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Efficient Procedure for Chemoselective N-Nitrosation of Secondary Amines with Trichloromelamine–$NaNO_2$*

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Abstract—A combination of trichloromelamine and sodium nitrite in the presence of wet silica gel was used as an effective nitrosating agent for the transformation of secondary amines into the corresponding *N*-nitroso derivatives under mild and heterogeneous conditions in good to excellent yields.

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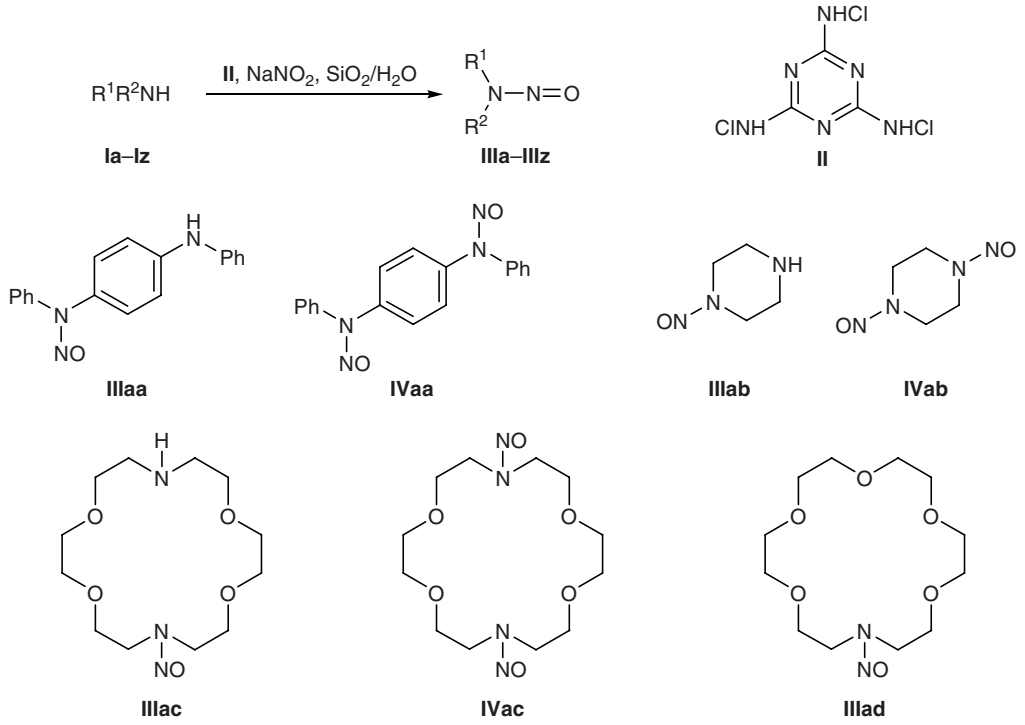
Nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists [1–3]. An effort has also been made to combine both synthetic and mechanistic aspects of nitrosation or transnitrosation [4, 5]. N-Nitrosation of amines is an important and well explored reaction in organic synthesis. In the recent years N-nitroso amines have attracted considerable interest due mainly to their strong mutagenic and carcinogenic properties. They have also been found to have vasorelaxant activity, and their use as pesticides, antioxidants, and lubricant additives has been described [6]. These compounds are also useful synthetic intermediates for the preparation of various N–N-containing functionalities. Furthermore, their easy lithiation, followed by reaction with electrophiles and subsequent denitrosation, ensures regio- and stereoselective electrophilic substitution at the α-carbon atom [7]. Hindered rotation about the N–N bond owing to its partially double character gives rise to many intriguing stereochemical features of N-nitroso amines [8, 9]. The most general reagent is nitrous acid generated from sodium nitrite and mineral acid in water or mixed alcohol–water solvents [10, 11]. Other nitrosating agents, such as Fremy's salt [12], bis(triphenylphosphine)-nitrogen(1+) nitrite [13], *N*-halo amides and sodium nitrite under phase-transfer conditions [14] oxyhyponitrite [15], dinitrogen tetraoxide and [$NO^+ \cdot$crown$\cdot H(NO_3)_2^-$] [16, 17], and solid acids or acetic anhydride and sodium nitrite have also been used [18–22]. Very recently, an excellent procedure was reported for the selective N-nitrosation of amines, *N*-alkylamides, and *N*-alkylureas by N_2O_4 supported on cross-linked polyvinylpyrrolidone (PVP–N_2O_4) [23]. Among many other authors, we have recently demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions, and minimization of chemical wastes compared to the liquid-phase counterparts [18–22]. Therefore, we tried to use a completely heterogeneous system and examined nitrosation of secondary amines under various conditions implying generation of HNO_2 *in situ* from sodium nitrite and trichloromelamine.

A wide range of secondary amines **I** was subjected to the nitrosation reaction in the presence of trichloromelamine (**II**), $NaNO_2$, and wet silica gel (50 wt %) in methylene chloride (Scheme 1). The reactions were performed under mild and completely heterogeneous conditions at room temperature, and they led to the formation of the corresponding N-nitoso amines in good to excellent yields (see table). The resulting nitroso amines **III** can be isolated simply by filtration and evaporation of the solvent. The reaction conditions are given in table.

All our attempts to synthesize 1,3,5-tris(*N*-nitrosophenylamino)benzene were unsuccessful. In contrast to the data reported in [24] on the nitrosation of 1,3,5-tris-(phenylamino)benzene to give 1-nitroso-2,4,6-tris-(phenylamino)benzene, among six possible nitrosation products of *N*,*N*-diphenyl-1,4-phenylenediamine (**Iaa**)

* The text was submitted by the authors in English.

Scheme 1.



I, **III**, R = R′ = Me (**a**), Et (**b**), *i*-Pr (**c**); R = Me, R′ = *cyclo*-C_6H_{11} (**d**); R = R′ = *cyclo*-C_6H_{11} (**e**); RR′N = morpholino (**f**), piperidino (**g**), 2-methylpiperidino (**h**), 4-hydroxypiperidino (**i**); RR′ = $(CH_2)_6$ (**j**), $(CH_2)_4$ (**k**); RR′N = 2,3-dihydro-1*H*-indol-1-yl (**l**), 1,2,3,4-tetrahydroquinolin-1-yl (**m**), 1,2,3,4-tetrahydroisoquinolin-2-yl (**n**), D-3-carboxy-1,2,3,4-tetrahydroisoquinolin-2-yl (**o**); R = R′ = Ph (**p**); R = Ph, R′ = $PhCH_2$ (**q**); R = R′ = $PhCH_2$ (**r**); R = Ph, R′ = 2-naphthyl (**s**); R = Me, R′ = Ph (**t**); R = Ph, R′ = *cyclo*-C_6H_{11} (**u**); R = R′ = $HOCH_2CH_2$ (**v**); RR′N = 2-carboxypyrrolidin-1-yl (**w**), 2-carboxy-4-hydroxypyrrolidin-1-yl (**x**), 4-phenylpiperazin-1-yl (**y**), 4-(2-hydroxyethyl)piperazin-1-yl (**z**).

we isolated only *N*-mono- and *N*,*N*′-dinitroso derivatives **IIIaa** and **IVaa**.

The nitrosation of *N*,*N*-diphenyl-1,4-phenylenediamine (**Iaa**), piperazine (**Iab**), and diaza crown ether **Iac** with 6 equiv of the reagent resulted in predominant formation of the corresponding *N*,*N*′-dinitroso derivatives **IVaa**–**IVac**, but we failed to effect selective mononitrosation of these compounds. In all cases, mixtures of mono- and dinitroso compounds were formed, and it was difficult to separate the products without resorting to column chromatography. These findings are consistent with the data reported by Singer et al. [25, 26] on transnitrosation phenomena.

In order to demonstrate chemoselectivity of the proposed procedure, a competitive reaction was performed using diphenylamine (**Ip**) and anisole. After 30 min, the nitrosation of only secondary amine **Ip** was observed, while anisole remained intact in the reaction mixture. In the mitrosation of L-proline (**Iw**), 4-hydroxy-L-proline (**Ix**), and D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**Io**), the chiral center also remained unchanged (see table). Amino acid derivatives **IVw**, **IVx**, and **IVo** are precursors of mesoionic moieties in an important class of dipolar heterocyclic compounds with special properties [27]. Some *N*-nitroso amines reported in this paper (**IVab**, **IVac**) are important models for mechanistic transnitrosation studies. These compounds can also be useful in the synthesis of special NO-releasing complexes [28].

No nitrosation occurred in the absence of wet silica gel. This means that the presence of water molecules is essential. Wet silica gel ensures a sufficient heterogeneous surface area for generation of HNO_2 *in situ* and facilitates work-up.

Thus the cheapness and availability of the reagents, chemoselectivity, and high yields make the proposed procedure attractive for organic chemists.

EXPERIMENTAL

The initial compounds and reagents were commercial products purchased from Fluka, Merck, and Aldrich. The nitrosation products were characterized

N-Nitrosation of secondary amines **I** with trichloromelamine (**II**)–$NaNO_2$ in the presence of wet silica gel (50 wt %) in methylene chloride at room temperature

Substrate	Product[a]	**II**-to-**I** molar ratio[b]	Time, min	Yield,[c] %	Substrate	Product[a]	**II**-to-**I** molar ratio[b]	Time, min	Yield,[c] %
Ia	**IVa**	1:3.5	2	100[d]	**Ir**	**IVr**	1:3.5	15	92
Ib	**IVb**	1:3.5	5	95	**Is**	**IVs**	1:3.5	25	92
Ic	**IVc**	1:3.5	10	95	**It**	**IVt**	1:3.5	25	90
Id	**IVd**	1:3.5	15	92	**Iu**	**IVu**	1:3.5	20	90
Ie	**IVe**	1:3.5	15	95	**Iv**	**IVv**	1:3.5	20	85
If	**IVf**	1:3.5	25	85	**Iw**	**IVw**	1:3.5	60	70
Ig	**IVg**	1:3.5	15	92	**Ix**	**IVx**	1:3.5	90	70
Ih	**IVh**	1:3.5	15	95	**Iy**	**IVy**	1:3.5	25	85
Ii	**IVi**	1:3.5	80	80	**Iz**	**IVz**	1:3.5	60	75
Ij	**IVj**	1:3.5	10	90	**Iaa**	**IVaa, Vaa**	1:3.5	30	20, 80
Ik	**IVk**	1:3.5	15	95	**Iaa**	**Vaa**	1:6	25	95
Il	**IVl**	1:3.5	20	85	**Iab**	**IVab, Vab**	1:3.5	15	20, 80
Im	**IVm**	1:3.5	20	80	**Iab**	**Vab**	1:6	10	95
In	**IVn**	1:3.5	20	80	**Iac**	**IVac, Vac**	1:3.5	25	25, 75
Io	**IVo**	1:3.5	30	75	**Iac**	**Vac**	1:6	20	92
Ip	**IVp**	1:3.5	25	90	**Iad**	**IVad**	1:3.5	0	85
Iq	**IVq**	1:3.5	20	92					

[a] All of the isolated products are known compounds; their spectral and physical data have been reported in the literature [5–22].
[b] Wet silica gel–substrate (**I**)–trichloromelamine molar ratio 4:1:1.
[c] Yield of isolated products.
[d] Conversion by chemical test (Cu^{2+}).

by comparison of their spectral (^1H and ^{13}C NMR), chromatographic (R_f), and physical data with those of authentic samples [6, 8, 18–22].

CAUTION! All *N*-nitroso amines R^1–N(NO)–R^2 should be regarded as potentially powerful carcinogens since most compounds of this type have been shown to possess high activity in experimental animals [10].

N-Nitrosation of diisopropylamine (Ic) with trichloromelamine (II), $NaNO_2$, and wet silica gel (*typical procedure*). A suspension of 0.202 g (2 mmol) of compound **Ic**, 0.459 g (2 mmol) of trichloromelamine (**II**), 0.4 g of wet silica gel (50 wt %,), and 0.438 g (7 mmol) of sodium nitrite in 10 ml of methylene dichloride was stirred at room temperature for 10 min (the progress of the reaction was monitored by TLC) and then filtered. Anhydrous Na_2SO_4, 4 g, was added to the filtrate. After 15 min, the resulting mixture was filtered. Methylene chloride was distilled off on a water bath (35–40°C). Yield of compound **IIIc** 0.219 g (95%), pale yellow crystalline substance, mp 43–45°C; published data [22]: mp 47–48°C.

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