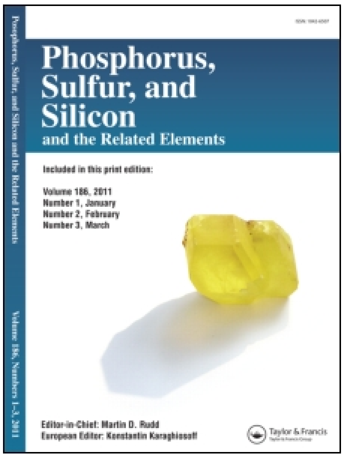

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Silica-Polyethyleneglycols/N 2 O 4 Complexes as Heterogeneous Nitrating and Nitrosating Agents

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SILICA-POLYETHYLENEGLYCOLS/N_2O_4 COMPLEXES AS HETEROGENEOUS NITRATING AND NITROSATING AGENTS

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*Silica-chloride was reacted with different quantities of $H(OCH_2CH_2)_nOH$ ($n = 2$–4) to furnish silica-based linear polyethylene glycols and cyclic polyethylene glycolic ethers. The N_2O_4 complex of silica-tetraethylene glycolic ether (**III**) was selected and used as a stable, cheap, and heterogeneous silica-based reagent for the selective mono- and dinitration of phenols and nitrosation of thiols.*

Keywords: Nitration; nitrosation; phenols; silica-polyethyleneglycols/N_2O_4; thiols; thionitrites

Polyethylene glycols (PEGs) are important components of crown ethers, cryptands, and other ion receptors[1] and their capability of binding with different ions are widely investigated.[2a,b] The binding of nitronium[3] and nitrosonium[4] ions, and N_2O_4[5] with crown ethers attracted organic chemists because of the application of these complexes as nitrating and nitrosating agents. Recently, we reported on the application of N_2O_4 complexes of 18-crown-6 and silica acetate for the selective mono- and dinitration of phenols, nitrosation of thiols, and oxidation of sulfides.[6,7] Although in comparison with the gaseous N_2O_4 the use of 18-crown-6/N_2O_4 complex for these synthetic aims has some reported advantages, the main problems with this complex remains that 18-crown-6 is relatively an expensive precursor and its N_2O_4 complex is very soluble in organic solvents. Due to the solubility of this complex in organic solvents, chromatography is required in the work-up procedure. Especially, in the case of *in situ* synthesis of unstable thionitrites from thiols, the presence of soluble 18-crown-6-N_2O_4 in the reaction mixture is a problem for having pure solution of thionitrites for further synthetic applications.

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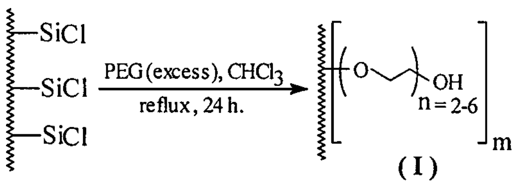
RESULTS AND DISCUSSION

In order to have a cheap and heterogeneous source of N_2O_4, we have prepared some silica-based linear polyethylene glycols and cyclic polyethylene glycolic ethers and their N_2O_4 complexes. In comparison with the reported PEG-NO_2,[2b] which is liquid, these easily prepared complexes are solid and can be used as efficient heterogeneous reagents for the selective mono- and dinitration of phenol, nitration of substituted phenols, and nitrosation of thiols.

Silica-chloride was prepared from the reaction of silica-gel with thionyl chloride under reflux conditions for 48–72 h according to the literature.[8]

Silica-based polyethylene glycols (**I**) can be easily prepared by refluxing a mixture of silica-chloride with excess of the appropriate glycol in $CHCl_3$; (Scheme 1).

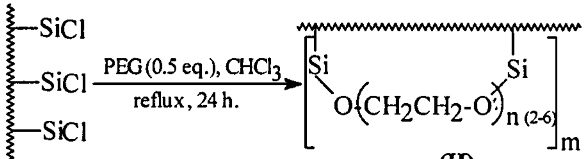


(I)

SCHEME 1

Displacement of chloride in SiO_2-Cl with different glycols, $H(OCH_2CH_2)_nOH$ ($n = 2$–4) offer different silica-based linear polyethylene glycols (**I**) having 1.55–2.07 mmol of glycol per gram of the silica-based reagent. The results of displacement of chloride in silica-chloride with different PEGs are shown in Table I.

Reaction of the resulted silica-based linear polyethylene glycols with N_2O_4 gas[9a] in CH_2Cl_2 at $-10°C$ for 3 h followed by the removal of solvent under reduced pressure, afforded their corresponding N_2O_4 complexes.



(II)

SCHEME 2

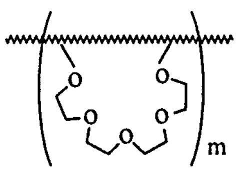
TABLE I Reaction of Silica-Chloride with Excess of PEGs Followed by Reaction with N_2O_4 Gas

Silica-Cl (g)	PEG	Silica-linear PEG (**I**) (g)	mmol of PEG/g of silica-linear PEG	mmol of N_2O_4/g of silica-linear PEG
5	Diethylene glycol	5.72	2.07	2.0
5	Triethylene glycol	6.03	1.82	2.5
5	Tetraethylene glycol	6.40	1.78	2.6
5	Pentaethylene glycol	6.64	1.63	3.0
5	Hexaethylene glycol	6.90	1.55	3.4

Table I shows the amount of absorbed N_2O_4 (mmol) per gram of silica-polyethylene glycol (**I**).

In order to prepare silica-based cyclic polyethylene glycols (**II**) as the analogs of crown ethers, silica-chloride was reacted with 0.5 molar equivalent of each of polyethylene glycols (Scheme 2). The resulted products then reacted with N_2O_4 gas to produce their N_2O_4 complexes (Table II).

The capacity of N_2O_4 in silica-linear PEGs/N_2O_4 complexes is higher than their cyclic analogs. This well could be due to the nitration of the terminal hydroxyl groups by N_2O_4 which results the consumption of higher amounts of N_2O_4. However, the stability of the cyclic complexes was found to be much higher than the linear silica compounds. The results of Table II shows that among the silica-based cyclic compounds, silica-tetraethylene glycolic ether (**III**) has the most suitable structure for giving the stable complex with N_2O_4 gas with highest capacity of dinitrogen tetroxide.



(III)

The amount of N_2O_4 absorbed by this compound (**III**) was found to be 1.4 mmol of N_2O_4 per gram of **III**/N_2O_4 complex. The IR spectrum of **III**/N_2O_4 showed a strong absorption band centered at 1370 cm^{-1} similar to that observed for N_2O_4 or its ether and amine complexes[9b–d] at 1360 cm^{-1} which suggests that a similar kind of complexation can occur between N_2O_4 and **III**/N_2O_4.

Although both N_2O_4 complexes of silica-linear and cyclic polyglcols (Tables I and II) can be used as efficient reagents for nitration of

TABLE II Reaction of Silica-Chloride with 0.5 molar equivalents of PEGs Followed by Reaction with N_2O_4 Gas To Give Silica-Cyclic Polyethylene Glycolic Ethers/N_2O_4 Complexes

Silica-Cl (g)	PEG	Silica-cyclic PEG (g)	mmol of PEG/g of silica-cyclic PEG	mmol of N_2O_4/g of silica-cyclic PEG
5.0	Diethylene glycol	5.14	0.84	1.2
5.0	Triethylene glycol	5.29	0.74	1.3
5.0	Tetraethylene glycol	5.44	0.72	1.4
5.0	Pentaethylene glycol	5.57	0.69	1.2
5.0	Hexaethylene glycol	5.64	0.61	1.1

phenols, due to the more stability of **III**/N_2O_4 among these complexes, we chose it as the preferred reagent and used it for the nitration of phenolic compounds and nitrosation of thiols in this studies under heterogonous conditions. We first optimized the reaction conditions by performing the nitration of phenol by **III**/N_2O_4 complex of in different solvents. When we carried out the reaction at room temperature, it was observed that the reaction of phenol occurs immediately in dichloromethane. Although the rate of the reaction changes by changing the solvent, but the ratio of *ortho*- and *para*-nitro phenol was found to be solvent independent (Table III).

Mononitration of substituted phenols with (**III**)/N_2O_4 in CH_2Cl_2 at room temperature afforded the mononitro compounds in high to excellent yields (Table IV).

We then tried dinitration of phenol. This reaction was performed in refluxing EtOAc with (**III**)/N_2O_4 for 30 min to produce 2,4-dinitrophenol in 75% yield. Dinitration of substituted phenols also was carried out under similar reaction conditions to afford dinitro substituted phenols from 70 to 98% yields (Table V).

The use of gaseous N_2O_4 in different solvents has been reported to convert thiols into their corresponding S-nitrosothiols (thionitrites) at

TABLE III Mononitration of Phenol with **III**/N_2O_4 in Different Solvents at Room Temperature

Entry	Solvent	Time (min)	Total isolated yield (%)	Products distribution (%) of *o*- and *p*-nitrophenol
1	CH_2Cl_2	Immediately	94	ortho (40), para (60)
2	$CHCl_3$	15	92	ortho (40), para (60)
3	Me_2CO	30	93	ortho (38), para (62)
4	Et_2O	30	91	ortho (39), para (61)
5	EtOAc	35	95	ortho (40), para (60)

TABLE IV Mononitration of Substituted Phenols with **III**/N_2O_4 in CH_2Cl_2 at Room Temperature

Entry	Substrate	Time (min)	Product (%)
1	4-Fluorophenol	5	4-Fluoro-2-nitrophenol (95)
2	4-Chlorophenol	5	4-Chloro-2-nitrophenol (96)
3	4-Bromophenol	7	4-Bromo-2-nitrophenol (93)
4	4-Methylphenol	5	4-Methyl-2-nitrophenol (86)
5	4-Acetylphenol	10	4-Acetyl-2-nitrophenol (91)
6	2,6-Dichlorophenol	5	2,6-Dichloro-4-nitrophenol (97)
7	2,6-Dimethylphenol	8	2,6-Dimethyl-4-nitrophenol (80)

low temperatures.[10,11] However, the reaction is very heat sensitive and should be controlled carefully to avoid over-oxidation reactions.[12]

The use of supported nitrosation reagents on inorganic K10 montmorillonite clay such as "claycop," "clayfen"[13] and $Cu(NO_3)_2{\cdot}N_2O_4$[14] for nitrosation of thiols suffer from the immediate over-oxidation reaction into the corresponding disulfides by the copper and iron ions present in the reagents.

In the case of $[NO^+{\cdot}18\text{-crown-6}{\cdot}H(NO_3)_2]$[7] the reagent is soluble and, due to the unstability of thionitrites, its separation from the reaction mixture is not an easy task. Similar problems can rise for the preparation of thionitrites using oxalic acid and sodium nitrite in *tert*-butanol.[15] The use of polyvinylpyrrolidone/N_2O_4,[16] with thiols also should be controlled to avoid over-oxidation to disulfides.

We therefore applied **III**/N_2O_4 as a heterogeneous reagent for the conversion of thiols to thionitrites (Scheme 3). Thiols were

$$\text{RSH} + \textbf{III}/\text{N}_2\text{O}_4 \xrightarrow{t\text{-Butanol,rt}} \text{RSNO}$$

SCHEME 3

TABLE V Dinitration of Substituted Phenols with **III**/N_2O_4 in Refluxing Ethyl Acetate

Entry	Substrate	Time (min)	Product (%)
1	4-Fluorophenol	40	4-Fluoro-2,6-dinitrophenol (97)
2	4-Chlorophenol	50	4-Chloro-2,6-dinitrophenol (98)
3	4-Bromophenol	75	4-Bromo-2,6-dinitrophenol (80)
4	4-Methylphenol	30	4-Methyl-2,6-dinitrophenol (94)
5	4-Acetylphenol[a]	30	4-Acetyl-2,6-dinitrophenol (70)

[a]The reaction was performed in refluxing n-butyl acetate.

TABLE VI Reaction of Thiols (R-SH) with **III**/N_2O_4 in *t* Butanol at Room Temperature[a]

Entry	R	Product[b]	λ_{max} (nm)/Absorbance
1	*n*-Bu	$CH_3(CH_2)_2CH_2SNO$	339.1/2.27, 551.3/0.18
2	Ph	PhSNO	368.0/0.89, 571.7/0.35
3	Cyclohexyl	Cyclohexyl-SNO	337.6/2.03, 552.8/0.39
4	*n*-Octyl	$CH_3(CH_2)_6CH_2SNO$	340.0/1.64, 551.2/0.31
5	Et	CH_3CH_2SNO	336.4/1.54, 551.2/0.31
6	$-CH_2CH_2CH_2-$	$ONS-CH_2CH_2CH_2-SNO$	339.2/2.01, 549.6/0.39
7	*n*-Pr	$CH_3CH_2CH_2SNO$	342.8/1.67, 598.9/0.16
8	$PhCH_2$	$PhCH_2SNO$	341.0/2.65, 552.4/0.13

[a]The reaction occurs immediately.

[b]The products are identified by comparison of their UV spectral data with the literature[11a] and their oxidation to their corresponding disulfides.

converted immediately to their corresponding thionitrites by this complex in different organic solvents such as acetone, dichloromethane, ethyl acetate, and *t*-butanol at room temperature. However, due to the easy freezing of *t*-butanol solution of thionitrites,[15] this solvent was preferred for this reaction. The use of heterogeneous **III**/N_2O_4 provides the possibility of having a pure solution of thionitrites by a simple filtration of the reagent and freezing the solution in order to preserve them for further manipulation. Table VI shows the UV spectral data of the thionitrites preserved in frozen *t*-butanol.

The yield of the reaction is quantitative. This was determined by oxidation of the obtained thionitrites to their corresponding disulfides in the presence of excess of the reagent (see Experimental).

In conclusion, this is the first report on the preparation of silica-based crown ethers/N_2O_4 complexes. The use of **III**/N_2O_4 as a heterogeneous reagent provides an easy, stable, and safe source of N_2O_4 compound. Selective mono- and dinitration of phenols can be performed with this reagent in high yields by just changing the solvent and the reaction temperature. This reagent also can be used for immediate formation of thionitrites from thiols. The hetereogeneous nature of the reagent provides an easy access to the pure solution of thionitrites.

EXPERIMENTAL

Thin layer chromatography on commercial plates of silica-gel 60 F_{254} was used to monitor the progress of the reactions. Column chromatography was carried out using silica gel 60. Yields refer to isolated pure products after column chromatography. UV spectra were recorded on Pye

Unicam 8725 spectrometer. Thionitrites were taken from the reaction mixture and characterized by comparison of their UV spectral data with those of authentic samples. The other products were characterized by comparison of their mp, IR, and NMR spectra with authentic samples.

Preparation of Complex of N_2O_4 with Silica-Linear Diethylene Glycolic Ether as a Typical Procedure

To a suspension of silica-chloride (5.0 g) in $CHCl_3$ (30 ml) was added diethylene glycol (2.4 ml, 25.0 mmol), and the mixture was refluxed for 24 h. The reaction mixture was filtered and washed with $CHCl_3$. After drying, the linear silica-diethylene glycolic ether was obtained (5.72 g). The product was suspend in CH_2Cl_2 (50 ml), and reacted with N_2O_4 gas[8] at $-10°C$ for 3 h. The solvent was evaporated at reduced pressure and the complex was obtained as a white powder.

Preparation of III/N_2O_4

To a suspension of silica chloride (5.0 g) in $CHCl_3$ (30 ml) was added tetraethylene glycol (5.0 mmol), and the mixture was refluxed for 24 h. The reaction mixture was filtered and washed with $CHCl_3$. After drying, compound **III** was obtained (5.44 g). The product was suspend in CH_2Cl_2 (50 ml) and reacted with N_2O_4 gas[8] at $-10°C$ for 3 h. The solvent was evaporated at reduced pressure and the complex was obtained as a white powder. The capacity of N_2O_4 was found to be 1.4 mmol per each gram of **III**/N_2O_4.

Mononitration of Phenol with III/N_2O_4 Complex as a Typical Experiment

A mixture of phenol (0.094 g, 1 mmol) and **III**/N_2O_4 complex (0.7 g) in CH_2Cl_2 (4 ml) was stirred vigorously at room temperature for 5 min. Acetone (5 ml) was added and the mixture was filtered. The resulted mixture was presorbed on silica gel (5.0 g) and was applied on silica-gel column and eluted with petroleum ether/acetone (9:1). 4-Nitrophenol 0.069 g, 53%, m.p. 112°C, [Lit.[16] m.p. 112–114°C] and 2-nitrophenol 0.049 g, 38%, m.p. 45°C, [Lit.[17] m.p. 45–46°C] were obtained respectively.

Dinitration of Phenol with III/N_2O_4 Complex

A mixture of phenol (0.094 g, 1 mmol) and **III**/N_2O_4 complex (1.5 g) in EtOAc (5 ml) was stirred for 30 min under reflux conditions.

Acetone (5 ml) was added and the mixture was filtered. The resulted mixture was presorbed on silica-gel (5.0 g) and was applied on silica-gel column and eluted with chloroform as an eluent. 2,4-Dinitrophenol 0.138 g, 75%, m.p. 111°C, [Lit.[17] m.p. 111–113°C] was obtained.

Mononitration of 4-Chlorophenol with III/N_2O_4 Complex as a Typical Procedure

A mixture of 4-chlorophenol (0.129 g, 1 mmol) and **III**/N_2O_4 complex (0.7 g) in CH_2Cl_2 (4 ml) was stirred vigorously at room temperature for 5 min. Acetone (5 ml) was added and the mixture was filtered. The resulted mixture was presorbed on silica-gel (5.0 g) and was applied on silica-gel column and eluted with petroleum ether/acetone (9:1). 4-Chloro-2-nitrophenol 0.166 g, 96%, m.p. 90°C, [Lit.[18] m.p. 91°C] was obtained as yellow needle crystals.

Dinitration of 4-Chlorophenol with III/N_2O_4 Complex as a Typical Procedure

To a solution of 4-chlorophenol (0.129 g, 1 mmol) in EtOAc (5 ml), **III**/N_2O_4 complex (1.50 g) was added. The mixture was refluxed for 50 min. Acetone (5 ml) was added and the mixture was filtered. The resulted mixture was presorbed on silica-gel (5.0 g) and was applied on silica-gel column and eluted with petroleum ether/acetone (8:2). 4-Chloro-2,6-dinitrphenol was obtained, 0.21 g, 98%, m.p. 80°C, [Lit.[19] m.p. 81°C].

Nitrosation of Thiophenol with III/N_2O_4 Complex as a Typical Procedure

To a solution of thiophenol (0.11 g, 1 mmol) in *t*-butanol (5 ml), **III**/N_2O_4 complex (0.7 g) was added. The resulting mixture was stirred at room temperature. The reaction was completed immediately and a bright red solution was obtained. This mixture can be frozen and kept for several days without any change. If to the obtained solution of thionitrite is added another equimolar of **III**/N_2O_4 (0.7 g) and stirred for an additional hour at room temperature, all the produced thionitrite is converted into diphenyl disulfide. Evaporation of the solvent followed by column chromatography on silica-gel eluted with CCl_4 gives diphenyl disulfide as colorless crystals, 106 mg, 98%, m.p. 60°C, [Lit.[20] m.p. 59–60°C].

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