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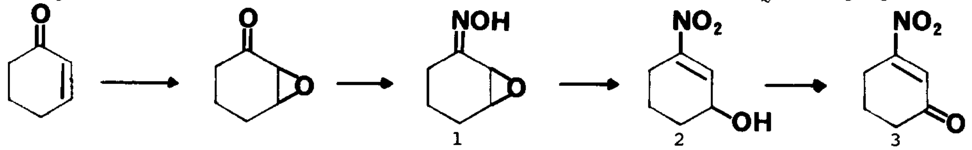
3-NITROCYCLOALKENONES, SYNTHESIS AND USE AS REVERSE AFFINITY CYCLOALKYNONE EQUIVALENTS

E. J. Corey* and Herbert Estreicher

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138 U.S.A.

Summary: A practical synthesis of 3-nitrocycloalkenones and their utilization as dienophiles in the Diels-Alder reaction are described. The results demonstrate a reverse affinity equivalency between these β-nitro-enones and "cycloalkynones".

We have recently reported a number of new processes for the synthesis of conjugated cyclic nitro olefins from either cyclic ketones or cyclic olefins.[1] These 1-nitro olefins provide an effective reversal of normal enolate and olefinic reactivity by means of a number of reactions including (1) addition of nucleophilic reagents, (2) activation of adjacent methylene groups in ionic reactions, and (3) cycloaddition with various unsymmetrical reagents. Another intriguing class of nitro olefins is the 3-nitro-2-cycloalkenone family. The C=C unit in these compounds is expected to be highly electrophilic especially at the carbon alpha to carbonyl, thus allowing at the same time the possibility of both intensification and positional reversal of reactivity of α,β-enones. The research described herein was aimed at demonstrating the usefulness and uniqueness of 3-nitro-2-cycloalkenones as cycloalkynone equivalents. 3-Nitro-2-cyclohexenone (3) was prepared in 65% overall yield from 2-cyclohexenone via the intermediates shown in eq. 1. Oxidation of the epoxy oxime 1[2] with trifluoroperoxyacetic acid[3] afforded nitro alcohol 2 in high yield and this upon



1 2 3

eq. 1

oxidation either with pyridinium chlorochromate or chromic acid-sulfuric acid gave nitro enone 3, m.p. 34.5-35°. 3-Nitro-2-cyclopentenone (4), m.p. 69-71°, was obtained in a similar way (62% overall from 2-cyclopentenone; chromic acid-sulfuric acid used in final step).

These nitro olefins are excellent dienophiles in the Diels-Alder reaction and allow for reaction at much lower temperatures than are required for the simple cyclic enones.[4,5] Further, the adducts obtained with unsymmetrical dienes possess a substitution pattern opposite to that available from the corresponding reaction with α,β-enones. Treatment of the adducts with 1.0 equiv. of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at 0° in tetrahydrofuran (THF) effected rapid conversion[6] of the β-nitro carbonyl system into the α,β-enone unit. The results of experiments with 3 or 4 and a number of dienes are summarized in the accompanying table.

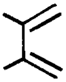
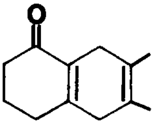
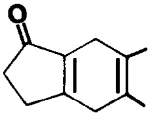
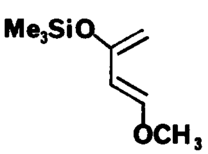
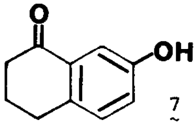
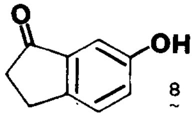
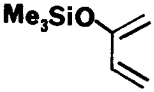
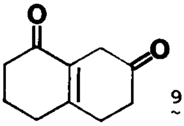
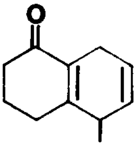
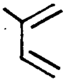
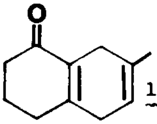
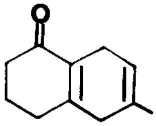
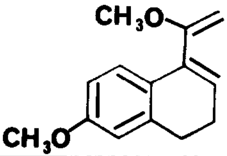
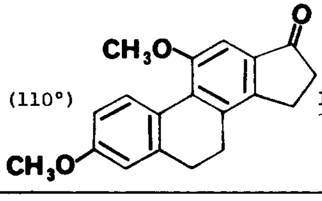
The Diels-Alder reaction with electron-rich 2-oxygenated butadienes (entries 3-5) was position selective and clearly demonstrated the dominant directing influence of the nitro group. Reaction with 2-substituted dienes possessing weakly directing groups (i.e., isoprene, entry 7) were understandably less selective. However, although reaction with 1-substituted butadienes (entries 3, 4, and 6) was position specific there was no corresponding "endo" stereoselectivity. The structures of products 5, 10, 11a, and 11b were confirmed by aromatization of the dihydrotetralones using 1.0 equiv of bromine in methylene chloride at 0°C followed by dehydrobromination with excess DBN at 23° for several hours.[7] The structures 7 and 8 were established by methylation (K_2CO_3-$(CH_3)_2SO_4$- acetone at reflux) and comparison with commercial samples of the corresponding methoxy ketones. The adduct 12, m.p. and lit. m. p. 142-143°, had previously been described.[8]

The results outlined herein provide an indication of the usefulness and potential of 3-nitro-2-cycloalkenones in synthesis as equivalents of "reversed affinity" 2-cycloalkynones in the Diels-Alder reaction. The experimental procedures which follow are illustrative.[9]

3-Nitro-2-cyclohexen-1-one. A freshly prepared solution of peroxytrifluoroacetic acid (68.5 mmol) in 100 ml of acetonitrile was added dropwise over 45 min to a stirred mixture of the α,β-epoxyoxime 1 (22.8 mmol, 2.9 g), sodium bicarbonate (0.137 mol, 11.51 g) and urea (6.85 mmol, 411.5 mg) in 60 ml of dry acetonitrile under argon at 0°.[3b] After an additional 40 min at 0°, aqueous workup followed by chromatography on silica gel (100 g SiO_2, 20% ether-hexane), to remove ca. 10% of a non-polar byproduct (R_f 0.8), afforded 2.33 g (72%) of pure 2 as a pale yellow oil, R_f 0.22 (20% ether-hexane); pmr ($CDCl_3$, ppm): 7.15 (1H, m, olefinic), 4.47 (1H, m, -CHOH), 2.57 (2H, m, allylic $-CH_2-$), 2.21-1.52 (5H, m, $-CH_2$'s and -OH). For larger scale preparation use of a more concentrated reaction mixture, destruction of any excess peracid with saturated aqueous bisulfite and removal of ca. 80% of the acetonitrile before extractive isolation are recommended.

To a stirred suspension of pyridinium chlorochromate (10.3 mmol, 2.26 g) in 5 ml of methylene chloride under argon at 23° was added a solution of nitro alcohol 2 (4.13 mmol, 591 mg) in 10 ml of methylene chloride. After 3.2 h at 23° the mixture was diluted with dry ether and the supernatant liquid was passed through a short pad of Florisil using dry ether to wash the filter pad. Removal of solvent and bulb-to-bulb distillation (at 0.5 torr and below 80°) afforded 3, 496 mg (85%) as light yellow plates, m.p. 34.5-35°; R_f 0.31 (SiO_2, 20% acetone-hexane); pmr ($CDCl_3$, ppm): 6.98 (1H, t, J = 2 Hz, olefinic), 2.98 (2H, m, allylic $-CH_2-$), 2.7-2.45 (2H, m, $-CH_2$ α to carbonyl), 2.43-2.13 (2H, m, saturated $-CH_2-$).

7-Methoxy-1-tetralone. A solution of 3-nitro-2-cyclohexen-1-one (3) (0.18 mmol, 26 mg) and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene[10] (0.37 mmol, 64 mg) in 0.7 ml of dry toluene was heated under argon at 80°C for 19 h. The reaction mixture was allowed to cool to 23° and a mixture of 5 ml of THF-0.08 N HCl-HOAc (1:1:0.1) was added and stirring was continued for 2 h. The product was isolated by extractive workup and treated with DBN (0.56 mmol, 71 mg) for 0.5 h at 23°. Aqueous workup afforded 7 which was treated with dimethylsulfate (0.27 mmol, 34 mg) and powdered K_2CO_3 (0.81 mmol, 112 mg) in 7 ml of acetone at reflux for 2.5 h to afford after isolation and chromatography 7-methoxy-1-tetralone, 24.6 mg (32.6 theo, 76%) identical with an authentic sample, m.p. 61-63°; R_f 0.45 (SiO_2, ether-hexane (1:1)).

Entry	Dienophile	Diene	Diels-Alder Cond. Time, (°C)	Elimination Product	(% Yield)
1	3		b, 23 h (89°)	 5	(83)[h]
2	4	"	b, 47 h (90°)	 6	(80)[h]
3	3		c, 19 h (80°)	 7	(76)[i]
4	4	"	c, 18.7 h (80°)	 8	(86)[i,j]
5	3		c, 20 h (110°)	 9	(70)[k]
6	3		b, e, 40 h (90°)	 10	(83)[h]
7	3		b, f, 30 h (105°)	 11a  11b	(2:1)(99)[h]
8	4		a, d, g, 32 h (110°)	 12	(51)[l]

a) Diene prepared in 64% overall yield from 6-methoxy-1-tetralone by reaction with 2 equiv of α-methoxyvinyllithium in THF-vinyl methyl ether (2:1) at -45° for 1.5 h and subsequent treatment with 3 equiv of MsCl and 6 equiv of triethylamine at -25° to 3° for 12 h. b) Reaction with 20-30 equiv of diene in the presence of 3 mol % 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy. c) Reaction with 2 equiv of diene in toluene. d) Reaction with 1 equiv of diene in toluene. e) 60:40 Mixture of *exo*- and *endo*-stereoisomers. f) 2:1 Mixture of positional isomers. g) Initial adduct was not isolated. h) Treatment of adduct under argon with 1 equiv of DBN in THF at 0° for 1 h. i) Produced after reaction of initial adduct with a mixture of 0.1 N hydrochloric acid in THF at 0° for 30 min (for enol ether cleavage) and subsequent treatment with 2 equiv of DBN at 0° for 1 h (to effect aromatization). j) A 20:1 mixture of positional isomers (major isomer shown). k) Reaction with 0.05 N aq. hydrochloric acid-THF (1:1) at 0° for 2 h and subsequent treatment with 1 equiv of DBN at 23° for 1 h. l) Treatment with 1.5 equiv of DBN in THF at 23° for 17 h.

References and Notes

1. 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.*, 1113 (1980); (c) E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, 1117 (1980).
2. See E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975). The reported procedure for the epoxidation of α,β-epoxy ketones was as described except that the reaction temperature was -25°.
3. See: (a) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955); (b) T. Takamoto, Y. Ikeda, Y. Tachimori, A. Seta, and R. Sudoh, *Chem. Commun.*, 350 (1978).
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5. For related Diels-Alder reactions of *trans*-methyl β-nitroacrylate see, S. Danishefsky, M. P. Prisbylla, and S. Hiner, *J. Am. Chem. Soc.*, **100**, 2918 (1978).
6. J. W. Patterson and J. E. McMurry, *Chem. Commun.*, 488 (1971).
7. The following correlations were performed: (1) **5** → 6,7-dimethyl-1-tetralone; (2) **10** → 5-methyl-1-tetralone; and (3) **11a** and **11b** → 7-methyl- and 6-methyl-1-tetralone, respectively. See, J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem.*, **39**, 1416 (1974) for spectral data of alkyl-substituted-1-tetralones.
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9. This research was assisted financially by a grant from the National Science Foundation.
10. For the preparation of this diene see, S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974); for 2-trimethylsilyloxy 1,3-butadiene see, M. C. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).

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