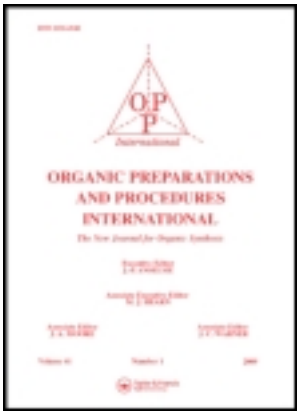

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Ultrasound Promoted One-Pot Synthesis of *gem*-Chloronitro Compounds from Oximes

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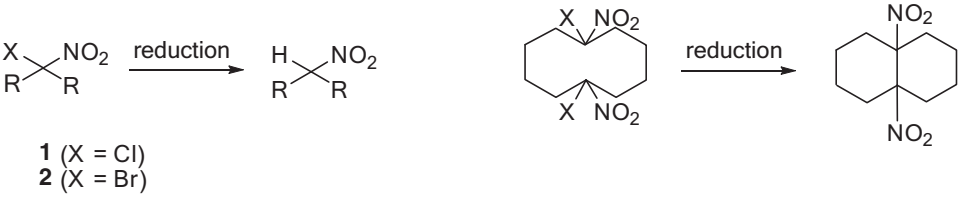
gem-Halonitro compounds **1** and **2** have proven to be versatile intermediates in the synthesis of molecules possessing one or more nitro groups. They have been prepared traditionally either by the direct halogenation of nitronate salts[16] or from oximes *via* a halogenation-oxidation sequence.[7–21] The utility of the *gem*-halonitro intermediates has been demonstrated by their transformation to nitro compounds *via* a reductive dehalogenation process (*Scheme 1*).[8,14] They have also functioned as important elements for assembling polycyclic frameworks by an intramolecular reductive coupling of two suitably located *gem*-halonitro-substituted carbons to yield compounds possessing dinitro substituents (*Scheme 1*).[6,18]



Scheme 1

The conversion of an oxime to a *gem*-halonitro compound is believed to occur in two distinct steps (*Scheme 2*).

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

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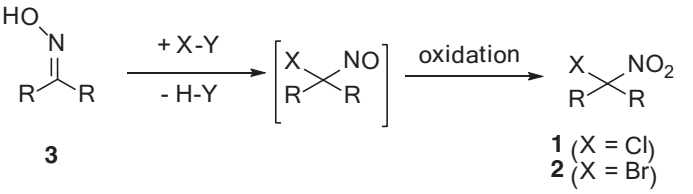


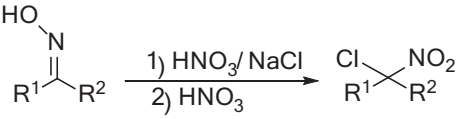
Scheme 2

that have been used for the first step include elemental chlorine,[5,7,17] bromine,[12,14,17,22] aqueous hypochlorous acid[2], *t*-butyl hypochlorite[6] or *N*-bromosuccinimide (NBS).[11]

The oxidizing agents that have proven successful for the second step are nitric acid, trifluoroperoxyacetic acid,[12–14] ozone,[7] hydrogen peroxide,[6] aqueous sodium hypochlorite solution[5] or *n*-butylammonium hypochlorite,[9] *m*-chloroperbenzoic acid. The second strategy involves the use of a combination halogenating-oxidizing reagent that is capable of performing the overall conversion. The combination reagents that have been investigated include hypochlorous acid/hypochlorite ion,[9] hypobromous acid/hypobromite ion,[19] the enzyme chloroperoxidase/hydrogen peroxide/NaCl or NaBr,[21] oxone/NaCl or NaBr[15] systems, NBS[12] and *N,N,N*-trihalo-1,3,5-triazines.[20] The reported methods have some limitations such as the use of toxic or expensive reagents, low yields, long reaction times and transformation of most of the oxime into the parent ketone. Therefore, there is considerable interest in developing new simple methodologies for the preparation of the *gem*-halonitro compounds.

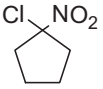
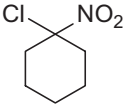
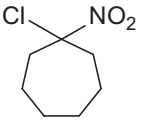
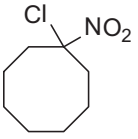
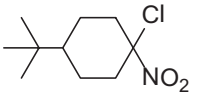
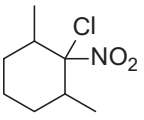
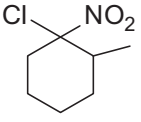
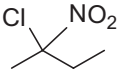
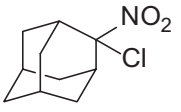
Ultrasound is an efficient and virtually innocuous means of activation in synthetic chemistry and has been employed for decades with varying success. Some advantages of ultrasound procedure are short reaction times and mild reaction conditions, formation of purer products and waste minimization. Ultrasonic irradiation can also be used to influence selectivity and yields of reactions.[23–27] In order to expand the application of ultrasound irradiation in organic synthesis and reactions, herein we report the preparation of *gem*-chloronitro compounds from corresponding oximes using nitric acid and sodium chloride under sonication. Our interest in finding a convenient and reliable combination reagent prompted us to examine the halogenation and oxidation properties of HNO_3/NaCl system.

The most convenient procedure involves stirring the oxime in a solution of sodium chloride/nitric acid at room temperature. Addition of excess amount of nitric acid to the blue mixture (nitroso compound) and stirring the solution for 2 and 5 h, lead to formation of desired product (*Scheme 3*). Shorter reaction times and the higher yields were achieved by employing ultrasound irradiation. The results of the investigation are summarized in *Table 1*.



Scheme 3

Table 1
gem-Chloronitro Compounds from Oximes

Product	Method A[a]		Method B[a]	
	Yield (%)	Time (min)	Yield (%)	Time (min)
	75	120	79	60
	86	150	92	60
	85	180	94	90
	80	180	85	100
	83	180	98	90
	75	300	79	165
	63	165	67	60
	65	300	68	180
	81	180	88	75
	80	240	84	120

[a]*Method A*: without sonication; *method B*: with sonication.

It is important to note that bromination–oxidation of oximes by HNO_3 and KBr leads to formation of a complex mixture of compounds including *gem*-bromonitro and ketones, in which, often, ketones are the major products. For example, halogenation-oxidation of 4-methylcyclohexanone oxime, by HNO_3 and KBr under sonication leads to a mixture containg 4-methylcyclohexanone (80%) and 1-bromo-1-nitrocyclohexane (20%).

In summary, nitric acid in the presence of sodium chloride has proven to be useful combination halogenating-oxidizing reagent for the conversion of oximes to *gem*-chloronitro compounds. The procedure is simple and the yields are good to excellent. Additionally, ultrasound may be used in this procedure to accelerate the conversion and increase yields.

Experimental Section

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 ^{1}H NMR and ^{13}C NMR) in some cases, and by 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 gem-*Chloronitro Compounds*

Method A (Without Sonication): The oxime (1 mmol) was added to a stirred solution of nitric acid (68%, 1 mL) and sodium chloride (233.7 mg, 4 mmol) at room temperature. The reaction mixture developed a distinct blue color immediately. Then nitric acid (68%, 10–15 mL) was added to the reaction mixture and stirring was continued at room temperature until the reaction mixture became colorless (generally between 2 and 5 h). The reaction mixture was transferred to a separatory funnel and a 10% aqueous Na_2CO_3 solution (25 mL) was added. After extraction with dichloromethane (3 × 15 mL), the organic layer was dried over anhydrous Na_2SO_4. The solution evaporated under reduced pressure to give the desired *gem*-chloronitro compound. All products were isolated as colorless oil except 2-chloro-2-nitroadamantane (white crystal, mp. 189–191°C, lit.[20] mp. 192–193°C).

Method B (With Sonication): The procedure above was followed with sonication after the addition of nitric acid.

Spectral Data of the Products

1-Chloro-1-nitrocyclopentane: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.41–1.59 (m, 4 H), 2.20–2.47 (m, 4 H); ^{13}C NMR ($CDCl_3$): δ 20.4, 34.5, 108.2; IR (Nujol): 1550 cm^{-1},[20]

Anal. Calcd for $C_5H_8ClNO_2$: C, 40.15; H, 5.39; N, 9.36. Found: C, 40.10; H. 5.34; N, 9.37.

1-Chloro-1-nitrocyclohexane: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.42–1.79 (m, 6 H), 2.20–2.53 (m, 4 H); ^{13}C NMR ($CDCl_3$): δ 22.9, 23.9, 38.2, 103.7; IR (Nujol): 1548 cm^{-1},[20]

Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 16.16; N, 8.56. Found: C, 43.93; H, 16.12; N, 8.51.

1-Chloro-1-nitrocycloheptane: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.50–1.83 (m, 8 H), 2.40–2.62 (m, 4 H); ^{13}C NMR ($CDCl_3$): δ 22.7, 28.2, 42.4, 108.6; IR (Nujol): 1561 cm^{-1},[28]

Anal. Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.30; H' 6.76; N, 7.86.

4-*tert*-Butyl-1-chloro-l-nitrocyclohexane: colorless solid, mp. 52–53°C; ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9 H), 1.20–1.52 (m, 5 H), 2.15–2.40 (m, 4 H); IR (thin film): 1560 cm^{-1}.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.61; H, 8.31; N, 6.36.

1-Chloro-2,6-dimethyl-1-nitrocyclohexane: ^{13}C NMR ($CDCl_3$): δ 11.1, 19.9, 26.7, 33.0, 118.3; IR (Nujol): 1552 cm^{-1}.

Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N, 7.31. Found: C, 50.13; H, 7.30; N, 7.34.

1-Chloro-2-methyl-1-nitrocyclohexane: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3 H), 1.20–1.57 (m, 6 H), 1.8 (m, 1 H), 2.11–2.40 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 11.7, 23.2, 24.0, 26.2, 33.6, 35.4, 111.6; IR (Nujol): 1557 cm^{-1};[28]

Anal. Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.30; H, 6.82; N, 7.85.

2-Chloro-2-nitrobutane: colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (t, 3 H), 2.11–2.20 (q, 2 H), 2.30 (s, 3 H); IR (Nujol): 1563 cm^{-1}.

Anal. Calcd for $C_4H_8ClNO_2$: C, 34.92; H, 5.86; N, 10.18. Found: C, 34.94; H, 5.81; N, 10.12.

2-Chloro-2-nitroadamantane: colorless solid, mp. 192–193°C; ^{13}C NMR ($CDCl_3$): δ 25.4, 25.9, 34.1, 34.8, 37.0, 37.4, 107.9; IR (thin film): 1553 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.63; H, 6.50; N, 6.44.

5-Chloro-5-nitrononane: colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.74–0.85(t, 6H), 1.10–1.42 (m, 8H), 2.20–2.46 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 13.80, 22.45, 26.01, 41.82, 110.02; IR (Nujol): 1551 cm^{-1}.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.74; N, 6.74. Found: C, 51.92; H, 8.78; N, 6.71.

1-Chloro-l-nitrocycloctane: colorless oil; ^{1}HNMR ($CDCl_3$): δ 1.20–1.37 (m, 10H), 1.90–2.30 (m,4H); ^{13}C NMR ($CDCl_3$): δ 22.91, 24.36, 27.30, 37.09, 108.66; IR (Nujol) 1559 cm^{-1}.

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.

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