the nitro group as shown below.



4-Tolylsulfinyl peroxy intermediate generated from 4-tolylsulfinyl chloride and O₂^{·-} meanwhile gave much poorer yields of the sulfoxides than these obtained using A (or A') or 4-nitrobenzenesulfinyl peroxy intermediate. Thus, the nitro group in 2-position of A (or A') appears to play an important role in accelerating the substitution of chlorine with superoxide and also in stabilizing the intermediate A (or A') by a neighboring group effect.

Various sulfonyl chlorides have been found to react with O₂^{·-} to generate sulfonyl peroxy compounds, which have been neither isolated nor confirmed. Although stable sulfonyl peroxy intermediates have been neither isolated nor confirmed successfully, nitrobenzenesulfonyl peroxy intermediates have been found to be quite stable at low temperatures. Both 2-nitro and 4-nitrobenzenesulfonyl chlorides readily react with O₂^{·-} in acetonitrile under mild conditions to form 2-nitro and 4-nitrobenzenesulfonyl peroxy intermediates. However, 2-nitrobenzenesulfonyl peroxy intermediate (*1r* or *1a*) has been shown to give better yields in the oxidation of olefins than 4-nitrobenzenesulfonyl peroxy intermediate. A neighboring

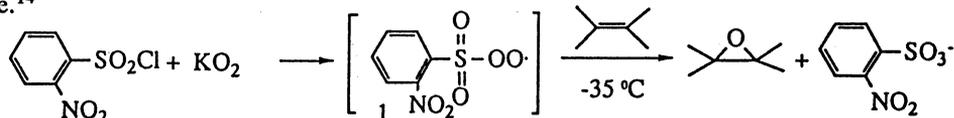
group effect of NO_2 at the 2-position appears to play an important role in stabilizing the peroxy intermediate ($\underline{1r}$ or $\underline{1a}$).



Here, the question of whether the active intermediate involves a radical $\underline{1r}$ or anion species $\underline{1a}$ which can be formed by one electron transfer from $\text{O}_2^{\cdot -}$ to $\underline{1r}$ arises. Judging from the recent results obtained from the various chemical reactions, an electrophilic radical species ($\underline{1r}$) of sulfonyl peroxy intermediate is believed to be involved in the oxidation of various substrates.¹⁴⁻¹⁶ 2-Nitrobenzenesulfonyl peroxy radical ($\underline{1a}$) has been trapped by the spin trapping studies using 5,5-dimethyl-1-oxide (DMPO).¹³ The sulfonyl peroxy intermediate ($\underline{1r}$ or $\underline{1a}$) seems to be stabilized by a neighboring group effect of the nitro group.

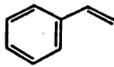
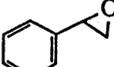
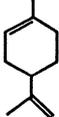
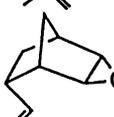
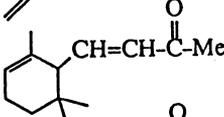
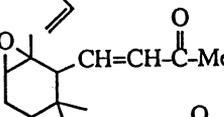
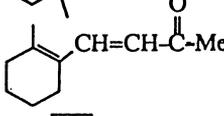
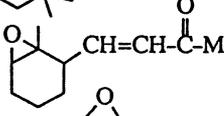
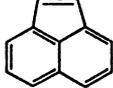
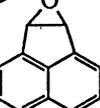
EPOXIDATION OF OLEFINS

Various olefins containing mono- and multidouble bonds in a molecule were readily oxidized to their epoxides in high regioselectivity and in excellent yields with 2-nitrobenzenesulfonyl peroxy intermediate ($\underline{1}$) generated *in situ* from 2-nitrobenzenesulfonyl chloride and superoxide at -35°C in acetonitrile.¹⁴



Epoxidation of olefins containing an α,β -unsaturated ketone moiety such as 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (α -ionone) and 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (β -ionone) affords their corresponding epoxides in excellent yields. (Table 3)

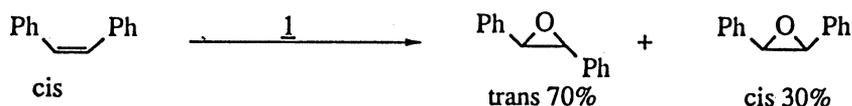
TABLE 3. Epoxidation of olefins by 2-nitrobenzenesulfonyl peroxy intermediate at ca. -30°C .

Substrate	Time (h)	Product	Yield (%) ^c
	4.5		92
	5.0		82
	4.5		87
	5.0		78
	3.0		85
	2.5		84
	12		95 ^b

a) Molar ratio ; olefin : ArSO_2Cl : KO_2 = 0.7 : 1.0 : 3.0.

b) Molar ratio ; olefin : ArSO_2Cl : KO_2 = 1.0 : 2.0 : 8.0. c) Isolated yields.

Highly strained acenaphthylene was smoothly epoxidized in quantitative yields at $-30\text{ }^{\circ}\text{C}$ in acetonitrile. ¹⁷ Acenaphthylene oxide is known to be unstable under acidic conditions, but more stable under basic conditions. ¹⁸ Thus, acenaphthylene oxide could be isolated in higher yields than those obtained from the known methods, ^{19,20} perhaps due to the stability of the product under basic conditions. The sulfonyl peroxy intermediate is likely to be of the character of a radical, rather than an anion, as in the case of the acyl peroxy radical ($\text{ArC}(\text{O})\text{OO}\cdot$) and phenyl nitroso oxide radical ($\text{PhNOO}\cdot$), ²² judging from the fact that oxidation of cis-stilbene by 1 gave both trans (70%) and cis-oxides (30%) under the same conditions. If the peroxy intermediate (1) is anionic, stereospecific epoxidation of cis-stilbene to cis-epoxide may occur.



Polyaromatic compounds such as phenanthrene and pyrene, which are inert to superoxide itself, were readily oxidized to the corresponding K-region arene oxides by treatment with 1. ²⁴ Anthracene was oxidized to anthraquinone under the same conditions. Since O_2^- is known to be a quite strong base, if the peroxy intermediate is an anion (1a), epoxidation of double bonds attached to ketone can be expected. However, no epoxidation of the double bond in the α,β -unsaturated ketone moiety took place. These results suggest that peroxy intermediate 1 is electrophilic rather than nucleophilic.

OXIDATION OF HYDRAZONES

Various alkyl-aryl and dialkyl tosylhydrazones react readily with 1 to give the corresponding carbonyl compounds in mostly quantitative yields at $-30\text{ }^{\circ}\text{C}$ under mild conditions. In the absence of 2-nitrobenzenesulfonyl chloride, tosylhydrazones were recovered quantitatively under the same conditions: superoxide is inert to tosylhydrazones. The regeneration of carbonyl groups from tosylhydrazones seems to be initiated via the oxidation of the imino double bond of the tosylhydrazones with 1 to oxaziridine derivatives.

TABLE 4. Oxidation of Tosylhydrazones to Ketones.^a

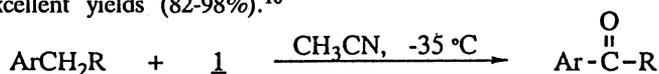
$$\begin{array}{c} \text{R}_1 \\ \diagdown \\ \text{C}=\text{N}-\text{NHTos} \\ \diagup \\ \text{R}_2 \end{array} \xrightarrow[\text{MeCN, } -30\text{ }^{\circ}\text{C}]{\text{1}} \begin{array}{c} \text{R}_1 \\ \diagdown \\ \text{C}=\text{O} \\ \diagup \\ \text{R}_2 \end{array}$$

R ₁	R ₂	Reaction. Time(h)	Yield(%) ^b
p-Cl-Ph	Me	5.3	90
2-NO ₂ -Ph	H	5.0	92
(Ph) ₂ CH	Me	9.0	97
Ph	Me	8.0	93
Et	Me	6.0	98
Me	Me	7.0	93
m-MeO-Ph	H	7.5	83

a) Molar ratio; substrate : ArSO_2Cl : KO_2 = 1 : 2 : 6. b) Isolated yields.

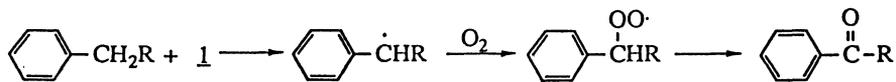
OXIDATION OF METHYLENE GROUPS TO KETONES

The oxidation of the active methylene group is important in the *in vivo* metabolic process catalyzed by oxygenase²⁴ as well as in the organic synthesis. Active methylene groups of lipids are known to be metabolized *in vivo* to the hydroxy or carbonyl group with no evidence of any conversion by activated species of oxygen such as superoxide. ²⁵ Various substrates containing the benzylic methylene group were readily reacted with 1 at $-35\text{ }^{\circ}\text{C}$ under mild conditions to give the corresponding carbonyl compounds in excellent yields (82-98%). ¹⁶



Oxidation of ethylbenzene to acetophenone by electrogenerated superoxide²⁶ and oxidation of substrates containing more labile hydrogen to ketones using potassium superoxide at room temperature²⁷ are reported. However, substrates containing the benzylic methylene group were not oxidized by potassium

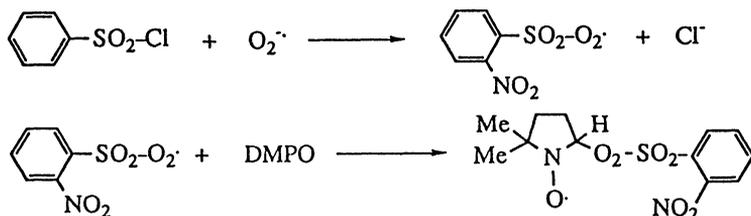
superoxide in the absence of 2-nitrobenzenesulfonyl chloride under the same conditions; starting materials were recovered quantitatively. A plausible reaction mechanism can be postulated as shown below.



One of the hydrogen atoms of the benzylic methylene group is abstracted by 1. The resulting benzylic radical may couple with molecular oxygen or $\text{O}_2\cdot^-$ to form a peroxy radical and then convert to the corresponding carbonyl group.

SPIN TRAPPING OF PEROXSULFUR INTERMEDIATES

The epoxidation of olefins and oxidation of benzylic methylene compounds to ketones described above demonstrate that the sulfonyl peroxy intermediate 1 may be of a radical species. In order to identify the reactive intermediates responsible for the oxidations, spin trapping studies by ESR have been carried out. The spin trapping method has been proved to be of great use for the elucidation of reaction mechanisms involving radical species.^{28,29} 5,5-Dimethyl-1-pyrroline-1-oxide (DMPO) was used as a trapping agent. The major species observed at ca. 5 min after the completion of the reaction shows the ESR spectrum which has hyperfine coupling constants, $a_N=12.8$ G and $a_H=10.1$ G.¹³ Since these values are very different from those reported for DMPO spin adducts of $\text{O}_2\cdot^-$ ($a_N=14.2$ G and $a_H=12.0$ G), $\text{HO}_2\cdot$, and $\cdot\text{OH}$, DMPO could be concluded to efficiently trap the radical produced by the reaction of $\text{O}_2\cdot^-$ and 2-nitrobenzenesulfonyl chloride. Taking account of the results described in this section of the studies on quenching of the peroxy radicals with 2-methyl-2-butenyl phenyl sulfide and triphenylphosphine,¹³ it was concluded that sulfonyl peroxy radical (1r) derived from the reaction between $\text{O}_2\cdot^-$ and 2-nitrobenzenesulfonyl chloride is one of the most reactive intermediates responsible for the oxidation of organic molecules.



REFERENCES

- J.M. McCord and I. Fridovich, *J. Biol. Chem.*, **244**, 6049 (1969).
- For recent reviews: a) E. Lee-Luff, *Chem. Soc. Rev.*, **6**, 195 (1977); b) D.T. Sawyer and J.S. Valentine, *Acc. Chem. Res.*, **14**, 393 (1981); c) A.A. Frimer, "The Chemistry of Functional Group Peroxide", and by S. Patai, John Wiley & Sons (1983), Chap. 14.
- D.T. Sawyer, M.J. Gibian, M.M. Morison, and E.T. Seo, *J. Am. Chem. Soc.*, **100**, 627 (1978).
- T. Takata, Y.H. Kim, and S. Oae, *Tetrahedron Lett.*, 821 (1979).
- S. Oae, T. Takata, and Y.H. Kim, *Tetrahedron*, **37**, 37 (1981).
- S. Oae, T. Takata, and Y.H. Kim, *Bull. Chem. Soc. Jpn.*, **54**, 2712 (1981).
- H. Yamamoto, T. Mashino, T. Nagano, and M. Hirobe, *J. Am. Chem. Soc.*, **108**, 539 (1986).
- a) Y.H. Kim and G.H. Yon, *J. Chem. Soc. Chem. Commun.*, 715 (1983). b) Y.H. Kim G.H. Yon, and H.J. Kim, *Chem. Lett.*, 309 (1984).
- Y.H. Kim, G.H. Yon, and H.J. Kim, *Chem. Lett.*, 309 (1984).
- Y.H. Kim, H.J. Kim, and G.H. Yon, *J. Chem. Soc. Chem. Commun.*, 1064 (1984).
- A. Le Berre and P. Goasguen, *Bull. Soc. Chem. Fr.*, 1682 (1962).
- Y.H. Kim and D.C. Yoon, *Tetrahedron Lett.*, **29**, 6453 (1988).
- Y.H. Kim, S.C. Lim, M. Hoshino, Y. Ohtsuka, and T. Ohishi, *Chem. Lett.*, 167 (1989).
- Y.H. Kim and B.C. Jung, *J. Org. Chem.*, **48**, 1562 (1983).
- H.K. Lee and Y.H. Kim, *Sulfur Lett.*, **7**, 1 (1987).
- Y.H. Kim, K.S. Kim, and H.K. Lee, *Tetrahedron Lett.*, **30**, 6357 (1989).
- H.K. Lee, K.S. Kim, J.C. Kim, and Y.H. Kim, *Chem. Lett.*, 561 (1988).
- K. Ishikawa, H.C. Charles, and G.W. Griffin, *Tetrahedron Lett.*, 427 (1977).
- S. Krishnan, D.G. Kuhn, and G.A. Hamilton, *J. Am. Chem. Soc.*, **99**, 8121 (1977).
- T.H. Kinstle and P.J. Ihig, *J. Org. Chem.*, **35**, 257 (1970).
- Y. Sawaki and Y. Ogata, *J. Org. Chem.*, **49**, 3344 (1984).
- Y. Sawaki, S. Ihikawa, and H. Iwamura, *J. Am. Chem. Soc.*, **109**, 584 (1987).
- Y.H. Kim, H.K. Lee and H.S. Chang, *Tetrahedron Lett.*, **28**, 285 (1987).
- J. Bland, *J. Chem. Educ.*, **55**, 151 (1978).
- J.A. Matthew and T. Galliard, *Photochemistry*, **17**, 1043 (1978).
- T. Matsue, M. Fujihira, and T. Osa, *J. Electrochem. Soc.*, **128**, 2565 (1981).
- Y. Moro-Oka, P.J. Chung, H. Arakawa, and T. Ikawa, *Chem. Lett.*, 1293 (1976).
- E.G. Janzene, *Acc. Chem. Res.*, **4**, 31 (1971).
- C. Langercrantz, *J. Phys. Chem.*, **75**, 3466 (1971).