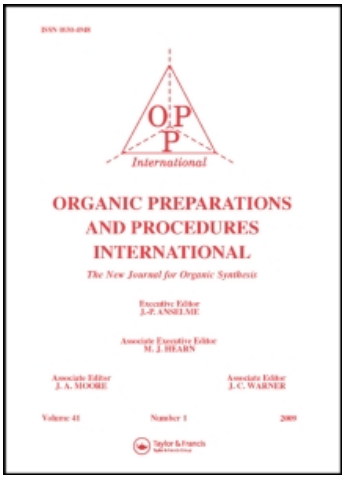

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A SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF *gem*-CHLORONITROSO COMPOUNDS

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A SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF *gem*-CHLORONITROSO COMPOUNDS

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(11/23/04)

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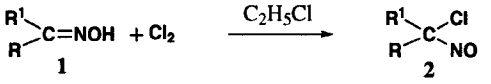
gem-Chloronitroso compounds are important intermediates for the synthesis of variety of compounds.[1-5] Because of their utility and our interest in their properties, we decided to reinvestigate their preparation. Several methods have been reported for the preparation of aliphatic and cyclic *gem*-chloronitroso compounds from the corresponding oximes with halogenating agents such as elemental chlorine,[6] aqueous hypochlorous acid,[6] nitrosyl chloride,[7] alkyl hypochlorites,[8] and N-chlorourea.[9] Though these procedures were considered the most effective for the preparation of nitroso compounds , these often results in the formation of nitro derivatives along with that of the desired nitroso compounds. Generally, it is important to stop the reaction at the nitroso stage by controlling the reaction temperature and by slow addition of the oxidant, but this requirement is often hard to meet and failure results in over oxidation to nitro compounds. Therefore, there is still considerable interest in the development of selective methods/reagents for these important transformations. Although, several methods are known[6-9] for the preparation of nitroso compounds, very few are sufficiently selective to terminate reaction at the nitroso stage and prevent over oxidation to nitro compounds. Some of these methods invariably result in the contamination of the products, involve pH dependent reactions, require stringent precautions, limited to specific substrates[10] and result in the formation of several by-products, thereby reducing the yields of the desired products. Furthermore, these methods are useful only for the synthesis of aliphatic *gem*-chloronitroso compounds and are not suitable for aromatic *gem*-chloronitroso compounds.[11] We were interested in a procedure which could allow us to easily prepared wide variety of both aliphatic and aromatic *gem*-chloronitroso compounds. Herein we describe a far more convenient method for the synthesis of both aromatic as well as aliphatic *gem*-chloronitroso compounds. This method has allowed us to obtain quantitative yields of products of improved purity in reduced reaction times.



a) R = CH_3, R^1 = C_2H_5; b) R = CH_3, R^1 = *n*-C_3H_7; c) R = CH_3, R^1 = *i*-C_4H_9; d) R = R^1 = $(CH_2)_5$;
e) R = CH_3, R^1 = *t*-C_4H_9; f) R = R^1 = C_6H_5; g) R = C_6H_5, R^1 = *p*-MeC_6H_4; h) R = R^1 = *p*-$MeOC_6H_4$

The reaction of oximes with elemental chlorine was carried out in ethyl chloride as a solvent. Various oximes were chosen to reflect a variety of structural types. Alkyl- and arylketoximes reacted smoothly with chlorine under the reaction conditions to produce the corresponding chloronitroso compounds in excellent yields. The results are summarized in *Table 1*. Many factors such as the temperature, the structure of alkyl or aryl group, pH of the medium and, to some extent, the effect of light profoundly influences the course of the reaction. Several investigations have also been carried out to understand the influence of structural variation of the alkyl or aryl moiety. Aliphatic oximes react more rapidly than aromatic oximes because of the diminished steric hindrance at the oximino carbon. The reaction with aliphatic oximes is complete in 15-30 min. while aromatic oxime required 3 h for complete conversion. Ethyl chloride, a gas, was used because it can be removed easily and thus facilitating isolation of the product. At the same time, the reaction need not be carried out in the dark as mentioned by earlier workers.[8]

Table 1. Preparation and Properties of Compounds **2**[a]

Cmpd	Yield (%)	Time (hrs)	bp (mm Hg) (°C)	*lit.*[12]	mp. (°C)	*lit.*[12]
2a	96	0.25	32/60	34/60	----	----
2b	97	0.33	32/23	32/23	----	----
2c	85	0.42	42/18	42/18	----	----
2d	98	0.50	52/13	52/13	----	----
2e	82	0.50	----	----	112	112
2f	82	3.00	----	----	101	----
2g	85	3.00	----	----	106	----
2h	80	3.00	----	----	82	----

a) ***CAUTION***! *gem*-Chloronitroso compounds are thermally unstable. Great caution should be exercized in distilling them because if the pressure is allowed to rise, explosions may occur.[6] b) Compounds **2a-2d** are liquids and **2e-2h** are solids. Compounds **2a-2e** had satisfactory IR, NMR and MS spectra which were compared to those of authentic samples. All the other compounds were characterized by spectroscopic methods as given in the Experimental Section. Compounds **2a-2c, 2e** and **2g** were isolated as racemic mixtures

Both aliphatic as well as aromatic *gem*-chloronitroso compounds are stable for several days if stored below 5°C, *tertiary* nitroso compounds are quite stable. The spectrophotometric measurement were conducted on the n-π^* transition of all the *gem*-chloronitroso compounds. The λ_{max} was found to be in the range of 650 to 680 nm. No doubt possibility of formation of dimer does exist in this type of reactions; this aspect was verified by GC-MS studies. The total ion chromatograms in all the cases showed only one peak and m/z also confirms the formation of *gem*-chloronitroso compounds only. Although the chlorination of oximes to chloronitroso compounds has been reported under variety of conditions,[8] our reaction was achieved under neutral conditions.

In conclusion, we have described a highly efficient method that produces both aliphatic and aromatic *gem*-chloronitroso compounds in excellent yields. This method has advantage over the previous one that besides its applicability to aromatic compounds, easy work up due to use of low boiling solvent, reaction does not need to be performed in the dark and it also dispenses with environmentally unfriendly (ozone depleting) solvent trichlorofluoromethane[8]

EXPERIMENTAL SECTION

In this method ketoximes were dissolved or suspended in ethyl chloride at –40°C and chlorine was passed with stirring and any suspended ketoxime, if remains, also dissolves on passing the chlorine. Completion of the reaction was indicated by either appearance of blue color (in case of aliphatic *gem*-chloronitroso compounds) or formation of white precipitate (in case of aromatic *gem*-chloronitroso compounds). Reaction mixture was brought to room temperature and dry nitrogen is passed to remove dissolved chlorine and solvent, which gave product in sufficient purity. Ultra purification was carried out by doing distillation at reduced pressure. Melting points were determined on a hot stage microscope and are uncorrected. Proton NMR spectra were recorded on Jeol FX-90Q at 89.55 MHz with TMS as an internal standard. IR spectra were recorded on a Perkin Elmer 577 Spectrophotometer. TheGC/MS analyses were performed by Varian3400 GC coupled to a TSQ 7000 mass spectrometer (Finnigan Mat). Elemental analyses were performed on a Carlo Erba elemental analyser model 1106. UV data was recorded on Unicam UV 300. Authentic *gem*-chloronitroso compounds were prepared by following the literature method.[6] Aliphatic and aromatic oximes were prepared by known method described in textbooks. (Note: this procedure should be carried out in an efficient hood).

General Procedure.-The oxime (0.05 mmol) was placed in a 250 mL two necked RB flask equipped with condenser and drying tube. The flask was cooled to –40°C in a Cryo Bath (Heto CBN 18-50, Denmark). Ethyl chloride was collected from the cylinder at –40°C in a flask containing anhydrous $CaCl_2$. It was distilled and collected ethyl chloride (bp12°C) in another receiver at –40°C. This dry ethyl chloride 60 mL was added to the flask and dry chlorine gas was bubbled for a period mentioned in the Table. Completion of reaction was indicated by the appearance of dark blue color in case of aliphatic *gem*-chloronitroso compounds and the formation of a white precipitate in case of aromatic *gem*-chloronitroso compounds. The reaction mixture was brought to room temperature and dry nitrogen was bubbled through to remove both the excess of chlorine as well as solvent. On evaporation of the solvent, the desired product was obtained. Aromatic *gem*-chloronitroso compounds were further purified by washing with hexane (2 x 50 mL), collected and dried in vacuum. All the aromatic compounds were characterized by spectroscopic techniques.

Typical spectral data are as follows:

Compound 2f: IR (KBr): 1590 (N=O), 690 (C-Cl) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.63 (10H, m, arom H); MS (EI) m/z: 231, 233, 201, 203, 196, 169.

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.53 H, 4.32; N, 6.06. Found: C, 67.59; H, 4.22; N, 5.98

Compound 2g: IR (KBr): 1587 (N=O), 680 (C-Cl) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.66

(9H, m, arom H); 2.4 (3H,s, CH_3), MS(EI) m/z: 245, 247 ,215, 217, 211, 210, 165.
Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.57; H, 4.89; N, 5.71. Found: C, 68.27; H, 5.12; N, 5.65
Compound 2h: IR (KBr) 1590 (N=O), 684 (C-Cl) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.58 (8H, m, arom H), 3.8 (6H,s, OCH_3), MS(EI) m/z: 291, 293, 261, 263, 256, 237, 233, 232.
Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.85; H, 4.81; N, 4.81. Found: C, 61.56; H, 5.10; N, 5.11

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SOLID STATE DEPROTECTION OF THIOACETALS AND THIOKETALS USING 1-BENZYL-4-AZA-1-AZONIABICYCLO[2.2.2]OCTANE PERIODATE AND ALUMINUM CHLORIDE

Submitted by (02/24//05)

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Carbonyl compounds are often protected as thioacetals and thioketals in organic synthesis,[1,2] due to their stability under both acidic and basic conditions. Many procedures are available for the preparation of these derivatives [3-4] and extensive studies on the deprotection of these derivatives to the parent carbonyl compounds have been carried out.[5] However, some of these methods for deprotection require higher temperatures, long reaction times and involve toxic metal ions and solvents which are detrimental to the environment.[5] Therefore, there is need for a simple, less expensive and safer methods for deprotection of thioacetals and thioketals.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvent due to reduced pollution, low costs and simplicity in process and straightforward work-up.[7] Because of our interest in development of solvent-free reactions,[8] we now report 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate **1** as an efficient and selective reagent for the deprotection of thioacetal **2** or **3** (1,3-dithioacetals and 1,3-dithianes) to the corresponding carbonyl compounds **4**. 1-Benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate (**1**) is a mild, efficient, stable and inexpensive reagent; it is a white powder, which is quite soluble in polar