Gaseous Nitrogen Dioxide for Sustainable Oxidative Deprotection of Trimethylsilyl Ethers

Mehdi Javaheri [a] , M. Reza Naimi-Jamal [a] , Mohammad G. Dekamin [a]
& Gerd Kaupp [b]

[a] Research Laboratory of Green Organic Synthesis, Department of
Chemistry, Iran University of Science and Technology, Tehran, 16846,
Iran

[b] Department of Organic Chemistry, Faculty V, University of
Oldenburg, Diekweg 15, Edewecht, Germany
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GASEOUS NITROGEN DIOXIDE FOR SUSTAINABLE OXIDATIVE DEPROTECTION OF TRIMETHYLSILYL ETHERS

Mehdi Javaheri,[1] M. Reza Naimi-Jamal,[1] Mohammad G. Dekamin,[1] and Gerd Kaupp[2]

[1]*Research Laboratory of Green Organic Synthesis, Department of Chemistry, Iran University of Science and Technology, Tehran 16846, Iran*
[2]*Department of Organic Chemistry, Faculty V, University of Oldenburg, Diekweg 15, Edewecht, Germany*

GRAPHICAL ABSTRACT

RR'CH-O-SiMe$_3$ + NO$_2$(gas) $\longrightarrow$ RHC=O or RR'C=O (quantitative yield)

Abstract *In this study, trialkylsilyl ethers of indispensable protected alcohols are oxidatively deprotected in neat form with gaseous nitrogen dioxide (NO$_2$). Quantitative yields of aldehydes or ketones are obtained without the necessity of chromatography. The byproducts, nitrogen monoxide, anhydrous nitric acid, and hexamethyldisiloxane, can be quantitatively separated by evaporation and distillation in closed systems for recycling or further use. The direct new method supersedes the previous techniques that produce dangerous wastes and require chromatographic workup, while the atmospheric gas NO$_2$ and its gaseous reduction products are easily kept in closed systems until further use.*

Keywords Catalyzed elimination; gaseous nitrogen dioxide; organic nitrate; oxidative deprotection; solvent-free liquid–gas reaction; solventless synthesis; trimethylsilyl ether

INTRODUCTION

Protection-group-free syntheses of natural products find increasing interest[1] and solid-state syntheses have been used for up to six-cascade "one-pot" conversions with 100% yield, for example, the reactions of mannitol or *myo*-inositol with phenylboronic acid.[2,3] However, protection–deprotection chemistry remains an important study in organic synthesis,[4] and recently, review articles have appeared.[5,6] Pressureless reactive gases for gas–solid and gas–liquid or gas–melt reactions in closed systems at ambient temperatures without catalysts are favorably used for wasteless syntheses, and exceptional reaction specificities and otherwise unattainable products come from this field.[2] The only equipment is a tight vacuum line for using easily available lecture bottles. The high reactivity of gaseous

nitrogen dioxide (NO_2) is no barrier for its non-use, because it is mostly less poisonous than liquid or solid reagents and does not produce wastes for disposal, since nitrogen monoxide (NO), dinitrogen trioxide (N_2O_3), and anhydrous nitric acid (HNO_3) are useful byproducts, in addition to the pure products that may also occur as nitrate salts. Handling of gases in small-scale and larger-scale industrial application is safe using simple equipment for dosage and temperature control,[2,7] and ubiquitous NO_2 has already been used for quantitative oxidations of alcohols, aldehydes, thioamides[4] and amines,[4,8–10] persistent radicals, heterocycles, active methylene compounds, aromatic compounds,[11] oximes,[12] and inorganic nitrites.[13] Many of these are discussed in the literature.[14]

Nevertheless, the direct use of the reactive gas has not yet been considered for one of the most important deprotection reactions, which is the oxidative deprotection of trimethylsilyl (TMS) ethers.[15] But numerous approaches for this direct conversion of a protected alcohol to an aldehyde or ketone prove its importance.

Oxygen required catalysts, for example, N-hydroxyphthalimide and $Co(OAc)_2$,[16] or Mn- and Co-(4-aminobenzoates), supported on silica gel.[17] Wasteful and complicated workup detracts from this technique.

Peroxides were used as $[PhCH_2NMe_2Ph]_2S_2O_8$[18] and cetyltrimethylammonium per-oxodisulfate $(CTA)_2S_2O_8$,[19] and also as risky t-BuOOH with $(Ph_3SiO)_2CrO_2$ catalyst,[20] or as peroxotungstate complex with amberlyst A-26 chloride (for secondary TMS ethers; 90–95% at 4.2–16 h in 1,2-dichloroethane at 50 °C).[21] These techniques require tedious workup and lead to inefficient recovery of the dangerous auxiliaries.

Halogens were used as bromine on polyvinylpyrrolidone,[22] as bromates such as $Ce(NO_3)BrO_3$ on $NaHSO_4·H_2O$ support[23] or as $NaBrO_3$ with catalyzing $(NH_4)_2Ce(NO_3)_6$ in CH_3CN.[24] Another approach was the oxidation with N-bromosuccinimide and 2,2′-azobisisobutyronitrile.[25] Also, the use of 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one supported on silica gel[26] and of $[Ce(NO_3)_3]_3·H_2IO_6$ in benzene is highly acclaimed.[27] But these are expensive and wasteful processes with hard to recover reagents. Also, the use of 2,3-dichloro-4,5-dicyano-benzoquinone (DDQ) in CH_2Cl_2 with 253.7-nm light (42–85% yield)[28] is not sustainable.

$SrMnO_4$ and $AlCl_3$ (84–98% yield),[29] or $BaMnO_4$ in the presence of $KMnO_4$ and Lewis acids,[30] produce dangerous wastes by chromatographic workup. Most used were CrO_3 and chromates (VI). These cover $CrO_3/H_2SO_4/acetone$,[31] $CrO_3·pyridine_2$ (this only with primary TMS ethers),[32] and CrO_3 on wet alumina (the "solvent-free" mixture gave 78–90% yield after extraction with CH_2Cl_2 and chromatography),[33] $(Me_3SiO)CrO_2$ on SiO_2,[34] $[Ce(NO_3)_3]_2CrO_4$,[35] $ClCrO_2OSiMe_3$ or pyridinium dichromate,[36] and pyridinium chlorochromate (PCC).[37] All of these popular variants may yield reasonable yields, but the production of carcinogenic wastes appears obsolete.

The indirect use of nitrogen oxides in solution reactions found interest with $NOBF_4$-,[38] $Fe(NO_3)_3·3/2N_2O_4$-, $Cu(NO_3)_2·N_2O_4$-,[39] and N_2O_4-impregnated activated charcoal.[40] But the bubbling of NO_2 gas into solvents or solutions for preparing the solid derivatives is dangerous and spoiling. Furthermore, choosing these detours and using solvents means incomplete reaction, less selectivity, longer reaction times, waste production, and poor atom economy. For example, yields >83% of benzaldehydes or phenones from seven benzylic TMS ethers in CH_2Cl_2 with N_2O_4/charcoal (0.2–8 h) after chromatography on SiO_2 and evaporation have recently been reported.[40] Clearly, a clean technique for the oxidative deprotection of TMS ethers is badly needed.

The wealth of using NO_2 gas for solvent-free oxidative deprotection of TMS ethers becomes particularly evident when comparison is made with all of these contemporary

techniques. We report now on the sustainable reaction of neat TMS ethers **1** with NO_2 gas in the absence of solvents or other auxiliaries, which provides the corresponding aldehydes and ketones with quantitative isolated yields. Fortunately, the stoichiometric byproduct, hexamethyldisiloxane, is volatile and thus gets easily separated.

RESULTS AND DISCUSSION

A clean synthetic technique should avoid chromatography and all of the other drawbacks of the contemporary techniques. Fortunately, gaseous NO_2 in a solvent-free environment easily meets these requirements when liquid or liquefying primary or secondary benzylic or aliphatic TMS ethers are to be oxidatively deprotected. The pure aldehydes or ketones were formed within 5–60 min, depending on the substitution pattern according to Eq. (1).

$$2\,ArCHR'OSiMe_3 + 5\,NO_2 \rightarrow 2\,ArCR'O + 2\,HONO_2 + 3\,NO + (Me_3Si)_2O \quad (1)$$

Excess NO_2 and NO (in equilibrium with N_2O_3), anhydrous $HONO_2$ (bp 83 °C), and $(Me_3Si)_2O$ (bp 99 °C) were easily separated from the aldehydes or ketones (Table 1) by evaporation to a cold trap for separation by distillation for further use.[4] This is an invaluable sustainable advantage.

Also, 2-phenylethyl TMS ether reacts with NO_2 gas (10 min) to give a quantitative yield of 2-phenylacetaldehyde. This secures the mechanism in Scheme 1 by excluding a necessity of benzylic activation (not benzyl–H abstraction) and widens the applicability. It opens the new technique also for the oxidative deprotection of aliphatic TMS ethers. No aromatic nitration competes irrespective of the substituents. The completion times depend on viscosity and gas dissolution rate, but chemical effects require the consideration of the mechanistic scheme of the complicated, though surprisingly clean, reaction. The proposed straightforward mechanism is the basis for the unusual success (Scheme 1). The high reactivity of TMS nitrite is already known.[41]
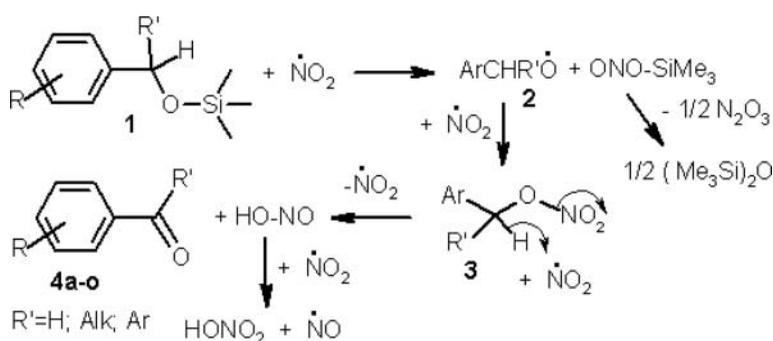
Scheme 1 Proposed mechanism for the quantitative oxidative deprotection of benzylic trimethylsilyl ethers with gaseous NO_2.

When the NO_2 radical binds to the silicon atom of the TMS ether **1**, it leaves the immediately trapped oxygen radical **2**, giving the HNO_3 ester **3** (**3f** was detected by MS and FTIR spectra, upon evaporation in early stages of the reaction). Importantly, the reaction

Table 1 Deprotection of benzylic TMS ethers **1a–o** with NO_2 gas to give quantitative isolated yields of **4a-o** at ambient conditions

1	R	R′	Time (min)	mp of **4** (°C)[a]
a	H	H	5	Liquid
b	2-Me	H	5	Liquid
c	4-Me	H	5	Liquid
d	3,4-di-MeO	H	10	42–45
e	2-Cl	H	60	10–12
f	4-Cl	H	5	45–47
g	2-NO$_2$	H	60	41–44
h	4-NO$_2$	H	60	103–107
i	4-MeO, 3-BzO	H	45	61–64
j	H	Me	30	Liquid
k	2-NO$_2$	Me	60	25–27
l	2-Br	Me	60	42–45
m	H	Ph	30	47–49
n	4-NO$_2$	Ph	60	136–138
o	4-F	Ph	60	47–49

[a]The data correspond to those listed in *Handbook of Chemistry and Physics* (86th edition) *Section 3; CRC Press, Taylor & Francis Group 2005; Boca Raton; Ed. D. L. Lide* and the Beilstein database.

does not stop at the stage of the stable benzylnitrates **3**, but these give **4** under the solvent-free conditions by elimination of nitrous acid (HNO_2), which is oxidized to HNO_3, in turn protecting the aldehydes and also the aromatic rings from further oxidation.[4] Clearly, the elimination step (**3** → **4** + HONO) is the key step of the mechanism that must be a catalyzed reaction. It is known that benzylnitrate functions survive the treatment with 7.5 mol L^{-1} anhydrous $HONO_2$ in CH_2Cl_2 for >1 h.[42] The increasingly formed anhydrous HNO_3 (Scheme 1) is thus not the catalyst. The occurrence of the carbonyl-forming step from stable benzyl nitrates must therefore be catalyzed by NO_2, as formulated in Scheme 1. Such unprecedented catalysis by NO_2 required scrutiny. It was supported by the formation of the typical carbonyl IR bands for aldehydes (1736 cm^{-1}) and ketones (1720 cm^{-1}), when for example, cellulose dinitrate foil was exposed to NO_2 gas. A similar catalysis by NO_2 may also be helpful in the gas–solid oxygenation of the methylene group in hydantoin or thiohydantoins via nitrite/nitrate intermediates.[11]

An important feature of the solventless technique should be emphasized: It easily provides anhydrous conditions so that hydrolysis of the nitrate esters **3** to give the initially protected alcohol[5] is completely impeded.

When triphenylmethyl TMS ether was similarly reacted (50 min), the formed tertiary nitrate ester (cf. Scheme 1) required final exposure to water vapors for quantitatively yielding the alcohol Ph_3COH. In this connection, we must settle a putative discrepancy: a literature report claimed that primary and secondary TMS ethers give alcohols when treated with dinitrogen tetraoxide (N_2O_4) on silica in "dry" CH_2Cl_2. This must not oppose the present results, as no stoichiometry and no pretreatment of the solid reagent were reported by Zolfigol et al.[43] It appears that the adsorbed water on silica ("mesh 60") was not removed prior to the loading with N_2O_4. Therefore, water and some amount of HNO_3 must have been present on the solid auxiliary for acid-catalyzed hydrolysis of the benzylnitrates **3**. Apparently, such hydrolysis superseded the elimination reaction (**3** → **4** + HONO). This

additionally urges the direct use of NO_2 gas in a solventless environment with the inherent anhydrous conditions.

CONCLUSIONS

Since the oxidative deprotection of TMS ethers will remain an indispensable tool in multistep syntheses, the commonly used dangerous or wasteful or expensive oxidation techniques (cf. "Introduction" section) should be replaced by the benign solventless pressureless NO_2 gas technique, which does not produce dangerous wastes that require disposal but pure products and easily recyclable useful byproducts. The new technique avoids chromatography and lacks all of the other drawbacks of the numerous contemporary techniques. The poisonous, though atmospheric gas, NO_2 compares favorably with poisonous or carcinogenic solids or liquids. It is easily handled all the way in closed systems without leakages. The new technique avoids bubbling of the gas into a solvent or its adsorption to an auxiliary for making it "solid". Only the latter procedures are complicated, dangerous, and spoiling, with emissions that must be avoided. The present gas–liquid technique avoids such emission in closed vacuum lines. Fortunately, numerous additional functionalities that would react with NO_2 gas[4,8–11] are suppressed by salt formation or complexation with anhydrous $HONO_2$. Such suppression is not available for the numerous techniques mentioned in the "Introduction" section, which limits their selection even further. The equally rapid (10 min) reaction of 2-phenylethyl TMS ether to give a quantitative yield of 2-phenylacetaldehyde promises a broad application in aliphatic and alicyclic synthetic chemistry that should be further explored. NO_2 gas is ubiquitous, NO is a physiological agent (see, for example, Li and Förstermann[44]), and also the stoichiometric anhydrous HNO_3 or hexamethyldisiloxane are interesting chemical reagents.

EXPERIMENTAL

Uncorrected melting points were determined using an electrothermal 9100 instrument. FTIR spectra were recorded as KBr pellets for solids, between NaCl plates for liquids, and in a gas cell for gases. A Shimadzu FT-IR 8400 spectrometer was used. Vapor phase chromatography (VPC) was executed on a Perkin Elmer 8420 instrument, analytical TLC with 0.2-mm silica gel 60 F-254 on aluminum plates from Merck AG. For the study, 500 MHz ^{1}H NMR spectra in $CDCl_3$ with internal TMS standard were recorded by a DRX-500 Bruker Avance spectrometer and GC-MS records by a Varian CP-3800 spectrometer. All TMS ethers were synthesized from the corresponding alcohols with hexamethyldisilazane and purified according to procedures mentioned in the literature.[45] The yields of aldehydes or ketones and Ph_3COH were determined by weight: the crystals after the thorough evaporation, and the liquids after short-path vacuum distillation. The measurements were quantitative in all cases. The time of completion for the liquid–gas reactions was determined using TLC after quenching by evaporation, with several test runs for every single reaction. No further determinations below 5 min were performed for the most rapid reactions in Table 1. All products are known compounds and were identified by comparing their physical and spectra data with those reported in the literature. The cellulose dinitrate foil was obtained by evaporation of a solution of collodion wool in ether/ethanol on a glass slide followed by 1 h of drying in vacuum.

General Procedure for the Oxidative Deprotection of TMS Ethers

No particular precautions, except vacuum tightness, were necessary when 1.00 mmol of the pure, known TMS ethers **1a**–**o** or triphenylmethyl TMS ether or 2-phenylethyl TMS ether were exposed to approximately 0.6 bars of NO_2/N_2O_4 gas from a lecture bottle in an evacuated 100 mL flask (about 5.8 mmol calculated for NO_2) at a vacuum line and at room temperature, with occasional shaking for the times mentioned in Table 1. The formed liquids changed their colors rapidly. After condensation of the reaction gas mixtures and $(Me_3Si)_2O$ to a cold trap at the vacuum line all of the solid benzaldehydes or ketones crystallized. The evaporated gases from various experiments were collected for distillative separation with FTIR control and further use.[4] The least volatile fraction was $(Me_3Si)_2O$, the identity of which was secured by its ^{1}H NMR, FTIR and MS spectra. The immediate purity of the known compounds **4a**–**o** (Table 1), 2-phenylacetaldehyde, and Ph_3COH was verified by VPC, TLC, and melting-point determinations. Also, ^{1}H NMR spectra excluded traces of the corresponding benzoic acids or aromatic nitrations by the not including spurious additional peaks.

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