α-NITRO KETONES 7:[1] SYNTHESIS OF CONJUGATED NITROCYCLOHEXENES

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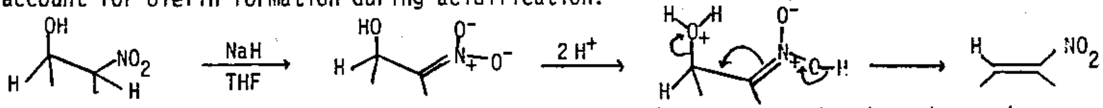
Summary: The reduction of 2-nitrocyclohexanones to the 2-nitrocyclohexanols with sodium borohydride followed by treatment of the β-nitroalcohols with sodium hydride and subsequent acidification of the salts leads to the regioselective synthesis of conjugated nitrocyclohexenes from cyclohexanones.

The resurgent interest in the chemistry of aliphatic nitrocompounds is evidenced by the recent reviews about such compounds.[2] 1-Nitrocycloalkenes[2,a,b,c,3] are one of the most useful types of aliphatic nitro compounds. There are three recent reports of new methods for the synthesis of 1-nitroalkenes: 1) the base catalyzed elimination of HHgCl from nitromercurials prepared by the nitromercuration of olefins[3a], 2) the replacement of tin by a nitro group in vinyl stannanes prepared from tosylhydrazones of cycloalkanones[3b] and 3) the oxidative elimination of C_6H_5SeOH from α-nitro(phenylseleno)alkanes prepared from nitroalkanes and phenylselenyl bromide[3c]. These methods are particularly suitable for the preparation of cyclic nitroalkenes. The classical method[4] of the elimination of water from β-nitroalcohols formed by the condensation of aldehydes and ketones with nitroalkanes (Henry reaction) is limited primarily to the synthesis of acyclic 1-nitroalkenes because of the inaccessibility of the acyclic nitro carbonyl compounds necessary for the condensation reaction to produce the cyclic β-nitroalcohols. However, if an alternate synthesis were available, β-nitroalcohols would serve as ideal precursors for the synthesis of conjugated nitrocycloalkenes. We have recently reported the synthesis of α-nitrocyclopentanones[5,6] and α-nitrocyclohexanones[1,7] by the nitration of ketone enol acetates with nitric acid. We now wish to report the chemoselective reduction of these α-nitroketones to the β-nitrocycloalkanols followed by dehydration as a method of synthesis of conjugated nitrocycloalkenes from cycloalkanones. This sequence of reactions is part of the overall process designed by

Hassner et.al.[8] for the transposition of a carbonyl group to an adjacent position. However, by using excess BH_4^-, the isolation of the β-nitroalcohol or the nitroalkene was precluded.

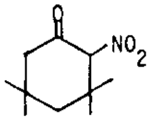
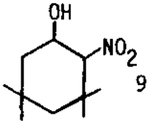
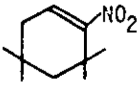
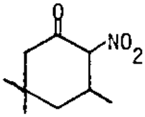
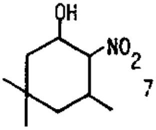
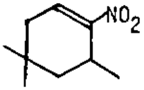
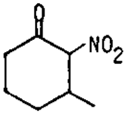
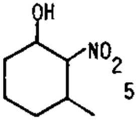
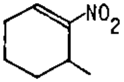
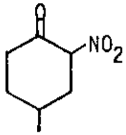
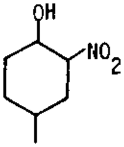
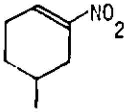
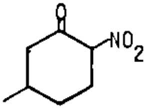
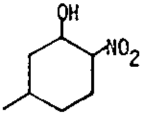
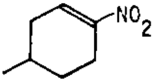
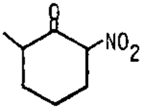
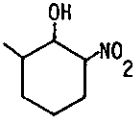
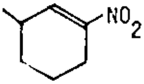
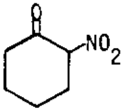
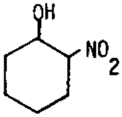
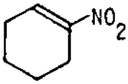
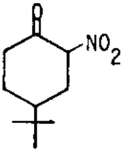
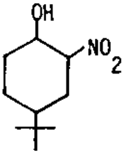
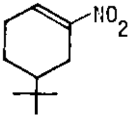
In Table I are listed the β-nitrocyclohexanols and nitrocyclohexenes prepared from the α-nitrocyclohexanones. We have used a variety of reducing agents to carry out the chemoselective reduction of the carbonyl group and different ratios of stereoisomeric β-nitroalcohols are obtained[9]. Since the dehydration reaction, as we carry it out, is not dependent on the stereochemistry of the β-nitroalcohols, $NaBH_4$ in ethanol was used as the reducing agent. Although there are a variety of methods[10] for the dehydration reaction, we found that the use of NaH in THF followed by acidification to pH 1-2 yielded the nitroolefins analytically pure. In fact, the preparation of the nitroolefins can be carried out without purification of the alcohol and is convenient for the synthesis of nitroolefins that are base-sensitive. The fact that an nmr spectrum of the solution after treatment of the β-nitroalcohol with NaH shows no olefinic proton at δ 7.12 demonstrates that the elimination reaction takes place during the acidification step. The following scheme can be written to account for olefin formation during acidification.



This scheme also accounts for the α-hydroxy ketones which appear to be the other major product resulting from a Nef reaction[11] of the nitronic acid and is in agreement with the results obtained by Hassner[8] in his work on carbonyl group transposition.

Our method of synthesis of nitroolefins is complementary to those in the literature. For example, 4-methyl-,4-tert-butyl- or 3,3,5,5-tetramethylcyclohexanones via the vinyl stannanes[3b] give the 1-nitro-alkylcyclohexenes while our method starting with the same ketones yielded the 2-nitro-alkylcyclohexenes. Although nitromercuration is regioselective for certain 4-substituted cyclohexenes,[3a] we have found that 4-methyl-or 4-tert-butylcyclohexene leads to a 1:1 mixture of the 1- and 2-nitro-4-alkylcyclohexenes via the nitromercuration-elimination sequence. Although formation of enol acetates from 3-substituted cyclohexanones leads to a mixture of enol acetates[7] and would eventually lead to a mixture of nitroolefins, we have used an alternative synthesis of 3-methyl-1-acetoxycyclohexene which is the regioselective trapping of the enolate derived from the lithium dimethylcuprate addition to cyclohexenone[12]. This method serves as a general one for the preparation

TABLE I Synthesis of Nitroalkenes Via Reduction-Dehydration of α-Nitroketones

α-Nitro ketone		β-Nitro alcohol (a)*			Nitro alkene (b)*		(f)
	80% →		95-105	85% →		78-9/1	7.12
	80% →		70-1	86% →		70-2/1	7.01
	80% →		57-65	30% →		74/1	7.24
	83% →		c	34% →		76/1.6	7.29
	83% →		74-5	24% →		75/1.3	7.29
	67% →		61-3	12% →		76/1.5	7.17
	60% →		d	72% →		e	7.32
	94% →		96-99	25% →		104/1.2	7.31

(a) mp(°C). (b) bp(°C/torr). (c) bp 106-7/1.4 torr. (d) bp 83-5/0.5 torr, H.Baldock, N.Levy and C.W.Scaife, J.Chem.Soc., 1949, 2627. (e) bp 73/2 torr, Ibid. *Satisfactory elemental analyses (±0.40%) were obtained for all new compounds. (f) ^1H NMR ($CDCl_3$) chemical shift (δ) of vinyl proton.

of 2-nitro-3-substituted cycloalkenes.

General Experimental Procedure: Reduction: In a 250-mL 3-necked flask under nitrogen, $NaBH_4$ (35 mmol) was suspended in 50 mL of anhydrous ethanol at 15°. A solution of (35 mmol) of the α-nitroketone in 60 mL of ethanol was added. The reaction mixture was allowed to warm to room temperature and then stirred for 24 hr. Ice was added and the solution was acidified with 2% HCl to pH 2 and the ethanol removed by rotary evaporation. The residual oil was extracted with ether and dried over Na_2SO_4. Evaporation of the solvent yielded the β-nitroalcohol that could be purified by either distillation or crystallization. Elimination: In a 100-mL three-necked flask under nitrogen, prewashed NaH([illegible]g of 57% oil dispersion, 5 mmol) was suspended in dry THF(50 mL). The β-nitroalcohol([illegible] mmol) in THF(15 mL) was added dropwise with stirring at room temperature and stirred for another [illegible] min. Anhydrous MeOH(1 mL) was added and the solvent was removed. The solid was washed with ether and dissolved in the minimum amount of H_2O and acidified to pH 1 with 2N HCl. Extraction with ether, drying over $MgSO_4$ and concentration gave the nitroalkene as a light yellow oil which, if necessary, could be further purified by distillation under reduced pressure or by dry column chromatography on silica gel (1:1 CH_2Cl_2/pet ether).

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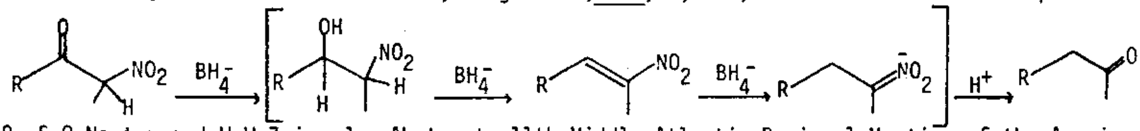

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