

New Reagent for a One-Step Synthesis of Gem-Chloronitro Compounds from Oximes

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The use of chlorine bleach (5% NaOCl) for the halogenation-oxidation of oximes to gem-chloronitro compounds is reported. Chlorine bleach afforded satisfactory yields when employed alone either at room temperature or under ultrasonic irradiation.

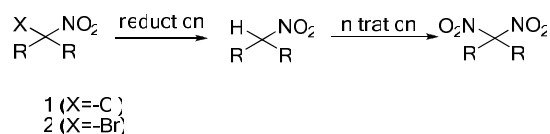
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INTRODUCTION

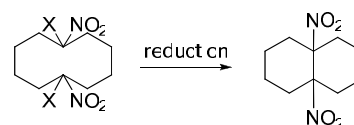
Gem-Halonitro compounds **1** and **2** have proven to be versatile intermediates in the synthesis of molecules possessing one or more nitro groups. They have been prepared traditionally either by the direct halogenation of nitronate salts [1-6] or from oximes *via* a halogenation-oxidation sequence [7-21]. The utility of the gem-halonitro intermediates has been demonstrated by their transformation to gem-dinitro compounds *via* a reductive dehalogenation-nitration sequence (Scheme 1) [9,16]. They have also functioned as important elements for assembling the polycyclic framework by an intramolecular reductive coupling of two suitably located gem-halonitro-substituted carbons to yield compounds possessing dinitro substituents (Scheme 2) [6-7].

Therefore, there is considerable interest among researchers to develop new simple methodologies for the preparation of gem-halonitro compounds. The conversion of an oxime to a gem-halonitro compound is believed to occur in two distinct steps (Scheme 3).

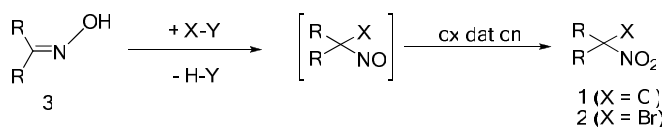
The initial halogenation of oxime **3** generates a gem-halonitroso intermediate which is oxidized in a subsequent step to the gem-halonitro compound **1** or **2**. Two distinct



Scheme 1



Scheme 2



Scheme 3

strategies have evolved to convert the oxime **3** to gem-halonitro **1** or **2**. One strategy uses a simple halogenating agent to generate the gem-halonitroso intermediate and then relies upon the use of a supplemental oxidant to oxidize the nitroso to the nitro group. The halogenating agents that have been

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used for the first step include bromine [7-10], elemental chlorine [10-12], aqueous hypochlorous acid [11], *t*-butyl hypochlorite [13] and *N*-bromosuccinimide (NBS) [14].

The oxidizing agents that have proven to be useful for the second step are nitric acid, trifluoroperoxyacetic acid [8-9], ozone [12], hydrogen peroxide [6], aqueous sodium [11], *n*-butylammonium hypochlorite [13] and *m*-chloroperbenzoic acid. The second strategy involves the use of a combination halogenating-oxidizing reagent that is capable of effecting the overall conversion. The combination reagents that have been investigated include both the hypochlorous acid/hypochlorite ion [13] and hypobromous acid/hypobromite ion [15], the enzyme chloroperoxidase/hydrogen peroxide/NaCl or NaBr [19], oxone/NaCl or NaBr [20-21] systems, NBS [8] and *N,N,N*-trihalo-1,3,5-triazines [18].

The methods reported above have some drawbacks such as the use of strong and non-selective oxidizing agents, toxic or expensive reagents, low yields, long reaction times and transformation of most of the oxime into the parent ketone.

EXPERIMENTAL

General

All chemicals were purchased from Merck and Fluka companies and used without any further purification. The products were characterized by their spectral data (IR and ^1H NMR and ^{13}C NMR) in some cases, and comparison with authentic samples. Sonication was performed in ELMA Transsonic 660/H (with a frequency of 35 KHz).

General Procedure for the Conversion of Oximes to the Corresponding Gem-Chloronitro Compounds

Method A (without sonication). Oxime (1 mmol) was added to a solution of chlorine bleach (1 ml) whereupon the reaction mixture developed a distinct blue color immediately. Chlorine bleach (10-15 ml) was added to the reaction mixture which was stirred at room temperature (between 2 and 10 h) until the reaction mixture became colorless. The reaction mixture was transferred to a separatory funnel and a 10% aqueous Na_2CO_3 solution (25 ml) was added. The aqueous fraction was extracted with dichloromethane (3×15 ml). The organic layer (Na_2SO_4) was dried; the solvent removed by distillation, and the product was purified by column

chromatography.

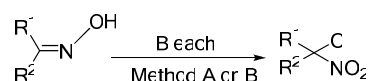
Method B (with sonication). Oxime (1 mmol) was added to a solution of chlorine bleach (1 ml) whereupon the reaction mixture developed a distinct blue color immediately. Chlorine bleach (10-15 ml) was added to the reaction mixture which was sonicated in an ultrasonic bath (between 0.5 to 6 h) until it became colorless. The reaction mixture was transferred to a separatory funnel and a 10% aqueous Na_2CO_3 solution (25 ml) was added. The aqueous fraction was extracted with dichloromethane (3×15 ml). The organic layer (Na_2SO_4) was dried; the solvent removed by distillation and the product was purified by column chromatography.

RESULTS AND DISCUSSION

Our interest in developing a convenient and reliable combination reagent prompted us to examine the halogenation and oxidation properties of cosmetic bleach. The cosmetic bleach is found in a large number of commercial products that are employed as sources of stabilized chlorine for swimming pool disinfection. However, this reagent has received only limited scrutiny as an oxidizing agent in the laboratory despite its widespread usage [22-25].




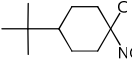
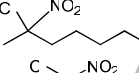


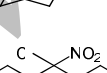
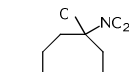

The most convenient procedure involves stirring the oxime in the aqueous media containing chlorine bleach at room temperature to create a blue color, adding excess amount of bleach and stirring the solution between 2 to 10 h which leads to the formation of the desired product (method A, Scheme 4). The results of the investigation are summarized in Table 1.

Ultrasound is found to be an efficient and virtually innocuous means of activation in synthetic chemistry and has been employed for decades with varying degrees of success. The findings of numerous experiments revealed that ultrasound had no effect on the chemical pathways and reaction rates and was often comparable to those of non-irradiated processes. Thus, in many heterogeneous reactions the application of ultrasound, whether by bath or probe, has



Method A Bleach/r t
Method B Bleach under sonication
Scheme 4

Table 1. Conversion of Oximes to Corresponding Gem-chloro-nitro Compounds Using Chlorine Bleach at Room Temperature (Method A) and under Ultrasound Irradiation (Method B)

| Entry | Substrate | Product | Time (h) | | Yield (%) ^a | | Ref. |
|-------|--------------------------------------|---|----------|----------|------------------------|----------|------|
| | | | Method A | Method B | Method A | Method B | |
| 1 | Cyclohexanone oxime |  | 3 | 1 | 83 | 90 | [20] |
| 2 | Cycloheptanone oxime |  | 10 | 6 | 83 | 91 | [8] |
| 3 | Cyclopentanone oxime |  | 4 | 1 | 78 | 80 | [8] |
| 4 | 4- <i>t</i> -Buylcyclohexanone oxime |  | 8 | 3 | 81 | 98 | [8] |
| 5 | 2-Octanone oxime |  | 5 | 2 | 73 | 79 | [26] |
| 6 | 2-Methylcyclohexanone oxime |  | 2 | 1 | 61 | 65 | [8] |
| 7 | 2-Butanone oxime |  | 4 | 1 | 65 | 68 | [19] |
| 8 | Adamantanone oxime |  | 6 | 2.5 | 80 | 82 | [23] |
| 9 | 5-Nonanone oxime |  | 5 | 3 | 80 | 84 | [23] |
| 10 | Cyclooctanone oxime |  | 10 | 6.5 | 82 | 85 | [23] |

^aRefers to isolated yields (the products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures).

Table 2. Chlorine Bleach Converted Cyclohexanone Oxime to the Corresponding Gem-chloro-nitro Compound in Comparison with other Methods

| Conditions | Time(h) | Yield(%) | Solvent requirement | Ref. |
|---|------------|--------------|---|--------------|
| Chlorine bleach | A: 3, B: 1 | A: 83, B: 90 | H ₂ O | Present work |
| Oxone [®] /NaCl/wet basic alumina | 4 | 79 | CHCl ₃ | [20,21] |
| NaHCO ₃ /dioxane | 48 | 78 | H ₂ O | [18] |
| Chloroperoxidase C fumago/KCl/H ₂ O ₂ | 5 | 29 | H ₂ O | [19] |
| HOCl | 10 min | 93 | C ₆ H ₆ /H ₂ O | [13] |

the same effect as a high-speed agitator or homogenizer in which fluids do not cavitate

Accordingly we became interested in studying the synergistic effect of ultrasonic irradiation in the conversion of oximes to gem-chloronitro compounds using bleach as both chlorinating and oxidizing agent.

Ultrasound was employed in a procedure similar to method A. The corresponding results are summarized in Table 1 (method B). The shortest reaction times and the highest yields using method B were achieved by employing ultrasound. The conversion of the oximes to the gem-halonitro compounds is assumed to follow the steps outlined in Scheme 3. The initial step is thought to be the halogenation of the oxime either directly by the sodium hypochlorite or by molecular halogen, which is present in the solution of the bleach. The intermediacy of the halonitroso species in the reaction sequence is suggested when the color of the mixture evolves rapidly to the characteristic blue of monomeric C-nitroso compounds. The disappearance of the blue color serves as a convenient method for monitoring the progress of the nitroso to nitro (blue to colorless) transformation. This oxidation is the overall rate-determining step using methods A or B, where it is thought to be accomplished by the sodium hypochlorite in the aqueous medium.

CONCLUSIONS

In summary, chlorine bleach has proven to be a useful combination halogenating-oxidizing reagent for the conversion of oximes to gem-chloronitro compounds. The procedure is simple and the yields are favorable to high. Additionally, ultrasound may be used in this procedure to make the conversion take place in a stepwise manner. Using sonication leads to the increase in the yield and decrease in the reaction time. Briefly speaking, by comparing the findings of our research, as illustrated in Table 2, with the results of other reports in the literature, we venture to suggest that our method is a better alternative for conversion of cyclohexanone oxime to the corresponding gem-chloro-nitro compounds.

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