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IONIC COMPLEX OF N_2O_4 WITH 18-CROWN-6: A HIGHLY EFFICIENT AND SELECTIVE REAGENT FOR NITRATION OF PHENOLS

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Abstract: Interaction of gaseous N_2O_4 with 18-crown-6 affords the stable crystalline complex of $NO^+ \cdot 18\text{-crown-}6 \cdot H(NO_3)_2^-$. This ionic complex is an efficient nitrating agent for the selective mono-, di-, and trinitration of phenol and also for the selective mono-, and dinitration of substituted phenols.

Gaseous nitrogen oxide has found wide applications for nitration of aromatic compounds,[1, 2] nitrosation of amines,[3 - 5] preparation of thionitrites[6] and sulfinyl nitrites,[7] oxidation of olefines,[8, 9] oxidation and oxidative cleavage reactions, [10-13] and some gas/solid reactions.[14] Molecular addition compounds of N_2O_4 gas with some oxygen containing organic compounds such as 1,4-dioxane or 18-crown-6 have been easily prepared and their structures have been elucidated.[15, 16] The structure of the crystalline complex of 18-crown-6 with N_2O_4

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has been confirmed to be $NO^{+}\cdot 18\text{-crown-6}\cdot H(NO_3)_2^{-}$.[16] Since these compounds are solid complexes of N_2O_4 gas with a relatively unreactive organic compounds, it is interesting if they could be used as a readily available solid source of N_2O_4 gas in organic synthesis. We have prepared both N_2O_4 complexes of 1,4-dioxane and 18-crown-6 according to the reported procedures.[15, 16] Complex of 18-crown-6 with N_2O_4 is more stable than 1,4-dioxane and could be stored in the refrigerator for months without loosing its reactivity. Now we report that $NO^{+}\cdot 18\text{-crown-6}\cdot H(NO_3)_2^{-}$ complex is an efficient and highly selective nitrating agent for nitration of phenols. Nitration of phenol was performed immediately in the presence of 0.85 molar equivalents of the complex at room temperature in chloroform, dichloromethane, THF, EtOAc and acetone to give excellent yields of mono-nitrated phenol. Acetone is the solvent of choice for this purpose and resulted the highest total isolated yield of mononitrated phenol (93%) with 58% of para and 35% of ortho isomers. (Scheme 1).

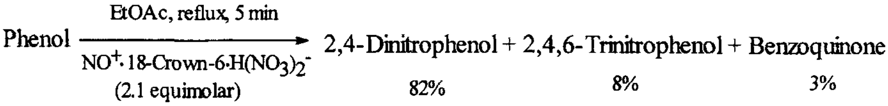
Scheme 1

$$\text{Phenol} \xrightarrow[\substack{NO^{+}\cdot 18\text{-Crown-6}\cdot H(NO_3)_2^{-} \\ (0.85\ \text{equimolar})}]{CH_3COCH_3,\ \text{rt, immediately}} \underset{35\%}{\text{2-Nitrophenol}} + \underset{58\%}{\text{4-Nitrophenol}}$$

Isolation of the crown ether from the reaction mixtures was performed successfully and was reused for the preparation of the reagent.

Dinitration of phenol was also performed with 2.1 molar equivalents of the reagent in refluxing EtOAc to give 2,4-dinitrophenol in 82% yield accompanied with the formation of 2,4,6-trinitrophenol in only 8% yield together with a trace amount of benzoquinone (Scheme 2).

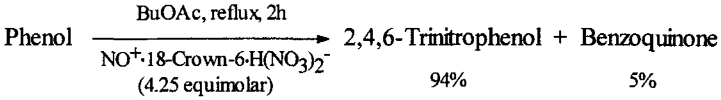
Scheme 2



$$\text{Phenol} \xrightarrow[\substack{NO^{+}\cdot 18\text{-Crown-6}\cdot H(NO_3)_2^{-} \\ (2.1\ \text{equimolar})}]{\text{EtOAc, reflux, 5 min}} \underset{82\%}{\text{2,4-Dinitrophenol}} + \underset{8\%}{\text{2,4,6-Trinitrophenol}} + \underset{3\%}{\text{Benzoquinone}}$$

Trinitration of phenol was also achieved successfully in the presence of 4.25 molar equivalents of the reagent in refluxing BuOAc within 2h in excellent yield (Scheme 3).

Scheme 3



$$\text{Phenol} \xrightarrow[\substack{NO^{+}\cdot 18\text{-Crown-6}\cdot H(NO_3)_2^{-} \\ (4.25\ \text{equimolar})}]{\text{BuOAc, reflux, 2h}} \underset{94\%}{\text{2,4,6-Trinitrophenol}} + \underset{5\%}{\text{Benzoquinone}}$$

Selective mono and dinitration of substituted phenols were also achieved using proper conditions. In the presence of 0.85 molar equivalents of the reagent in acetone at room temperature, selective mononitration was proceeded well in 70-94% yields (Table 1).

Dinitration of 4-substituted phenols with 2.1 molar equivalents of the reagent was performed in refluxing ethyl EtOAc to give excellent yields of dinitrated products (92-97%). The results of these reactions are shown in Table 2. The results obtained for mono and dinitration of 4-methyl phenol with this reagent

Table 1. Mononitration of substituted phenols with 0.85 molar equivalents of $NO^+ \cdot 18\text{-crown-}6 \cdot H(NO_3)_2^-$ in acetone at room temperature.

Entry	Substrate	Time (min.)	%Yield [a] of Mononitration
1	4-Fluorophenol	immediately	90
2	4-Chlorophenol	immediately	92
3	4-Bromophenol	5	90
4	4-Methyphenol	immediately	78
6	2,4-Dichlorophenol	5	94
5	4-Hydroxybenzophenone	immediately	70

a) Isolated yield.

Table 2. Dinitration of 4-substituted phenols with two molar amounts of $NO^+ \cdot 18\text{-crown-}6 \cdot H(NO_3)_2^-$ in EtOAc under reflux conditions.

Entry	Substrate	Time (min.)	%Yield [a] of Dinitration
1	Fluorophenol	3	96
2	Chlorophenol	5	97
3	Bromophenol	5	94
4	Methylphenol	3	92

a) Isolated yield.

are compared with those reported for N_2O_4 gas and metal nitrate analogs[17] in Table 3 to show the efficiency of the presented method.

Conclusion: In this study we have investigated the possibility of using stable crystalline $NO^+ \cdot 18\text{-crown-}6 \cdot H(NO_3)_2^-$ for nitration of phenols. The selectivity of the reaction for formation of mono-, di-, and trinitrophenol and also selective

Table 3. Nitration of 4-methyl phenol with different nitrating agents.

Reagent	Mononitration		Dinitration	
	Time(h)	% Yield	Time(min)	% Yield
$Cr(NO_3)_3{\cdot}2N_2O_4$[17]	15	68	5	64
$Cu(NO_3)_2{\cdot}N_2O_4$[17]	30	-[a]	15	-[a]
$Fe(NO_3)_3{\cdot}1.5\,N_2O_4$[17]	2	62	3	75
N_2O_4 gas[19]	-	57	-	-
$NO^+{\cdot}18\text{-crown-}6{\cdot}H(NO_3)_2^-$	-[b]	78	3	92

a) The reaction is sluggish with this reagent and gives poor yield of the nitrated product.
b) Immediate reaction.

formation of mono-, and dinitrated products from 4-substituted phenols can be easily achieved by changing the amounts of the reagent, solvent and temperature. Formation of 2,4,6-trinitrophenol and nitration of 2,4-dichlorophenol in excellent yields, show the efficiency of this complex for the nitration of strongly deactivated phenols. Short reaction times, high yields of the products, easy handling and stability of the reagent and excellent selectivity of the reactions make this complex a very suitable nitrating reagent for phenols.

Experimental: Chemicals were purchased from Fluka, Aldrich, Merck and Riedel-Dehaen AG Chemical Companies. All solvents are dried and redistilled. Thin layer chromatography (TLC) 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. Products were characterized by comparison with authentic samples (mp, IR and NMR spectra).

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

Mononitration of Phenol with $NO^+ \cdot$18-Crown-6$\cdot H(NO_3)_2^-$ Complex. A mixture of phenol (0.094 g, 1 mmol) and $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ complex (0.356 g 0.85 mmol) in acetone (3 mL) was stirred vigorously at room temperature. The reaction was completed immediately. After column chromatography on silica gel with petroleum ether/acetone (9:1), 4-nitrophenol 0.08 g (58%) and 2-nitrophenol 0.049 g (35%) were obtained respectively.

Dinitration of Phenol with $NO^+ \cdot$18-Crown-6$\cdot H(NO_3)_2^-$ Complex. A mixture of phenol (0.094 g, 1 mmol) and $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$complex (0.89 g, 2.1 mmol) in EtOAc (3 mL) was stirred for 10 min. under reflux conditions. Column chromatography on silica gel using chloroform as an eluent gave 2,4-dinitrophenol 0.151 g (82%) and 2,4,6-trinitrophenol in 8% yields respectively.

Trinitration of Phenol with $NO^+ \cdot$18-Crown-6$\cdot H(NO_3)_2^-$. Phenol (0.094 g, 1 mmol) and $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ complex (1.78 g, 4.25 mmol) were mixed together in BuOAc (3 mL) and was stirred under reflux conditions for 2 h. After column chromatography on silica gel with chloroform 2,4,6-trinitrophenol was obtained as yellow crystals, 0.215 g (94%).

Mononitration of 4-Chlorophenol with $NO^+ \cdot$18-Crown-6$\cdot H(NO_3)_2^-$ Complex as a Typical Procedure: A mixture of 4-Chlorophenol (0.129 g, 1 mmol) and $NO^+ \cdot$18-crown-6$\cdot H(NO_3)_2^-$ complex (0.356 g, 0.85 mmol) in acetone (3 mL) was stirred vigorously at room temperature. The reaction was completed immediately.

Column chromatography on silica gel with petroleum ether/acetone (9:1) gave 4-chloro-2-nitrophenol as yellow needle crystals, 0.17 g (98%).

Dinitration of 4-Chlorophenol with NO^+·18-Crown-6·$H(NO_3)_2^-$ as a Typical Procedure: 4-Chlorophenol (0.129 g, 1 mmol) and NO^+·18-crown-6·$H(NO_3)_2^-$ complex (0.89 g, 2.1 mmol) were mixed together in EtOAc (3 mL) and was stirred under reflux conditions for 5 min. After column chromatography on silica gel 4-chloro-2, 6-dinitrophenol was obtained, 0.21 g (97%)

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