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A New Method for The One-Step Conversion of Oximes into *gem*-Halo-Nitro Derivatives*

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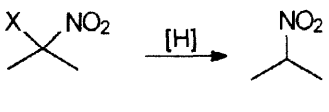
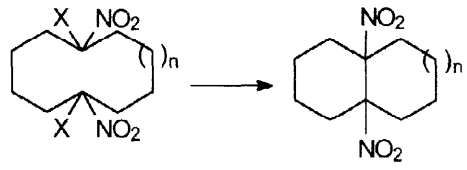
Abstract: A mild and efficient process for one-step conversion of oximes into *gem*-halo-nitro compounds using Oxone® and sodium chloride or potassium bromide is described.

Keywords: oximes; oxidation; halogenation; nitro compounds.

Gem-halo-nitro compounds have many applications in organic synthesis, particularly as precursors of aliphatic nitro-derivatives, *via* a reductive dehalogenation process (eq. 1)[1-4] and of vicinal dinitro compounds *via* an intramolecular reductive coupling of two suitably oriented *gem*-halo-nitro substituted carbon atoms (eq. 2).[5-6]



X = -Cl, -Br eq.1



X = -Cl, -Br eq. 2

Therefore, there is considerable interest in developing new simple methodologies for the preparation of the *gem*-halo-nitro compounds.

Gem-halo-nitro compounds have usually been prepared by the halogenation-oxidation of oximes. In this process the oxime is initially transformed into a *gem*-halo-nitroso derivative, which is then oxidized to the desired *gem*-halo-nitro compound (eq. 3).

* Dedicated to the memory of Prof. Paolo Ceccherelli.

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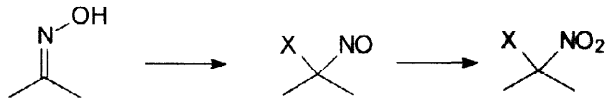


X = -Cl, -Br eq. 3

The first step of this transformation can be achieved by the use of elemental chlorine,[7] bromine,[1-6] aqueous hypochlorous acid,[7] *t*-butyl hypochlorite[8] or *N*-bromo succinimide (NBS).[9] The resulting halo-nitroso compound can be further oxidized with nitric,[10] trifluoroperoxyacetic,[1-4] or *m*-chloroperbenzoic acids,[11] ozone,[12] hydrogen peroxide,[5-6] aqueous sodium[7] or *n*-butyl ammonium hypochlorite.[8] The one-step conversion of the oxime directly into the halo-nitro compound can be obtained by using *N,N,N*,-trihalo-1,3,5-triazines[13] or the enzyme chloroperoxidase in the presence of hydrogen peroxide and sodium chloride or potassium bromide.[14] The methods reported have some limitations 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.

In a preliminary communication,[15] we reported that commercial potassium hydrogen monopersulfate (Oxone®), supported on wet basic alumina,[16] in the presence of sodium chloride could be used effectively for the selective conversion of oximes into *gem*-chloro-nitro derivatives in good yields under mild conditions in a one step procedure. Herein we report the extension of this methodology to the conversion of oximes into *gem*-bromo-nitro compounds.

Recently Oxone® has found extensive synthetic applications in organic chemistry. These include: the preparation of dioxiranes;[17] the oxidation of sulfides to sulfoxides and sulfones,[16] of selenides to selenones,[18] of alkenes to epoxides,[19] of nitrocompounds to carbonyl derivatives;[20] the Bayer-Villiger oxidation of ketones;[21] carbonyl regeneration from thioketals,[22] and oxidative ring cleavage of α-nitrocycloalkanones to α,ω-dicarboxylic acids and to α,ω-dicarboxylic acid monomethyl esters.[23]

Our interest in finding a convenient reagent to effect the conversion of oximes directly into *gem*-halo-nitro compounds, prompted us to examine the halogenation and oxidation properties of Oxone® in combination with NaCl or KBr. When oximes are treated with Oxone® and NaCl or KBr supported on wet basic alumina in chloroform at 45 °C, *gem*-halo-nitro compounds are produced in good yield (Table). The use of wet basic alumina is crucial for the success of the reaction because, in the same reaction conditions, wet neutral alumina leads to the formation of

a complex mixture of compounds in which parent ketones are the most abundant products (>50%), due to the oxidative deprotection of oximes.

The overall process is carried out by the species produced as a result of the Oxone® oxidation of the halide anion.[24] The intermediacy of halo-nitroso species in the reaction sequence is suggested when the color of the mixture evolves rapidly, after the addition of Oxone®, to the characteristic blue, in the case of chlorination, or green, in the case of bromination, of monomeric C-nitroso compounds. The disappearance of these colors is helpful in monitoring the progress of the nitroso to nitro transformation.

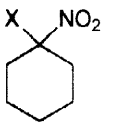
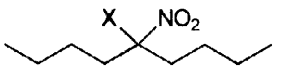
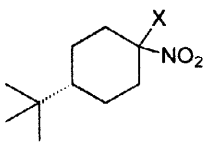
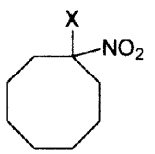
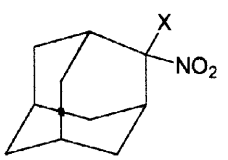
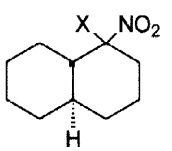
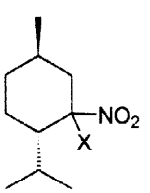
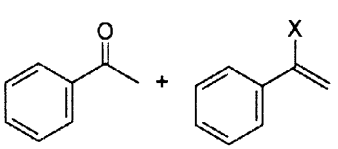
It is important to note that, according to the literature,[14] this reaction leads to the formation of the parent ketone only in the case of the halogenation-oxidation of acetophenone oxime while the formation of 1-halo-1-phenyl-ethene (compounds **8a** and **8b)** is unprecedented. The chlorination-oxidation reaction of oximes is diasteroselective, giving the diasteroisomer in which the nitro group occupies an axial position, as shown by GC-MS and comparison of the NMR data of compounds **3a**, **6a** and **7a** with those reported in the literature.[25] The bromination-oxidation reaction gives an equimolecular mixture of diasteroisomers (compounds **3b**, **6b** and **7b**). This result may be explained by the fact that, in our reaction conditions, a fast stereochemical isomerization of *gem*-chloro-nitroso intermediates, obtained from the addition of the halogenating species to the carbon-nitrogen double bond, may occur[26] giving only one nitroso diasteroisomer which is then oxidized.

In summary, Oxone® and NaCl or KBr, supported on wet basic alumina, have proved to be a useful combination of reagents for the halogenation-oxidation of oximes to *gem*-halo-nitro compounds. The reaction is never accompanied by the formation of the corresponding ketones (except for acetophenone oxime) and the chlorination-oxidation reaction also shows a very high degree of diasteroselectivity.

EXPERIMENTAL

Melting points were obtained on a micro hot stage and are uncorrected. IR spectra were obtained as $CHCl_3$ solutions. ^1H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 200.1 MHz and 50.3 MHz respectively. Column chromatography was executed on 100-125 mesh Fluka aluminum oxide type 507C (activity III). Wet alumina was prepared as described in

Table. Halogenation-oxidation of oximes

Reactant	Product	Time (h)	Yield
cyclohexanone oxime		4	**1a** X = Cl 79% **1b** X = Br 81%
5-nonanone oxime		2	**2a** X = Cl 84% **2b** X = Br 85%
4-*t*butyl-cyclohexanone oxime		4	**3a** X = β-Cl 80% **3b** X = Br 86%
cycloctanone oxime		1	**4a** X = Cl 83% **4b** X = Br 77%
2-adamantanone oxime		1	**5a** X = Cl 74% **5b** X = Br 83%
trans-1-decalone oxime		2	**6a** X = β-Cl 77% **6b** X = Br 77%
(1R,5S)-menthone oxime		7	**7a** X = β-Cl 66% **7b** X = Br 73%
acetophenone oxime		0.5	**8a** X = Cl 83% **8b** X = Br 87%

8 : 1

the literature,[16] using Fluka basic aluminum oxide type 5016A. Oximes were synthetized from the corresponding ketones according to the general procedure.[27]

Chlorination-oxidation of oximes. General procedure. Oxone® (1.85 g, 3 mmol) was added to a well stirred suspension of NaCl (175 mg, 3 mmol) and wet basic alumina (6 g) in chloroform (15 mL) and the mixture heated at 45 °C for 5 min. A solution of oxime (0.6 mmol) in chloroform (1.5 mL) was then added and the reaction mixture stirred until the deep blue colour disappeared (0.5-7 h, see Table). The mixture was filtered under vacuum and the solution evaporated under reduced pressure. The crude material was purified by chromatography on Al_2O_3 (activity III, eluent petroleum ether) affording the desired *gem*-chloro-nitro compound.

1-Chloro-1-nitro-cyclohexane (1a): yellow oil; IR;[14] ^{1}H NMR;[14] ^{13}C NMR;[13] GC/EI MS 117 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.01; H, 6.13; N, 8.58.

5-Chloro-5-nitro-nonane (2a): colourless oil; IR NO_2 1559 (s) cm^{-1}; ^{1}H NMR δ 0.87-0.98 (t, 6H, J = 7.2 Hz), 1.15-1.62 (m, 8H), 2.09-2.45 (m, 4H); ^{13}C NMR δ 13.59, 22.04, 26.14, 41.73, 110.32; GC/EI MS 161 (M^+ - NO_2). Anal. Calcd. for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74. Found: C, 52.07; H, 8.69; N, 6.72.

1-Chloro-1-nitro-4-*t*butyl-cyclohexane (3a): colourless solid, m.p. 52-53° C; IR;[14] ^{1}H NMR;[14] ^{13}C NMR;[14] GC/EI MS 173 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.61; H, 8.31; N, 6.36.

1-Chloro-1-nitro-cycloctane (4a): colourless oil; IR NO_2 1559 (s) cm^{-1}; ^{1}H NMR δ 1.50-1.90 (m, 10H), 2.33-2.85 (m, 4H); ^{13}C NMR δ 22.91, 24.41, 27.29, 37.17, 108.60; GC/EI MS 145 (M^+ - NO_2). Anal. Calcd. for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found: C, 50.13: H, 7.33: N, 7.35.

2-Chloro-2-nitro-adamantane (5a): colourless solid, m.p. 203-204° C (lit.[1] m.p. 200-201 °C); IR;[14] ^{1}H NMR;[14] ^{13}C NMR;[14] GC/EI MS;[14]. Anal. Calcd. for $C_9H_{13}ClNO_2$: C, 53.34; H, 6.47; N, 6.91. Found: C, 53.30; H, 6.44; N, 6.96.

1β-Chloro-1-nitro-*trans*-decaline (6a): colourless oil; IR NO_2 1559 (s) cm^{-1}; ^{1}H NMR δ 0.80-1.92 (m, 13H), 2.08-2.17 (m, 2H), 2.67-2.82 (m, 1H); ^{13}C NMR δ 22.73, 25.75, 25.79, 26.49,

32.49, 34.58, 38.27, 42.30, 54.12, 108.15; GC/EI MS 171 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; N, 6.43. Found: C, 55.18; H, 7.44; N, 6.40.

(1R,3R,5S)-3-Chloro-3-nitro-menthane (7a): colourless oil; IR NO_2 1560 (s) cm^{-1}; ^1H NMR;[25] ^{13}C NMR δ 16.84, 21.56, 23.14, 24.87, 26.27, 29.87, 33.71, 50.48, 54.21, 108.32; GC/EI MS 173 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.65; H, 8.28; N, 6.34.

2-Chloro-styrene (8a): yellow oil; ^1H NMR δ 5.52-5-55 (d, 1H, J = 1.70 Hz), 5.74-5.77 (d, 1H), 7.32-7.67 (m, 5H); ^{13}C NMR δ 116.43, 128.50, 129.46, 129.60, 138.59, 141.58; GC/EI MS 138 (M^+); Anal. Calcd. for C_8H_7Cl: C, 69.33; H, 5.09. Found: C, 69.35; H, 5.11.

Bromination-oxidation of oximes. General procedure. Oxone® (1.85 g, 3 mmol) was added to a well stirred suspension of KBr (360 mg, 3 mmol) and wet basic alumina (6 g) in chloroform (15 mL) and the mixture heated at 45 °C for 5 min. A solution of oxime (0.6 mmol) in chloroform (1.5 mL) was then added and the reaction mixture stirred until the green colour disappeared (0.5-7 h, see Table). The mixture was filtered under vacuum and the solution washed once with a 1% aqueous solution of $Na_2S_2O_3$, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by chromatography on Al_2O_3 (activity III, eluent petroleum ether) affording the desired *gem*-bromo-nitro compound.

1-Bromo-1-nitro-cyclohexane (1b): colourless oil; IR NO_2 1555 (s) cm^{-1}; ^1H NMR δ 1.32-1.90 (m, 6H), 2.38-2.52 (m, 4H); ^{13}C NMR;[13] GC/EI MS 161 (M^+ - NO_2). Anal. Calcd. for $C_6H_{10}BrNO_2$: C, 34.64; H, 4.84; N, 6.73. Found: C, 34.67; H, 4.87; N, 6.69.

5-Bromo-5-nitro-nonane (2b): colourless oil; IR NO_2 1556 (s) cm^{-1}; ^1H NMR δ 0.80-0.96 (t, 6H, J = 7.2 Hz), 1.20-1,65 (m, 8H), 2.25-2.48 (m, 4H); ^{13}C NMR δ 14.10, 22.51, 27.73, 42.48, 103.64; GC/EI MS 205 (M^+ - NO_2). Anal. Calcd. for $C_9H_{18}BrNO_2$: C, 42.87; H, 7.20; N, 5.55. Found: C, 42.90; H, 7.16; N, 5.52.

1-Bromo-1-nitro-4-*t*butyl-cyclohexane (3b): colourless oil; IR NO_2 1558 (s) cm^{-1}; ^1H NMR (isomer 1) δ 0.82 (s, 9H), 0.90-1.35 (m, 5H), 1.81-1.95 (m, 2H), 2.97-3.12 (m, 2H); (isomer 2) δ 0.83 (s, 9H), 0.95-1.40 (m, 5H), 2.02-2.27 (m, 2H), 3.13-3.28 (m, 2H); ^{13}C NMR (isomer 1) δ 25.67, 27.30, 29.68, 40.24, 45.75, 91.51; (isomer 2) δ 24.91, 27.33, 34.16, 38.66, 45.79, 101.38;

GC/EI MS 217 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{18}BrNO_2$: C, 45.47; H, 6.87; N, 5.30. Found: C, 45.49; H, 6.92; N, 5.26.

1-Bromo-1-nitro-cycloctane (4b): colourless oil; IR NO_2 1555 (s) cm^{-1}; ^1H NMR δ 1.45-1.90 (m, 8H), 2.30-2.95 (m, 4H); ^{13}C NMR δ 24.18, 24.93, 27.75, 38.30, 100.69; GC/EI MS 190 (M^+ - NO_2). Anal. Calcd. for $C_8H_{14}BrNO_2$: C, 40.70; H, 5.98; N, 5.93. Found: C, 40.65; H, 5.99; N, 5.96.

2-Bromo-2-nitro-adamantane (5b): colourless solid, m.p. 184-186° C (lit.[13] m.p. 185-186 °C); IR NO_2 1553 (s) cm^{-1}; ^1H NMR δ 1.72-2.05 (m, 8H), 2.23-2.45 (m, 4H), 2.77-2.93 (m, 2H); ^{13}C NMR[13]; GC/EI MS 213 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{14}BrNO_2$: C, 46.17; H, 5.42; N, 5.38. Found: C, 46.21; H, 5.38; N, 5.41.

1-Bromo-1-nitro-*trans*-decaline (6b): yellow oil; IR NO_2 1553 (s) cm^{-1}; ^1H NMR (isomer 1) δ 0.85-1.95 (m, 12H), 2.08-2.25 (m, 3H), 2.66-2.82 (m, 1H); (isomer 2) δ 0.90-2.00 (m, 12H), 2.23-2.40 (m, 3H), 2.93-3.08 (m, 1H); ^{13}C NMR (isomer 1) δ 22.78, 25.84, 25.92, 29.19, 29.69, 32.97, 34.64, 39.39, 50.09, 101.81; (isomer 2) δ 23.67, 25.90, 26.12, 29.43, 29.58, 33.68, 34.84, 39.58, 54.20, 108.23; GC/EI MS 213 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{16}BrNO_2$: C, 45.82; H, 6.15; N, 5.34. Found: C, 45.85; H, 6.12; N, 5.30.

3-Bromo-3-nitro-menthane (7b): yellow oil; IR NO_2 1553 (s) cm^{-1}; ^1H NMR;[25] ^{13}C NMR (isomer 1) δ 18.00, 21.03, 23.14, 24.36, 26.28, 29.35, 34.00, 50.50, 54.24, 102.03; (isomer 2) δ 19.28, 22.12, 23.99, 24.65, 26.01, 29.69, 34.29, 52.03, 54.99, 90.66; GC/EI MS 217 (M^+ - NO_2). Anal. Calcd. for $C_{10}H_{18}BrNO_2$: C, 45.47; H, 6.87; N, 5.30. Found: C, 45.49; H, 6.83; N, 5.27.

2-Bromo-styrene (8b): yellow oil. Identified by comparison with a commercial sample.

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