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AN EFFECTIVE AND MILD METHOD FOR THE CONVERSION OF OXIMES TO SECONDARY NITRO COMPOUNDS

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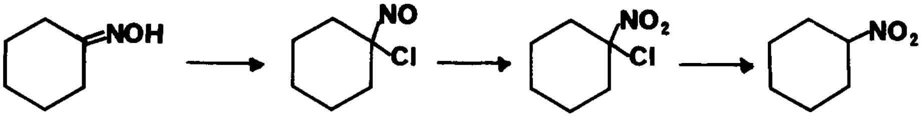
Summary. A mild and efficient process for the conversion of cyclic ketones to saturated nitro compounds, as outlined in eq. 1 below, is described.

The carbonyl and nitro functional groups play a major role in organic synthesis.[1, 2] The efficient replacement of one by the other, which enhances this utility, is readily accomplished in the nitro to carbonyl direction. However, the conversion of carbonyl to nitro groups, which is generally effected via oximes using very strong and non-selective oxidants (CF_3CO_3H,[3a] and ozone,[3b] principally), is at present only narrowly applicable. This paper reports an especially mild method for the carbonyl to nitro transformation, which should greatly broaden the scope and use of this process. Upon initial examination, a number of reagents (e.g. tert-butyl hydroperoxide/VO(acac)$_2$ in tetrahydrofuran, pyridinium dichromate in dimethylformamide (DMF), or lithium hypochlorite in DMF) were found to be inapplicable for conversion of oxime to nitro, since they yielded only ketone. Attention was then turned to the use of Iffland's[4] α-halonitroso intermediates, despite the problems previously encountered in their efficient synthesis and use,[5] with excellent results. It was found (see eq. 1) that aqueous hypochlorous acid at 25°C rapidly transforms oximes to α-chloronitroso derivatives in high yield. Further, the oxidation of α-chloronitroso to α-chloronitro compounds occurs smoothly using the mild and very convenient oxidant tetra-n-butylammonium hypochlorite. Finally a number of reagents were found for the dechlorination of α-chloronitro compounds to secondary nitro compounds.



eq. 1

Although the chlorination of oximes to α-chloronitroso compounds could be accomplished under a variety of conditions,[6,7] the use of hypochlorous acid (1.0 equiv) in a two phase benzene-water mixture (1.2:1) at pH 5.5[8] was optimal with respect to purity and yield of α-chloronitroso product. The pH of the chlorination medium was found to be critical. Reaction at higher pH (i.e., higher hypochlorite concentration) resulted in significant oxidative hydrolysis to ketone, and reaction at lower pH (below 5.0) resulted in the formation of polar side products. The oxidation of α-chloronitroso compounds is generally performed under extremely harsh reaction conditions, e.g., nitric acid, ozone or excess m-chloroperbenzoic acid at elevated temperature. It was therefore not surprising that milder oxidants, such as N-methylmorpholine N-oxide in aqueous acetone at

23°C, excess sodium metaperiodate in aqueous methanol at 65°C, or excess chromium trioxide in ether-water (3:1), were totally ineffective. Although use of aqueous sodium hypochlorite in THF, pyridine, DMF or DMSO was unsatisfactory, since little or no reaction occurred (particularly in the case of β-substituted α-chloronitroso compounds), the use of $\underline{n}Bu_4\overset{+}{N}O\overset{-}{Cl}$ in benzene-H_2O was highly effective for the rapid oxidation of nitroso to nitro.

The reductive dechlorination of the α-chloronitro compounds to the desired saturated nitro compounds could be effected by the judicious choice of one of the following procedures: (1) reaction with magnesium turnings in dry THF at 25°C under argon followed by protonation of the resulting magnesium nitronate with glacial acetic acid; (2) reaction at 25°C with a small excess of zinc dust in THF-H_2O (6:1) containing either ammonium chloride or hydroxylamine hydrochloride as a proton source; or (3) catalytic hydrogenolysis with 1 atm. of H_2 over 5% Pd-C in methanol-water (4:1) containing sodium hydroxide (10-20 equiv) at 25°C, followed by nitronate to nitro conversion using glacial acetic acid. The results of several experiments with a variety of substrates are summarized in the accompanying Table. The experimental procedures which follow are illustrative. The oxime→α-chloronitro change thus becomes a one-flask operation.

1-Chloronitrocyclohexane. To cyclohexanone oxime (5.0 mmol, 566 mg) in 25 ml benzene was added aqueous hypochlorous acid (5.0 mmol, 18.5 ml of a 0.272 M soln at pH 5.5, 1.0 equiv) and the resulting deep blue biphasic mixture was stirred at 27°C for 25 min. The benzene layer was then treated with a mixture of tetra-*n*-butylammonium hydrogensulfate (1.7 mmol, 577 mg, 0.34 equiv) and aqueous sodium hypochlorite (10.0 mmol, 20 ml of a 0.5 M pH 10.0 soln , 2.0 equiv). The biphasic mixture was stirred at 27°C until the blue color was discharged (10 min). After an additional 45 min, aqueous workup followed by filtration through a short column (SiO_2, hexanes) afforded 1-chloronitrocyclohexane, 801 mg (98%, routinely 93-98%).

Reduction Conditions.

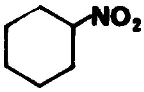
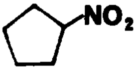
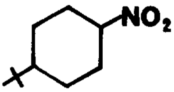
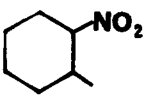
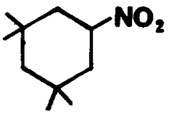
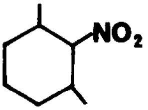
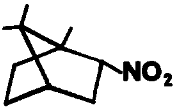
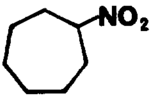
(a) **Mg method.** To a suspension of active magnesium turnings[9] (1.6 equiv) in dry THF (8 ml per mmol of substrate) was added 1-chloronitrocyclohexane. The suspension was stirred at 23°C under argon for 45 min. The solution was then decanted from the residual magnesium (washed with additional THF). Glacial HOAc (4.0 equiv) was added and stirring was continued for 15 min. The reaction mixture was extracted with ether and washed with bicarbonate and water and dried over $MgSO_4$. Bulb to bulb distillation gave nitrocyclohexane in 95% yield.

(b) **Zn dust method.** To a soln of 4-*t*-butyl-1-chloronitrocyclohexane (0.5 mmol, 109.8 mg) in 1.9 ml of tetrahydrofuran was added a solution of hydroxylamine hydrochloride (0.52 mmol, 36.5 mg, 1.05 equiv) in 0.3 ml of water. Zinc dust (0.61 mmols, 40 mg, 1.22 equiv) was added in small batches over 5 min to the stirred reaction mixture at 23°C. After reaction for 30 min, aqueous workup followed by preparative tlc (SiO_2, 7.5% acetone-hexanes, R_f 0.33-0.59) gave a mixture of *cis* and *trans* 4-*t*-butyl-1-nitrocyclohexane (85.9 mg, 92%).

(c) **H_2/Pd-C method.** 1-Chloronitrocamphane (0.37 mmol, 80 mg) in a mixture of methanol (8.0 ml) and 1 N aqueous sodium hydroxide (2.2 mmol, 6.0 equiv) was hydrogenated over 5% Pd-C (13.4 mg) for 6.5 hr at 23°C and 1 atm. The mixture was filtered through celite and treated with glacial acetic acid (0.45 ml) for 3 hr at 23°C. Aqueous workup was followed by preparative tlc (8% ether-hexanes, R_f 0.32-0.44) to give *endo*-nitrocamphane[10] (63 mg, 93.5%), m.p. 149°C.

The method described herein for the conversion of ketones to nitro compounds lends itself to many applications.[11-13]

Table

Oxime	α-Chloro-nitro cpd.,%	React. Cond. time, (°C)	Nitro Product, (% yield)	Reduct. Cond. Time, (°C)	Nitronate→ Nitro Cond. Time, (°C)
cyclohexanone oxime	93%	a, b 10 min (27°C)	 95%	g, 45 min (23°C)	h, 15 min (23°C)
cyclopentanone oxime	89%	a, b 70 min (22°C)	 85%	i, 3 hr (25°C)	h, 4 hr (3°C)
4-t-butylcyclohexanone oxime	89%	a, c 1.3 hr (23°C)	 92%[k]	j, 30 min (25°C)	
2-methylcyclohexanone oxime	90%	a, b 20 min (25°C)	 84%[k]	j, 1.2 hr (25°C)	
3, 3, 5, 5-tetramethylcyclohexanone oxime	75%	a, c 2.2 hr (3°C)	 86%	i, 4.7 hr (30°C)	h, 4 hr (3°C)
2, 6 dimethylcyclohexanone oxime	77%	a, d	 88%	i, 7 hr (25°C)	h, 4 hr (23°C)
d-camphor oxime	82%	e, b	 94%	i, 6.5 hr (23°C)	h, 3 hr (23°C)
cycloheptanone oxime	71%	f, c 1.5 h (27°C)	 77%	i, 3 hr (30°C)	h, 0.7 hr (30°C)

[a] Treatment of the oxime in benzene (0.2M) with aqueous hypochlorous acid (pH 5.52, 1.0 equiv) at 23°C for 15–30 min

[b] Addition of tetra-n-butylammonium hydrogensulfate (0.34–0.5 equiv) and aqueous sodium hypochlorite (pH 10.0, 2.0 to 2.5 equiv) and reaction at described time and temperature until the blue color is discharged.

[c] Slow addition of the chloronitroso compound in benzene to the stirred oxidation medium.

[d] 1.0 equivalent of catalyst was used.

[e] t-Butylhypochlorite (2.2 equiv) in benzene at 20°C for 1 hr.

[f] Dry chlorine gas (1.0 equiv) was added to a solution of the oxime in benzene containing calcium carbonate (5.0 equiv)

[g] Magnesium turnings[9] (1.6 equiv) in tetrahydrofuran for 45 min at 23°C.

[h] Glacial acetic acid (4.0 equiv) for described time.

[i] C-Cl bond hydrogenolysis with H_2/Pd-C in methanol-water (4:1) containing sodium hydroxide (10–20 equiv).

[j] Zn dust in THF-water (3:1) containing either ammonium chloride or hydroxylamine hydrochloride as proton source

[k] Mixture of cis and trans isomers.

References and Notes

1. For reviews on the synthesis and chemistry of nitro compounds, see: (a) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979), (b) Houben-Weyl, "Methoden der Organischen Chemie", E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1971, Band 10/1, pp 1-462, (c) H. Feuer, Ed., "The Chemistry of the Nitro and Nitroso Group", Part 1. Wiley-Interscience, New York, 1969, (d) N. Kornblum, *Org. React.*, **12**, 101 (1962).
2. For recent work from this laboratory see: (a) E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, **100**, 6294 (1978); (b) E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, preceding paper.
3. (a) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955); (b) M. W. Barnes, J. M. Patterson, *J. Org. Chem.*, **41**, 733 (1976).
4. D. C. Iffland et. al., *J. Am. Chem. Soc.*, **75**, 4044, 4047 (1953).
5. See: (a) A. T. Nielsen, *J. Org. Chem.*, **27**, 1993 (1962); (b) A. A. Patchett, F. Hoffman, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, **27**, 3822 (1962); (c) J. R. Bull, E. R. H. Jones, G. D. Meakins, *J. Chem. Soc.*, 2601 (1965).
6. See: H. Diekmann, W. Lüttke, *Angew. Chem. Int. Ed. Eng.*, **7**, 387 (1968).
7. The comparative study of the chlorination of 3, 3, 5, 5-tetramethylcyclohexanone oxime which follows is illustrative. (a) Treatment of the oxime in benzene (0.25 M) with aqueous hypochlorous acid (1.0 equiv) for 36 min at 23°C gave the chloronitroso in 99% yield. (b) Treatment of the oxime in benzene (0.2M) with *t*-butylhypochlorite (1.1 equiv) at 23°C for 35 min gave an 80% yield. (c) Addition of a slow stream of dry chlorine gas to a solution of the O-lithiooxime anion in dry ether at -10° C for 21 min resulted in a 75% yield. (d) Addition of a Cl_2/O_2 stream to a solution of the oxime in ether afforded a 92% yield. (e) Slow addition of a chlorine/oxygen stream to a solution of the oxime in dry benzene (0.5 M) at 23°C affords the chloronitroso product in 96% yield.
8. Preparation of aqueous hypochlorous acid solution of pH 5.5: A 100 ml portion of commercial bleach (initial pH 11.8 to 12.0) was acidified to pH 5.5 by dropwise addition of 3N aqueous sulfuric acid. The change in pH was monitored with a pH meter. The amount of available chlorine was determined iodometrically. The reagent prepared in this manner was used immediately.
9. The magnesium turnings (2.1 equiv) were activated by treatment with 0.5 equiv of dibromoethane.
10. For the stereochemistry of nitrocamphane ion protonation see: S. Ranganathan, *Tetrahedron*, **34**, 3129 (1978).
11. The nitrocompounds thus obtained can be converted to nitroolefins by the following procedure: treatment of the sodium nitronate with phenylselenenyl chloride (1.3 equiv) in THF at 0°C followed by oxidation of the selenide with *m*-chloroperbenzoic acid in methylene chloride affords the desired nitro olefin in high yield.
12. The above described procedure could not be extended to conjugated unsaturated oximes due to the low C-nucleophilicity of such oximes towards halogen electrophiles.
13. This research was assisted financially by a grant from the National Science Foundation.

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