

- (14) All potentials are quoted with respect to a reference electrode consisting of a saturated cadmium amalgam in contact with dimethylformamide saturated with both cadmium chloride and sodium chloride; this electrode has a potential of -0.750 V vs. the aqueous saturated calomel electrode.
- (15) A similar result is obtained in experiments with relatively long drop times if the concentration of tetramethylammonium perchlorate is decreased from 0.1 to 0.005 F. Work we are presently doing should help to explain this effect.
- (16) Fleet, B.; Jee, R. D. *J. Electroanal. Chem.* **1970**, *25*, 397-408.
- (17) Tysee, D. A. *J. Electroanal. Chem.* **1971**, *30*, App. 14-16.
- (18) Electrolytic reduction of $C_8H_{17}CD_2CH_2Br$ produces only a small amount of 1,2,2-trideuteriododecane, which indicates that attack on starting material by decyl carbanion is not a favored process. In addition, none of the dimer (eicosane) is produced.
- (19) The water content of typical solutions ready to be electrolyzed that are prepared from dimethylformamide redistilled from calcium hydride is ~ 50 mM. Observations concerning the importance of water for the electrolytic reduction of 1-bromohexane at mercury have been discussed by Reed, R. C. Ph.D. Thesis, Wesleyan University, Middletown, Conn., 1971.
- (20) Dry solvent was obtained by passage of the supporting electrolyte-dimethylformamide solution through a column containing activated neutral alumina. In addition, the electrolysis cell was charged with a small amount of the alumina. The water content of the solution to be electrolyzed was found to be ~ 2 mM.

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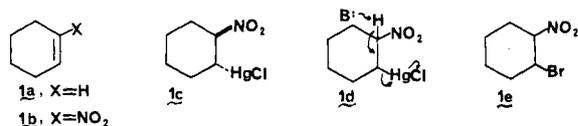
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A New Synthesis of Conjugated Nitro Cyclo Olefins, Unusually Versatile Synthetic Intermediates

Sir:

The position of the endocyclic carbon-carbon double bond as one of the most useful centers of reactivity for the elaboration of complex organic structures would be augmented by the availability of a *mild, position-selective* method for the replacement of a hydrogen on one of the olefinic carbons by a nitro group. Such conjugated cyclic nitro olefins are potentially both versatile and unique as synthetic intermediates, for example, for the stereoselective attachments of appendages and/or functional groups, for the extension of functionality to adjacent methylene groups, or for annulation reactions. Unfortunately the lack of general, selective, and suitably mild processes for the synthesis of cyclic nitro olefins has impeded the development of this whole domain of synthetic methodology.^{1,2} We now describe a new and widely applicable route to cyclic (and noncyclic³) nitro olefins, and in addition we demonstrate some of the manifold ways in which these intermediates can be utilized in organic synthesis.

Our process for olefin nitration is typified by the conversion of cyclohexene (**1a**) to the 1-nitro derivative **1b**.⁴ Reaction of



cyclohexene with 1 equiv of mercuric chloride and 2 equiv of sodium nitrite in aqueous solution at 25 °C for 30 h effected nitromercuration⁵ and afforded after collection of the resulting precipitate the nitromercurial **1c** (80%). Treatment of **1c** in methylene chloride solution with 1.0 equiv of 2.5 N aqueous sodium hydroxide at 25 °C for 5 min with stirring followed by acidification (1 N hydrochloric acid), filtration through Celite (quantitative recovery of metallic mercury), extractive isolation, and distillation produced in $>98\%$ yield pure 1-nitrocyclohexene (**1b**).^{6,7} The novel base-catalyzed elimination of mercury from **1c** can be formulated mechanistically as shown

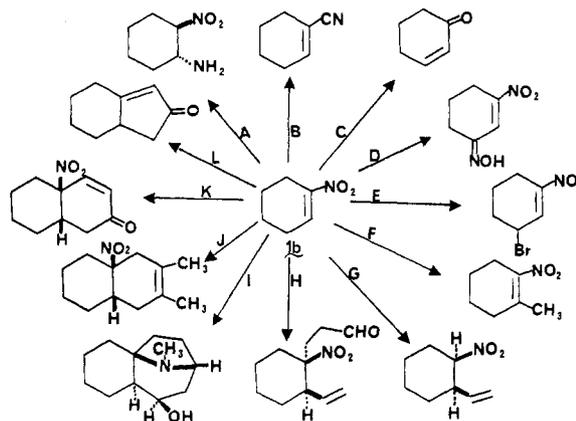
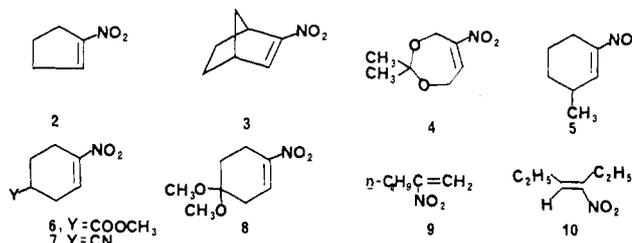


Figure 1. Some elaboration products of cyclohexene via the nitro olefin **1b**. Reagents used for transformations A-L are indicated in the text.

in expression **1d**.⁸ An alternative, but less practical, and less general sequence for the conversion of **1c** to nitro olefin **1b** was also devised and consisted of the following steps: (1) bromination of **1c** by reaction with 1.6 equiv of bromine in a two-phase water-ether system at 0 °C for 10 min and 25 °C for 3.8 h to form **1e** and (2) reaction of **1e** with a small excess of triethylamine in tetrahydrofuran (THF) solution for 12 h at 25 °C to form **1b** (87% overall yield from **1c**).

The base-catalyzed conversion of nitromercurials to nitro olefins can also be effected by various tertiary amine bases, e.g., triethylamine or diazabicycloundecene (DBU), and these reagents are preferable to hydroxide ion in the case of base-sensitive nitro olefins. Studies with a range of substrates have led to a reasonably clear definition of the scope and selectivity of the new nitro olefin synthesis. In all cases investigated the demercuration step was rapid and remarkably clean (with hydroxide ion or tertiary amine as base) and uniformly gave essentially quantitative yield of the nitro olefin. As expected, the nitromercuration step was more variable with regard to rate and yield. In general this process was conducted at 25 °C in aqueous solution of pH 6.5 to 5.5 (phosphate buffer) until analysis of the reaction mixture (by GC or TLC) indicated complete or nearly complete consumption of starting olefin (45-60 h). The nitro olefins in the series **2-10** could be pre-



pared cleanly and selectively with overall isolated yields as follows: **2**, 61%; **3**,^{9c} 77% (DBU as base); **4**, 67%; **5**, 80%; **6**, 78%; **7**, 75%; **8**, 80%; **9**,^{9b,c} 71% (triethylamine as base); **10**, 65%. The clean formation of **3** indicates that carbanion ion rearrangement is not a problem, and the successful preparation of **4** and **8** shows the lack of interference by acid-sensitive functionality in the substrate. Cases **5**, **6**, **7**, and **8** for which complete position selectivity prevails (by chromatographic and spectroscopic analysis) illustrate the operation (and utility) of the remarkable directive effects (presumably involving bis coordination of mercuric ion) which Henbest and Nicholls first observed for olefinic acetoxymercuration,¹⁰ and in the case of **5** the importance of steric effects. The structures of the nitro olefins **5-8** were proved by transformation of the nitrovinyl unit to methylenecarbonyl ($-CH=C-NO_2 \rightarrow -CH_2CO-$) using

4 equiv of titanium trichloride¹¹ in aqueous methanol buffered with excess ammonium acetate at 3 °C for several hours by the following correlations: (1) **5** → 3-methylcyclohexanone; (2) **6** and **7** → 4-carbomethoxy- and 4-cyanocyclohexanone, respectively, and (3) **8** → 4,4-dimethoxycyclohexanone. Markownikoff control is evident in the conversion of 1-hexene exclusively to **9** (correlated with 2-hexanone).

3-Nitro-*cis*-3-hexene (**10**)¹² was formed *stereospecifically* from either *cis*- or *trans*-3-hexene despite the fact that *different* diastereomers were formed in the nitromercuration step. Control experiments showed that neither **10** nor its *Z* stereoisomer nor 3-nitro-4-hexene are equilibrated under the conditions for the synthesis of **10**.¹³

A definite but not unexpected limitation to the above-described conversion of olefins to nitro olefins has been found to occur in cases where the olefin is relatively unreactive in mercuration or very insoluble in the aqueous medium required for mercuration.

The versatility of the cyclo olefinic nitro unit in synthesis is noteworthy, as is its complementary relationship to other key functional groups. The transformations shown for 1-nitrocyclohexene (**1b**) in Figure 1, which are obviously also *transformations* of cyclohexene, illustrate the broad range of applications which follow from the present studies. The specific reagents, conditions and chemical steps of these transformations are as follows: (A) treatment of **1b** with 4 equiv of concentrated ammonium hydroxide in THF at 45 °C for 24 h (95%);^{14,15} (B) addition of **1b** to a cold solution of 1.2 equiv of sodium cyanide and 1.0 equiv of 1 N HCl in methanol and reaction at 0 °C for 15 h, isolation of the HCN adduct, and subsequent treatment with 1.5 equiv of DBU at 50 °C in THF for 3.5 h (85%); (C) conversion of **1b** to the crystalline potassium nitronate (KO-*t*-Bu, *t*-BuOH-THF) followed by exposure to 4 M sulfuric acid at 0 °C for 1 h (Nef reaction) (70% overall); (D) reaction of **1b** with 1 equiv of isoamyl nitrite and 1 equiv of sodium nitrite in dry dimethyl sulfoxide at 25 °C for 2 h (88%); (E) treatment of the potassium nitronate from **1b** (see C) with 1 equiv of bromine in methanol-water at -65 °C (90%); (F) treatment with excess diazomethane in ether at 25 °C for 7 days to form the nitropyrazoline (94%), followed by heating at reflux in dioxane for 8.5 h in the presence of 5% Pd/C catalyst (80%); (G) slow addition of 1.2 equiv of vinylmagnesium bromide in THF to **1b** at -10 °C followed by nitronate → nitro conversion using a mixture of acetic acid and 0.1 N HCl (1:2) for 1 h at 25 °C (80%);^{14,16} (H) treatment of the product from G with 3 equiv of acrolein and 1 equiv of tetramethylguanidine in methanol at -10 to -5 °C for 45 min (83%); (I) (1) reduction of the product from H with 5 equiv of zinc dust and 2 equiv of ammonium chloride in THF-water (2.5:1) for 2 h at 25 °C followed by isolation of the resulting spiro nitron (83%), (2) heating in toluene at reflux (argon atmosphere, 0.01 M) for 5 h to form the intramolecular cycloadduct (mp 44 °C, 100%);¹⁷ (3) N-methylation with excess methyl iodide at 25 °C for 11 h (92%), and (4) N-O bond hydrogenolysis with H₂/Pt in methanol at 1 atm and 25 °C for 11 h (100%) (the overall yield for the 6 steps from **1b** was 50%); (J) Diels-Alder reaction of **1b** at 125 °C under argon with excess 2,3-dimethylbutadiene for 25 h in the presence of 5 mol % of 2,6-di-*tert*-butyl-*p*-cresol as polymerization inhibitor (51%); (K) Diels-Alder reaction of **1b** with 1 equiv of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene in xylene at reflux under argon¹⁹ for 13 h followed by stirring with 0.05 N hydrochloric acid in aqueous THF for 30 min at 0 °C (for enol ether cleavage) and subsequent heating at reflux in benzene with a trace of *p*-toluenesulfonic acid for 2 h (to eliminate methanol) (69% overall); (L) conjugate addition of 1 equiv of ethyl acetoacetate to **1b** (dioxane, 30 min) at 25 °C with benzyltrimethylammonium methoxide as catalyst followed by exposure to 7.2 equiv of sodium hydroxide (EtOH-H₂O) and

subsequent heating with 20 equiv of 3 N hydrochloric acid at 70 °C for 20 min producing 2-acetonylcyclohexanone (70%) which was then cyclized to the hydrindenone by heating with 2 N aqueous sodium hydroxide at reflux for 50 min (91%).

The methodology outlined above provides the groundwork and incentive for much further experimentation. We plan to report further studies in this area and some interesting synthetic applications in the near future.²⁰

References and Notes

- (1) The principal reactions which have been used for the nitration of cyclic olefins have been (a) reaction with concentrated nitric acid (essentially for acid-stable trisubstituted olefins such as cholesterol acetate (cf. A. Windaus, *Chem. Ber.*, **36**, 3752 (1903)) and (b) addition of N₂O₄ followed by base-catalyzed elimination of the elements of HONO from the "nitro-nitrite" component of the mixture of adducts (see, for example, W. K. Seifert, *Org. Synth.*, **50**, 84 (1970) for an especially favorable case).
- (2) For general reviews on the synthesis and chemistry of nitro olefins, see (a) N. Kornblum, *Org. React.*, **12**, 101 (1962), and (b) Houben-Weyl, "Methoden der Organischen Chemie", E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1971, Band 10/1, pp 1-462.
- (3) Acyclic conjugated nitro olefins in general are more readily available than their cyclic counterparts since they can often be obtained by the classical condensation of aldehydes or ketones with nitro alkanes to form β -hydroxy nitro compounds and subsequent elimination.²
- (4) 1-Nitrocyclohexene has been produced by a variety of reactions, none of which are preparatively satisfactory; e.g., see (a) A. A. Griswold and P. S. Starcher, *J. Org. Chem.*, **31**, 357 (1966); (b) J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958); and (c) T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6008 (1957).
- (5) G. B. Bachman and M. Whitehouse, *J. Org. Chem.*, **32**, 2303 (1967).
- (6) All nitro olefins and derived products were fully characterized by infrared, proton magnetic resonance (¹H NMR), and mass spectral data with purified and chromatographically (GC and/or TLC) homogeneous samples.
- (7) The complete and convenient recovery of metallic mercury in the demercuration step allows effective recycling of this moderately valuable material, an important feature of this synthetic method.
- (8) The nitromercurial **1c** as prepared exists in the *trans* form as indicated by the ¹H NMR spectrum. The elimination symbolized by **1d** is not intended to imply stereochemistry or relative timing of the bond-breaking steps.
- (9) (a) With less reactive olefins mercuric perchlorate is preferable to mercuric chloride as reagent; (b) mercuric perchlorate was used in this case; (c) tertiary amine was used for the elimination step.
- (10) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).
- (11) See (a) J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974); (b) J. E. McMurry and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973).
- (12) The stereochemical assignment was made on the basis of ¹H NMR data, specifically the appearance of the olefinic proton at δ 7.04 (triplet, *J* = 7.8 Hz) in CDCl₃ solution. See (a) J. Melton and J. E. McMurry, *J. Org. Chem.*, **40**, 2138 (1975); (b) G. Descotes, Y. Bahural, M. Bourillot, G. Pingon, and R. Rostaing, *Bull. Soc. Chim. Fr.*, 282 (1970); and (c) J. Kochany and H. Plotrowska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **21**, 75 (1973). It is clear that **10** (*E* isomer) is thermodynamically more stable than the isomeric *Z* form.
- (13) In addition, when the formation of **10** was conducted with D₂O-NaOD-CH₂Cl₂, no deuterium was incorporated in either starting nitromercurial or nitro olefin **10**. Therefore it is likely that **10** is formed by syn elimination from one diastereomeric nitromercurial and anti elimination from the other organomercurial. Treatment of the three nitromercurial (from *cis*-3-hexene) in methylene chloride with triethylamine (1 equiv at 25 °C) resulted in formation of **10** with a *t*_{1/2} of ~8 h. Identical reaction of the erythro isomer (from *trans*-3-hexene) occurred with a *t*_{1/2} of ~0.33 h, from which it is clear that anti elimination is faster than syn elimination.
- (14) Stereochemistry follows from ¹H NMR analysis.
- (15) Shorter reaction times produce a product containing ~15% *cis* isomer. Since the reaction of **1b** with hydrazoic acid-sodium azide produces mainly the *cis*-nitro azide, the methodology disclosed herein provides stereoselective routes to either *cis*- or *trans*-1,2-diamines.
- (16) For stereochemistry of nitronate protonation, see (a) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957); and (b) S. J. Angyal and B. M. Luttrell, *Aust. J. Chem.*, **23**, 1485 (1970), and references therein cited.
- (17) See (a) J. B. Bapat, D. St. C. Black, R. F. C. Brown, and C. Ichlov, *Aust. J. Chem.*, **25**, 2445 (1972); and (b) J. J. Tufariello and E. J. Trybulski, *J. Chem. Soc., Chem. Comm.*, 720 (1973).
- (18) Modification of the tertiary nitro function in the adduct from J can lead to a wide variety of interesting products; e.g., the tertiary hydroxylamine, mp 101.5 °C is obtained in high yield from the adduct by reduction with zinc dust-NH₄Cl in aqueous THF. Replacement of nitro by hydrogen in a stereospecific fashion is also potentially useful.
- (19) See S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974); *J. Org. Chem.*, **40**, 538 (1975).
- (20) This work was assisted financially by a grant from the National Science Foundation to which we are grateful.

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