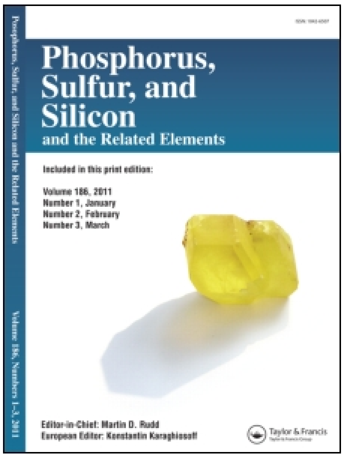

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Application of Ionic Complex of N 2 O 4 with 18-Crown-6 as an Oxidizing Agent for the Oxidation of Organosulfur Compounds

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APPLICATION OF IONIC COMPLEX OF N_2O_4 WITH 18-CROWN-6 AS AN OXIDIZING AGENT FOR THE OXIDATION OF ORGANOSULFUR COMPOUNDS

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Complexation of gaseous N_2O_4 with 18-Crown-6 affords an ionic complex of $NO^+ \cdot 18\text{-crown-6} \cdot H(NO_3)_2^-$. This reagent is a nitrosating agent for conversion of thiols to thionitrites. Disulfides can be obtained from coupling of thiols via thionitrites. Moreover this reagent is an oxidizing agent for conversion of thioethers into their corresponding sulfoxides and dithianes into their carbonyl compounds in an oxidative deprotection reaction.

Keywords: Nitrogen, tetroxide; 18-crown-6; oxidation; organosulphide

INTRODUCTION

The liquid dinitrogen tetroxide freezes at −11°C and boils at 21°C. In polar organic solvents with high dielectric constants, N_2O_4 dissociates into NO^+ and NO_3^-.[1] In ethereal solution at low temperature, liquid dinitrogen tetroxide reacts with tertiary amines to form yellow precipitates of the general formula $N_2O_4.2B$, where B is pyridine, quinoline, isoquinoline, acridine, β-picoline, α-picoline or triethylamine.[2] All these complexes are considered to be unstable at room temperature. In addition, N_2O_4 reacts with several aliphatic and alicyclic ethers such as ethylene glycol diethyl ether, 1,3-dioxane, trioxane, perfluorotetrahydrofuran, α-methyltetrahydrofuran, and 1,4-dioxane to form addition compounds.[3–5] The results of thermal, magnetic, and spectroscopic studies indicate the existence of the compounds with formulas $N_2O_4.2B$ and $N_2O_4.B$, where B is aliphatic or alicyclic ethers. These studies also show the absence of NO_2, NO_2^+, NO_2^-, NO^+, and NO_3^- species in their structures. All of these compounds are unstable at room temperature. When a metal or its salts react with N_2O_4 (alone or mixed with an organic solvent), the product is a metal nitrate combined with N_2O_4 in

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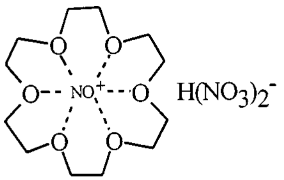


FIGURE 1

stoichiometric ratio.[1] Among the addition compounds of N_2O_4, only two metal nitrates, $Fe(NO_3)_3.1.5N_2O_4$ and $Cu(NO_3)_2.N_2O_4$, have been used for nitration and oxidation of organic compounds.[6,7]

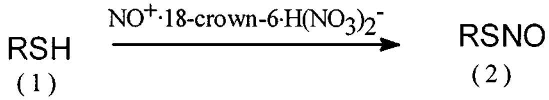
Interaction of N_2O_4 with 18-Crown-6 affords NO^+·18-crown-6·$H(NO_3)_2^-$ as a stable crystalline complex (Figure 1).[8] We have recently reported using this complex for the facile preparation of S-nitrosothiols from thiols[9] and for nitration of phenols with para selectivity.[10] Very recently, oxidation of urazoles and nitrosation of secondary amines with NO^+·18-crown-6·$H(NO_3)_2^-$ was reported.[11,12]

In this article we used NO^+·18-crown-6·$H(NO_3)_2^-$ complex as an efficient oxidizing agent for oxidative transformation of organosulfur compounds.

RESULTS AND DISCUSSIONS

Nitrosation of Thiols

Thionitrites are interesting class of organic compounds and are becoming increasingly useful not only as a source of thiyl radicals[13] or as nitrosating reagents[14] but also as vasodilatory drugs due to their therapeutic use and their remarkable physiological importance.[15–17] As a source of nitrosonum ion, gaseous dinitrogen tetroxide (N_2O_4) has also been used for this transformation. However, the control of the reaction with this gas is important, and the intermediate thionitrite can be converted to disulfides or other oxidation products. The ionic complex of NO^+·18-crown-6·$H(NO_3)_2^-$ in solvents such as ethyl acetate, diethyl ether, *t*-butanol, carbon tetrachloride, and dichlorometane reacts immediately with thiols at room temperature and produces the corresponding thionitrite. The reaction in *t*-butanol is more advantageous than the other solvents in this study in which the reaction mixture solidifies on freezing and can be stored for days without change. UV and IR spectral analysis of the products in solution showed the characteristic absorption bands for the thionitrite group which are similar to those reported in the literature (Scheme 1 and Table I).[18,19]



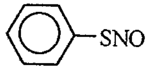
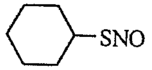
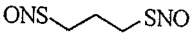
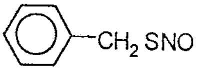
R = (a) n- C_4H_9- (b) Ph- (c) cylohexyl- (d) n- octyl- (e) ethyl-
(f) -CH_2-CH_2-CH_2- (g) n- propyl- (h) $PhCH_2$-

SCHEME 1

Oxidation of Thioethers

The oxidation of thioethers is the most widely used route for the synthesis of sulfoxides. This oxidation can yield either the corresponding sulfoxide or the sulfone or both, depending on the method used. The over-oxidation to a sulfone, an undesired by-product, has accounted for many works done in this area in recent years.[20,21] The ionic complex of NO$^+$·18-crown-6·H(NO$_3$)$_2^-$ is a selective reagent for the transformation of thioethers to the corresponding sulfoxides without the formation of sulfone. The reaction proceeds to completion from immediate to 30 min in CH_2Cl_2 at room temperature (Scheme 2 and Table II).

TABLE I Reaction of Thiols with NO$^+$·18-Crown-6·H(NO$_3$)$_2^-$ in *t*-Butanol at Room Temperature[a]

Thiol	Product[b]	λ_{max} (nm)/Absorbance[c,18,19]
1a	$CH_3(CH_2)_2CH_2SNO$	339/1.99, 551.2/0.09
1b		368/0.91, 572/0.16
1c		342/0.76, 557/0.06
1d	$CH_3(CH_2)_6CH_2SNO$	339/2.89, 551/0.12
1e	CH_3CH_2SNO	337/2.8, 552/0.12
1f		339/1.4, 551/0.11
1g	$CH_3CH_2CH_2SNO$	343/1.67, 600/0.14
1h		341/2.65, 550.4/0.07

[a] The reaction occurred immediately.

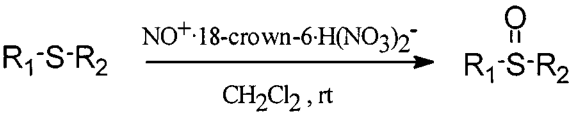
[b] The products were identified by comparison of their UV spectral data with the literature.

[c] All the products show a weak absorption band at about 520 nm that is also a characteristic band of the products.[18,19]

TABLE II Oxidation of Thioethers to Their Corresponding Sulfoxides by $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ in CH_2Cl_2 at Room Temperature

Entry	R_1	R_2	Time (min)	Yield (%)^a
1	C_6H_5	CH_3	^{b}	96
2	C_6H_5	C_2H_5	^{b}	94
3	C_6H_5	$(CH_3)_2CH$	^{b}	94
4	C_6H_5	C_4H_9	^{b}	95
5	C_6H_5	$C_6H_5CH_2$	^{b}	91
6	$C_6H_5CH_2$	C_4H_9	15	90
7	$C_6H_5CH_2$	$C_6H_5CH_2$	15	87
8	C_4H_9	C_4H_9	30	93

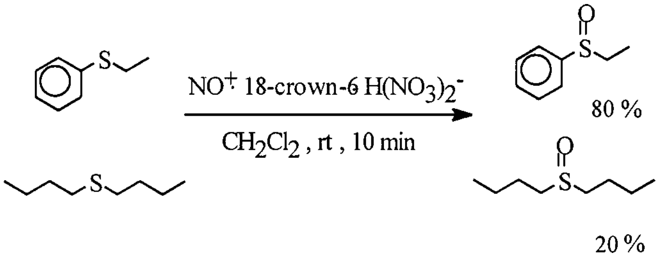
^{a}Isolated yields after column chromatography.
^{b}Reactions were completed immediately.



$$R_1\text{-}S\text{-}R_2 \xrightarrow[CH_2Cl_2\text{, rt}]{NO^+\cdot 18\text{-crown-6}\cdot H(NO_3)_2^-} R_1\text{-}\overset{O}{\overset{\|}{S}}\text{-}R_2$$

SCHEME 2

Even though this reagent is quite reactive and efficient for the oxidation of structurally different thioethers, it shows high selectivity among them. This selectivity is demonstrated by a competitive reaction between ethyl phenyl thioether and dibuthyl thioether (Scheme 3).



SCHEME 3

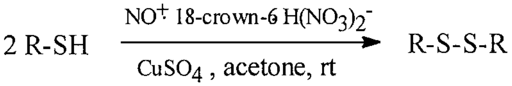
Oxidative Coupling of Thiols

Conversion of thiols to their corresponding disulfides via a thionitrite is a known reaction.[18,19,22,23] This reaction proceeds by the formation of RSNO which distintegrates into RS and NO species. This disintegration needs several hours to occur, but, in the presence of copper ion, a fast reaction occurs. Catalytic activity of copper ions has been suggested to occur through the interaction of copper ions with lone pair electrons of nitrogen in the thionitrite intermediate.[24–26] The ionic complex of

TABLE III Formation of Disulfides from Thiols Using $NO^+ \cdot 18\text{-crown-6} \cdot H(NO_3)_2^-$

Entry	R	Time (min)	Yield (%)
1	Phenyl	5	98
2	Furyl	5	94
3	Benzyl	10	87
4	Cyclohexyl	8	76
5	n-Octyl	5	84
6	3-Methyl Phenyl	3	96
7	n-Buthyl	5	88
8	i-Propyl	15	70

$NO^+ \cdot 18\text{-crown-6} \cdot H(NO_3)_2^-$ conducts in a one pot the transformation of thiols to disulfides in the presence of cupric ion in 3–15 minutes. In situ formation of thionitrites in these reactions is quite evident by the fast development and disappearence of the red colour in the reaction mixture (Scheme 4 and Table III).

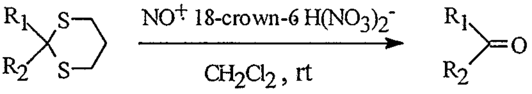


$$2\,\text{R-SH} \xrightarrow[\text{CuSO}_4\text{, acetone, rt}]{NO^+\ 18\text{-crown-6}\ H(NO_3)_2^-} \text{R-S-S-R}$$

SCHEME 4

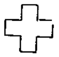
Deprotection of Dithianes

Protection of ketones and aldehydes by the conversion to their corresponding dithio compounds is an important method. Dithio ketals and acetals are resistant to both acid- and base-catalyzed hydrolysis. Deprotection of dithio ketals and acetals into the corresponding carbonyl compound is also an important reaction. Various dithioacetalization methods[27–29] have been used for this transformation. Since the sulfur of the dithio compound is a soft base, it can be attacked by soft acids such as heavy transition metals, Br^+, Cl^+, NO^+, and alkylating reagents.We have successfully used $NO^+ \cdot 18\text{-crown-6} \cdot H(NO_3)_2^-$ as a source of NO^+ for the fast conversion of dithianes into their carbonyl compounds under nonhydrolytic conditions at room temperature (Scheme 5 and Table IV). This reaction proceeds via in situ formation of dithionitrite that is evident by the development of the light red color in reaction media.



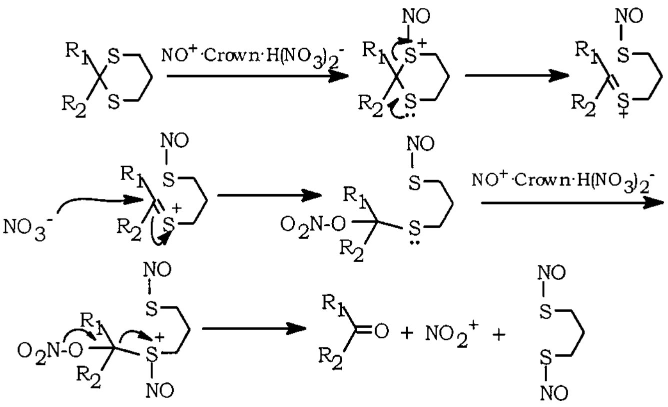
SCHEME 5

TABLE IV Deprotection of Dithianes with $NO^{+}\cdot$18-crown-6$\cdot H(NO_3)_2^-$ in CH_2Cl_2 at Room Temperature

Entry	R_1	R_2	Time (min)	Yield (%)
1	p-BrC_6H_4	H	[a]	94
2	p-ClC_6H_4	H	[a]	91
3	p-MeC_6H_4	H	[a]	90
4	p-$MeOC_6H_4$	H	fa	97
5	p-$NO_2C_6H_4$	H	20	82
6	m-MeC_6H_4	H	[a]	96
7	C_6H_5	Me	[a]	70
8	p-$NO_2C_6H_4$	Me	30	65
9	C_6H_5	C_6H_5	[a]	98
10	p-ClC_6H_4	Me	[a]	87
11	p-MeC_6H_4	Me	[a]	92
12			[a]	75
13			[a]	73
14			[a]	71
15			fa	63

[a] The reaction occurs immediately.

We have proposed a mecanism for the oxidative dethioacetalization of dithianes by $NO^{+}\cdot$18-Crown-6$\cdot H(NO_3)_2^-$ in organic solvents (Scheme 6).



SCHEME 6

EXPERIMENTAL

Products were characterized by comparison of their physical and spectral data with those of authentic samples. Chemicals were either purchased from Fluka, Merck, Chemical Companies, or were prepared in our laboratories by the known procedures. IR spectra were recorded on a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Bruker DPX 250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX. The purity determination of the substrates and reaction monitoring were accomplished by TLC analysis on silica gel polygram SILG/UV 254 plates or on a GLC on a Shimadzu GC-14A instrument.

Preparation of $NO^+ \cdot$18-Crown-6$\cdot H(NO_3)_2^-$

A solution of 18-crown-6 (10 g, 38 mmol) in CH_2Cl_2 (150 ml) was cooled to -10°C in an ice-salt bath while being stirred. Generated N_2O_4 gas[30] was bubbled through this solution for about 1 h. The solvent was evaporated under reduced pressure to give the $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ complex as a white crystalline solid (m.p. 52–55,[8] 14.26 g, 90%).

Nitrosation of Thiophenol, a Typical Procedure

To a stirred solution of thiophenol (0.11 g, 1 mmol) in *t*-butanol (5 ml), was added $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ (0.42 g 1 mmol) at room temperature. The reaction was completed immediately, and a bright red solution was obtained. UV and IR spectral data of the mixture in *t*-butanol was compared with the reported data in the literature.[18,19] The frozen mixture can be stored for several days without any change.

Oxidation of Methyl Phenyl Thioether, a Typical Procedure

To a vigorously stirred solution of methyl phenyl thioether (0.124, 1 mmol) in CH_2Cl_2 (5 ml) at room temperature was added $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ (0.42 g 1 mmol). The reaction was completed immediately. After column chromatography on silica gel eluted with petroleum ether:acetone (6:4), methyl phenyl sulfoxide as a yellow oily material was obtained (0.136 g 96%, b.p. 100–104°C, lit[31] 102°C).

Conversion of Thiophenol into Phenyl Disulfide by $NO^+\cdot$18-Crown-6$\cdot H(NO_3)_2^-$: A Typical Procedure

To a solution of thiophenol(0.11 g, 1 mmol) in acetone (5 ml) was added $NO^+\cdot$18-crown-6$\cdot H(NO_3)_2^-$ (0.21 g 0.5 mmol) and anhydrous $CuSO_4$ (0.1g). The mixture was stirred at room temperature for 5 min. The solvent was evaporated, sodium hydroxide (2 N,10 ml) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 ml). After the removal of solvent and column chromatography on silica gel eluted with CCl_4, phenyl disulfide was obtained (0.21 g, 98%, b.p. 59–60°C, lit[32] b.p. 60°C).

Oxidative Deprotection of 2,2-Diphenyl-1,3-dithiane with $NO^+\cdot$18-Crown-6$\cdot H(NO_3)_2^-$: A Typical Procedure

To a stirred solution of 2,2-diphenyl-1,3-dithiane (0.272 g 1 mmol) in CH_2Cl_2 (5 ml) at room temperature was added $NO^+\cdot$18-crown-6$\cdot H(NO_3)_2^-$ (0.84 g 2 mmol). The reaction was completed immediately. After column chromatography on silica gel eluted with petroleum ether/acetone (9/1), pure diphenyl ketone was obtained (0.178 g, 98%, m.p. 47°C, lit[31] m.p. 47–49°C).

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