

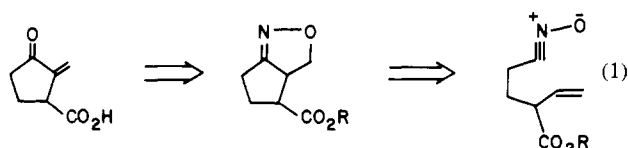
[3.2.0]hept-2-en-6-one, 62182-73-4; (\pm)-4,4a,5,7,8-hexahydro-4-methyl-2(3*H*)-naphthalenone, 40573-28-2; (\pm)-2-(*tert*-butyl)cyclohexanone, 13495-19-7; (\pm)-2-phenylcyclohexanone, 55700-93-1; (\pm)-1,2-diphenyl-2-methoxyethanone, 5987-95-1.

INOC Route to Carbocyclics: A Formal Total Synthesis of (\pm)-Sarkomycin

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Although the intramolecular nitrile oxide cycloaddition (INOC) reaction has now found a wealth of applications in the synthesis of heterocyclic and alkaloid systems,¹ its use in the construction of cycloalkanones has been virtually unexplored.² In order to test its utility in the arena of five-membered ring synthesis and thus to provide the initial touchstone for investigations in this area, we decided to explore an INOC-based approach to the structurally simple antitumor agent sarkomycin (eq 1).³



Sarkomycin

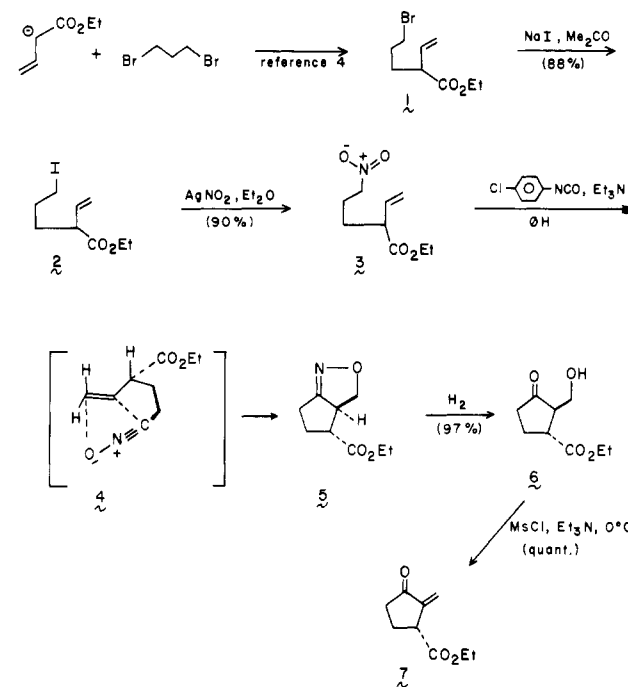
The anion of ethyl crotonate was thus generated by LDA/HMPA treatment and alkylated with the bis-electrophile 1,3-dibromopropane as described by Schlessinger.⁴

Bromide **1** was converted to its corresponding iodide **2** by stirring with 5 equiv of sodium iodide in acetone. While the reaction of **1** with silver nitrite in ether was sluggish, the iodide **2** reacted readily to provide the nitroalkene **3** of sufficient purity (VPC analysis) for use directly in the next reaction (Scheme I).⁵

Nitroalkene **3** was then reacted with excess *p*-chlorophenyl isocyanate⁶ and a catalytic amount of triethylamine in benzene at room temperature. The transient nitrile oxide was intercepted by the tethered olefin to deliver a single isoxazoline **5** in 55% yield after column chromatography.

The fact that **5** suffered no change when exposed to DBU in methanol and that **6** (vide infra) exhibited no tendency to lactonize provides evidence for the stereochemistry depicted in **5**. This stereochemistry is presumed to arise from reaction through that transition state (see **4**) that minimizes A^{1,3} strain. It may, of course, be argued that any of the other isomer [cis arrangement of the C-2 and C-3 substituents (sarkomycin numbering)] formed during the INOC reaction could have undergone epimerization

Scheme I



carbocyclics. Simple modifications in the above scheme should make it possible, for example, to utilize the INOC reaction in the construction of other cyclopentanoids (e.g., pentenomycin and the methylenomycins¹⁰). By a building of additional oxygen functionality into the nitroalkene, the synthesis of prostaglandins and prostaglandin analogues becomes equally feasible.¹¹

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. HL20579) for support of these investigations.

Registry No. (±)-1, 82065-11-0; (±)-2, 82065-12-1; (±)-3, 82065-13-2; (±)-5, 82065-14-3; (±)-6, 82065-15-4; (±)-7, 82080-50-0; (±)-sarkomycin, 72581-31-8; *p*-ClC₆H₄NCO, 104-12-1.

(10) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233. Haneishi, T.; Kitiyara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393. Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977.

(11) All new compounds reported herein gave satisfactory NMR, IR, and mass spectral data.

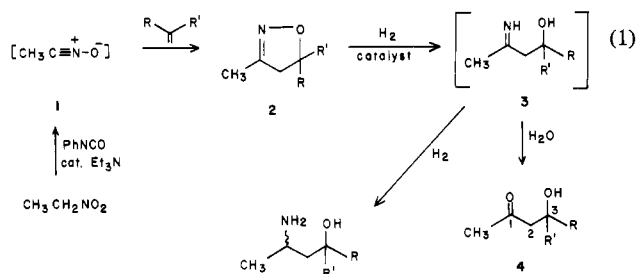
Reduction of Δ²-Isoxazolines: A Conceptually Different Approach to the Formation of Aldol Adducts

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The aldol reaction and related carbonyl condensations continue to be of fundamental importance in organic chemistry.² We now report a conceptually different approach to aldol adducts that involves cycloaddition, rather than carbonyl condensation, in the key carbon-carbon bond-forming reaction. The two-step sequence exploits the potential synthetic equivalency of Δ²-isoxazolines and β-hydroxy ketones as outlined in eq 1. Well-known cycloaddition



of an in situ generated nitrile oxide **1** with a mono- or 1,1-disubstituted olefin typically produces the 5-substituted Δ²-isoxazoline **2** in high yield with complete regioselectivity.³ Although most of the previous conditions used to reduce Δ²-isoxazolines have resulted in complete reduction to the amino alcohol,⁴ we felt that supported metal-type catalysts should reduce the weak N-O bond first. In the presence of water, rapid hydrolysis of the labile hydroxyimine **3** should then occur.⁵

(1) Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1981-1986.

(2) (a) Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 629-682. (b) Barco, A.; Bennetti, S.; Baraldi, R.; Guarneri, M.; Pollini, G. P.; Simoni, O. *J. Chem. Soc., Chem. Commun.* **1981**, 599.

(3) For an excellent review of the chemistry of nitrile oxides see: Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971.

(4) Jäger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133. Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101. Jäger, V.; Buss, V.; Schwab, W. *Ibid.* **1980**, 122. Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601. For reduction to aziridines see: Kotera, K.; Takano, Y.; Matsuura, A.; Kotahonoki, K. *Tetrahedron* **1970**, *26*, 539.

Table I

entry	isoxazoline ^a	con- di- tions	pro- duct	yield, ^b %	% epimeri- zation ^c
1	2a R ₁ = R ₂ = H; R ₃ = <i>n</i> -C ₄ H ₉	<i>d</i>	4a	81	
2	2a	<i>e</i>	4a	(90)	
3	2b R ₁ = R ₂ = H; R ₃ = Ph	<i>f</i>	4b	79	
4	2c R ₁ = H; R ₂ = CH ₃ ; R ₃ = <i>n</i> -C ₃ H ₇	<i>g</i>	4c	84	
5	6a R ₁ = R ₃ = CH ₃ ; R ₂ = H	<i>d</i>	8a	(88)	9
6	6a	<i>e</i>	8a	(86)	6
7	6a	<i>f</i>	8a	83	<2
8	R ₁ = R ₃ = <i>n</i> -C ₃ H ₇ ; R ₂ = H	<i>f</i>		79	<2
9	7a R ₁ = R ₂ = CH ₃ ; R ₃ = H	<i>f</i>	9a	77	<2
10	R ₁ , R ₂ = (CH ₂) ₄ ; R ₃ = H	<i>f</i>		87	<2
11	R ₁ , R ₂ = (CH ₂) ₃ ; R ₃ = H	<i>g</i>		(97)	<2
12	6b <i>n</i> = 2; R ₁ = H; R ₂ = CH ₃	<i>f</i>	8b	(92)	4
13	6b	<i>g</i>	8b	85	<2
14	<i>n</i> = 2; R ₁ = H; R ₂ = Ph	<i>g</i>		73	<2
15	6c <i>n</i> = 1; R ₁ = H; R ₂ = CH ₃	<i>g</i>	8c	(84)	<2
16	7b <i>n</i> = 2; R ₁ = CH ₃ ; R ₂ = H	<i>f</i>	9b	(89)	5
17	7b	<i>g</i>	9b	90	<2
18	<i>n</i> = 2; R ₁ = Ph; R ₂ = H	<i>g</i>		74	<2
19	7c <i>n</i> = 1; R ₁ = CH ₃ ; R ₂ = H	<i>f</i>	9c	(81)	15
20	7c	<i>g</i>	9c	(86)	<2
21	10 <i>n</i> = 2; R ₁ = CH ₃ ; R ₂ = CH ₂ OAc	<i>g</i>	11	82	<5 ^h

^a Nitro olefins were prepared intentionally as a mixture of isomers via Wittig reaction. After cycloaddition, the isomers were separated by flash chromatography. ^b Yields refer to isolated yield of product purified by recrystallization or evaporative distillation. Crude yields were generally above 90%. Yields in parentheses refer to crude product. ^c Diastereomeric ratios were determined by integration of the carbinol proton region in the expanded 300-MHz spectra of crude products. In most cases the ratios were confirmed by integration of other appropriate resonances.

^d NaOAc/HOAc buffer. ^e NaH₂PO₄/Na₂HPO₄ buffer. ^f Catalytic Raney nickel, 15:1 MeOH/H₂O, 2 equiv of B(OCH₃)₃, H₂ gas, 0.4-6 h, room temperature. ^g Catalytic Raney nickel, 5:1 MeOH/H₂O, 2-5 equiv of B(OH)₃, H₂ gas, 0.5-6 h, room temperature.

^h Due to absence of a carbinol proton resonance, a more accurate determination was not possible.

A survey of common catalysts⁶ using adduct **2a** indicated that Raney nickel⁷ (catalytic amount, 15:1 MeOH/H₂O, 1 atm of H₂) was most satisfactory. Thus **2a** was reduced to **4a** in 81% yield after evaporative distillation⁸ (see Table I, entry 1). The presence

(5) Most recently, two isolated examples of this type of reduction have been published. (a) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (b) Asoaka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735. (c) The amino alcohol has also been oxidized to the hydroxy ketone. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.

(6) Platinum oxide (MeOH, H₂O, AcOH) produced the amino alcohol. Palladium on carbon (MeOH, H₂O, HOAc) produced variable amounts of the hydroxy ketone and amino alcohol. Subsequently, we have found that reduction of **2a** to **4a** is cleanly accomplished by 10% Pd-C (MeOH, H₂O, B(OH)₃); however, the generality of these conditions has not been determined.

(7) Most of the reductions were performed with commercially available Ra-Ni (Alfa Inorganics), which was carefully washed free of hydroxide by repeated stirring with water and decantation (~20 times) and stored under MeOH. Subsequently, it was found that W-2 Ra-Ni (Mozino, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 181) was effective, with a faster reaction rate. This was also carefully washed free of hydroxide and stored under MeOH.

(8) Known β-hydroxy ketones exhibited spectra and physical data identical with those obtained from literature sources. New β-hydroxy ketones exhibited spectra consistent with proposed structures as well as satisfactory elemental analysis and/or high-resolution mass spectra.