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N-Nitrosation of Secondary Amines with $[NO^+\cdot Crown\cdot H(NO_3)_2^-]$

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N-Nitrosation chemistry of amines is an important and well-established reaction in organic synthesis.[1] The most general reagent is nitrous acid, generated from sodium nitrite and mineral acid in water or in mixed alcohol−water solvents.[2] Other nitrosating agents, such as Fremy's salt,[3] bis(triphenylphosphine)nitrogen(1+) nitrite,[4] *N*-haloamides and sodium nitrite under phase-transfer conditions,[5] oxyhyponitrite,[6] dinitrogen tetroxide,[7] solid acids (i.e., oxalic acid dihydrate,[8] inorganic acidic salts[9] and hydrolyzable chloride salts[10]), and sodium nitrite have also been used. We were interested to find a completely homogeneous reagent for the N-nitrosation of secondary amines, and thus we have investigated a number of different reaction conditions based upon the in situ generation of NO^+. In continuing of our studies on the application of NOX,[11] N_2O_4,[12] metal nitrate dinitrogen tetroxide complexes.[13] and complexation of transition metals with macrocyclic ethers,[14] we found that 18-Crown-6 gives an ionic complex with N_2O_4 gas as $[NO^+\cdot Crown\cdot H(NO_3)_2^-]$ in quantitative yields. In this communication we now report a simple and convenient method using this new reagent for the effective N-nitrosation of secondary amines (**1**) to their corresponding *N*-nitroso derivatives (**2**) under mild conditions.

Different types of secondary amines (**1**) were subjected to the nitrosation reaction in the presence of $[NO^+\cdot Crown\cdot H(NO_3)_2^-]$ (**I**) and dry SiO_2 in dichloromethane. The nitrosation reactions were performed under mild conditions at room temperature and take place with quantitative yields (Scheme 1).

This present nitrosation reaction can be readily carried out by placing the complex $[NO^+\cdot Crown\cdot H(NO_3)_2^-]$ (**I**), amine (**1**), dry SiO_2 and CH_2Cl_2 as the solvent in a reaction vessel and efficiently stirring the resulting mixture at room temperature. The reactions were completed after 5 min. The reaction mixture was filtered, and dichloromethane was also removed by water bath (40−50 °C) and simple distillation. The highly pure nitrosoamines (**2**) were obtained by passing the residue through a pad of silica gel.

A competitive reaction was performed between dicyclohexylamine (**1c**) and anisole. It was observed that amine nitrosation occurred exclusively, whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation reaction of diphenylamine shows the chemoselectivity of the method as the *N*-nitrosodiphenylamine is the only product. This system thus behaves differently from some reported methods[2] so that the nitrosonium ion (NO^+) attacks the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to the nitrogen atom.

Furthermore, the chiral center of L-proline (**1h**) also remained intact in the course of the reaction so that L-nitrosoproline (**2h**) was obtained quantitatively. L-Nitrosoproline (**2h**) is a precursor of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties.[15,16]

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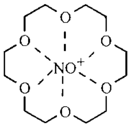
Scheme 1



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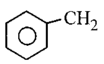
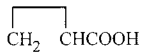
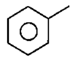
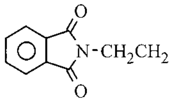
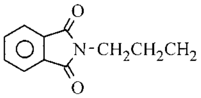
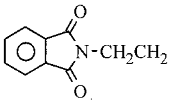
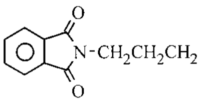
$$R_1R_2NH \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt.}]{\text{I}} R_1R_2N\text{-}N{=}O$$

1 2

5 min.
Quantitative yields

1 or 2	$R_1 = R_2$	1 or 2	$R_1 = R_2$
a	Et	f	
b	*iso*-Pr	g	$-(CH_2)_2-O-(CH_2)_2-$
c		h	
d		i	
e	$-(CH_2)_5-$	j	
	R_1		R_2
k			

Some of the amines used are very important precursors for the synthesis of symmetrical and asymmetrical tripodal tetraamines (**1i**–**k**).[17] We therefore believe that their *N*-nitroso derivatives were also very useful for synthesis of special NO releasing complexes.[18]

In conclusion, practical and efficient N-nitrosation of secondary amines was achieved using the present methodology. The $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$ complex, with easy preparation and handling, can act as a relatively stable and efficient reagent as a source for the delivery of nitrosonium ion (NO^+) under mild and homogeneous conditions. Meanwhile 18-Crown-6 can be recycled and reused. The $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$ is completely soluble in dichloromethane and also more reactive than those reagents that were reported previously.[1–10] We believe that the present methodology is an important addition to existing methodologies.

Experimental Section

General. Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemical companies. Silica gel mesh 60–70 was used. The nitrosation products were characterized by comparison of their spectral (IR, ^1H NMR, ^{13}C NMR, and TLC) and physical data with the authentic samples.[8–10] $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$ was synthesized according to the reported procedure,[19] with a slight modification. Here, we used N_2O_4 gas instead of liquid N_2O_4. Dinitrogen tetroxide (N_2O_4) gas was generated in situ according to our previously reported procedure as follows.[12,13]

Caution: All *N*-nitroso amines [R′-N(NO)-R] should be regarded as potentially poweful carcinogens, since most compounds of these types have been shown to possess high activity in experimental animals.[2a]

Generation of NO_2–N_2O_4 Gas.[12,13] Lead(II) nitrate (50 g) was crushed into a powder and was dried in an oven at 120 °C for 3 days. The resulting powder was transferred into a one-necked round-bottomed flask (250 mL), which was equipped with an air condenser and a gas trap containing P_2O_5. The flask was heated by a Bunsen burner to generate a brownish-red NO_2–N_2O_4 gas, which was used immediately for the subsequent preparation of $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$.

Preparation of $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$. A solution of 18-Crown-6 (5.286 g, 0.02 mol) in CH_2Cl_2 (10 mL) was prepared in a three-necked round-bottomed flask (50 mL) equipped with a magnetic stirrer, a gas inlet tube, a thermometer, and a drying tube and cooled to −10 °C with an ice–salt bath while being stirred. Generated NO_2–N_2O_4 gas was bubbled through this solution for 30 min. The solvent was evaporated under vacuum at 20 °C to give the $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$ complex as a pale yellow deliquescent solid compound **I** [8.380 g, 0.02 mol (~100%)]: mp 50–55 °C [lit.[19] mp 53–55 °C]. ^1H NMR (FT-90 MHz, $CDCl_3$/TMS): 3.536 (s, 24 H), 11.464 (s, 1H).

General Procedure for N-Nitrosation of Secondary Amines. A solution of amine (**1**, 1 mmol), $[NO^+{\cdot}Crown{\cdot}H(NO_3)_2^-]$ (0.523 g, 1.25 mmol) and dry SiO_2 (0.4 g) in dichloromethane (10 mL for compounds **1a**–**g** and 50 mL for compounds **1i**–**k**) was stirred vigorously magnetically at room temperature. The progress of the reaction was followed by TLC. The reaction was completed after 5 min. The reaction mixture was filtered. The residue was washed with CH_2Cl_2 (2 × 5 mL). Dichloromethane was removed by water bath (40–50 °C) and simple distillation. The residue was passed through a pad of silica gel [eluent, acetone/petroleum ether (10:90)]. The solvent was evaporated, and the highly pure *N*-nitroso compounds (**2**) were obtained quantitatively. For recycling 18-Crown-6 the pad of silica gel was washed with acetone. Evaporation of acetone gave pure 18-Crown-6.

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