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THE INTRAMOLECULAR CYCLOADDITION OF α-NITRONE ESTERS: A STEREOCONTROLLED SYNTHESIS OF γ-HYDROXY-α-AMINOESTERS

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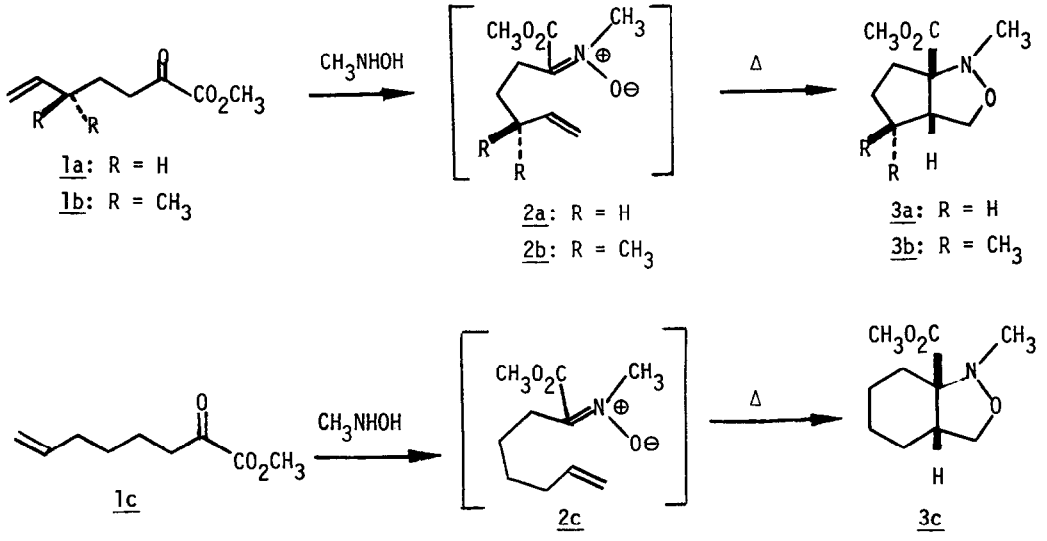
Summary: The intramolecular cycloaddition chemistry, and synthetic utility of α-nitrone esters for the preparation of cyclic α-aminoesters is described.

Since LeBel first reported the facile intramolecular cycloaddition of unsaturated nitrones to form bicyclic isoxazolidines,[1] there has been considerable interest in utilizing this elegant methodology for alkaloid synthesis.[2] We became interested in the nitrones derived from the biologically important α-ketoester functional group (α-nitrone esters 2) since their intramolecular 1,3-dipolar cycloaddition would provide intermediates useful for the stereocontrolled synthesis of γ-functionalized-α-aminoesters (4).

We report here that the readily available α-ketoesters 1a-c[3] are smoothly converted into the resonance stabilized α-nitrone esters 2a-c which in turn undergo facile intramolecular cycloaddition on warming in dilute solution to form the bicyclic isoxazolidines 3a-c.



1a: R = H
1b: R = CH_3

2a: R = H
2b: R = CH_3

3a: R = H
3b: R = CH_3

1c

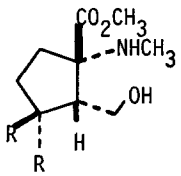
2c

3c

The novel α-nitrone esters 2b and 2c could be isolated in excellent yield from the reaction of α-ketoesters 1b and 1c with N-methylhydroxylamine (1.5 equivalents $CH_3\overset{+}{N}H_2OH$ 1.5 equivalents of triethylamine) in dichloromethane.[4] In refluxing toluene solution these nitrones underwent an intramolecular 1,3-dipolar cycloaddition reaction yielding the bicyclic isoxazolidines 3b and 3c (83 and 78% respectively). For the large scale preparation of the isoxazolidines it was more convenient not to isolate the α-nitrone esters, but to carry out the overall synthetic transformation in one pot starting with the crude α-keto-esters 1a-c.[5]

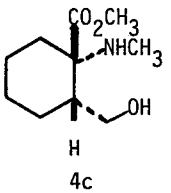
While the bicyclic isoxazolidines were easily purified by silica gel chromatography, due to the reversible nature[6,7] of the 1,3-dipolar cycloaddition, distillation was avoided. When the bicyclic isoxazolidine 3b was subjected to evaporative distillation at reduced pressure (oven temperature = 70°C; P = 0.5mm) the distillate contained, in addition to the desired product 3b, a second component in varying amounts (TLC; 10% ethyl acetate in dichloro-methane). Storage of isoxazolidines 3a-c at room temperature or below for up to 2 weeks did not lead to any noticeable decomposition however. Reconversion of the distillate containing the more polar impurity (~50%) back into the pure isoxazolidine 3b was easily effected by warming a dilute solution of the mixture to reflux in toluene for 8 hours.[9]

Catalytic reduction of isoxazolidines 3a-c to the γ-hydroxy-amino esters 4a-c proceeded smoothly using 5% rhodium on carbon catalyst in methanol solution.[10] Of the four catalysts investigated for this reduction (5% Pd or Rh on carbon and 5% Pd or Rh on alumina) only the rhodium catalysts were generally effective. Alternatively, the bicyclic isoxazolidine 3b could be reduced in 83% yield to the amino diol 5 using lithium aluminum hydride in tetra-hydrofuran (THF).[11]

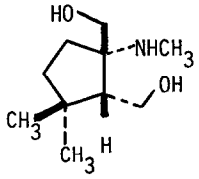


4a: R = H

4b: R = CH_3



4c



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The utility of the α-aminoesters 4a-c for the synthesis of rationally designed analogs of the neurotoxin marcfortine[12] is currently under investigation.

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References and Notes:

1) N.A. LeBel and J.J. Whang, J. Am. Chem. Soc., 1959, 81, 6334-5; N.A. LeBel, Trans. N.Y. Acad. Sci., 1965, 27, 858-67.

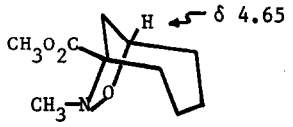
2) D.S.C. Black, R.F. Crozier and V.C. Davis, Synthesis, 1975, 205-21; J.J. Tufariello, Acc. Chem. Res., 1979, 12, 396-403.

3) For the preparation of the α-ketoesters (1), see the preceding communication, this journal.

4) General procedure for the α-nitrone esters (2):[13] A mixture of 10 mmol of the α-ketoester (1b or 1c), 1.25g (15 mmole) of N-methylhydroxylamine hydrochloride and 3.0 mL of triethylamine in 100 mL of CH_2Cl_2 was allowed to stir for 2-3 h at 25°C (reaction progress monitored by TLC). The reaction mixture was washed wth 10% aqueous HCl, saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvents under reduced pressure followed by flash chromatography[8] on silica gel afforded the pure α-nitrone ester. **2b** :Rf = .25 (10% ethyl acetate in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.0 (s, 6H), 1.5 (t, 2H, J = 6 Hz), 2.7 (t, 2H, J = 6 Hz), 3.8 (s, 3H), 4.1 (s, 3H), 4.8 (dd, 1H, J_1 = 10 Hz, J_2 = 2 Hz), 5.1 (dd, 1H, J_1 = 18 Hz, J_2 = 2 Hz), 5.8 (dd, 1H, J_1 = 18 Hz, J_2 = 10 Hz); IR (CCl_4) 1720, 1640, 1530, 1440 cm^{-1}; UV (EtOH) λ_{max} = 270 nm (log ε = 4.43). **2c** :Rf = .5 (20% ether in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.4-1.7 (m, 2H), 2.0-2.3 (m, 2H), 2.6-2.9 (m, 2H), 3.8 (s. 3H), 4.2 (s, 3H), 4.8 (dd, 1H, J_1 = 10 Hz, J_2 = 2 Hz), 5.1 (dd, 1H, J_1 = 18 Hz, J_2 = 2Hz), 5.8 (dd, 1H, J_1 = 18 Hz, J_2 = 10 Hz); IR (CCl_4) 1720, 1645, 1530, 1440 cm^{-1}; UV (EtOH) λ_{max} = 270 nm (log ε = 4.47).

5) General procedure for the preparation of the isoxazolidines (3):[13,14] A mixture of 100 mmol of the α-ketoester, 10g (120 mmole) of $MeNH_2OH^+$ Cl^-, and 30 mL Et_3N in 2L of 6% MeOH in toluene was rapidly stirred at 60°C for 12 h, then warmed to reflux under a nitrogen atmosphere for 4 h. After cooling, the reaction mixture was washed with water (500 mL), then dried ($MgSO_4$). After removal of solvents under reduced pressure (water aspirator only), keeping the water bath temperature below 35°C, the residue was purified by flash chromatography[8] on silica gel and afforded the bicyclic isoxazolidines. **3a** :(72%): Rf = .40 (10% ethylacetate in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.4-1.9 (m, 6H), 2.6 (s, 3H), 3.2 (m, 1H), 3.4 (dd, 1H, J_1 = 5 Hz, J_2 = 8 Hz), 3.7 (s, 3H), 4.0 (t, 1H, J = 8 Hz): IR (CCl_4) 1740, 1475, 1440, 1330, 1310, 1225 cm^{-1}. **3b** :(82%): Rf = .4 (10% ethyl acetate in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.00 (s, 3H), 1.04 (s, 3H), 1.4-1.9 (m, 4H), 2.67 (s, 3H), 2.95 (t, 1H, J = 7.5 Hz), 3.78 (s, 3H), 3.8-4.0 (m, 2H); IR (neat)1725, 1450, 1430, 1255, 1225, 1190 cm^{-1}. **3c** :(74%): Rf = .30 (20% ether in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.1-1.5 (m, 3H), 1.6-1.8 (m, 4H), 2.0-2.1 (m, 1H), 2.6 (s, 3H), 3.2 (m, 1H), 3.7 (t, 1H, J = 7.4 Hz), 3.8 (s, 3H), 4.1-4.2 (dd, 1H, J_1 = 7.4 Hz, J_2 = 10 Hz).

6a) At lower temperatures of reaction (T < 80°C) the bicyclic isoxazolidine **3c** was accompanied with a minor product (< 26%) which proved to be the bridged bicyclic isoxazolidine **3d** . This type of byproduct was also observed as the kinetic product in the cycloaddition of the nitrone derived from 7-octene-2-one.[7]



3d

3d :Rf = .25 (20% ether in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.5-1.8 (m, 6H), 2.0 (m, 1H), 2.2 (m, 1H), 2.3 (m, 1H), 2.65 (s, 3H), 2.8-2.95 (m, 1H), 2.75 (s, 3H), 4.65 (d, 1H, J = 10 Hz); IR (CCl_4) 1740, 1490, 1480, 1450, 1440 cm^{-1}.

b) Unequivocal assignment of the bicyclo-[3,3,0]-octane and bicyclo-[4,3,0]-nonane ring skeletons to the isoxazolidines 3b and 3c was established using the Delayed Noise Decoupling (DND) technique (F.A.L. Anet, N. Jaffer and J. Strouse, Presented at the 21st Experimental NMR Conference, Tallahassee, Fl., 1980) on the ^{13}C-FTNMR spectrum (200 MHz Bruker WP 200 spectrometer, purchased with NSF grant CHE 76-05926). The DND technique consists of applying a ^{1}H coupled ^{13}C pulse, a variable time delay (τ) and a ^{1}H decoupled data acquisition of the ^{13}C-FID. Since $J(^{13}C-^1H)$ varies with the degree of C-H substitution, the line intensity of a carbon atom is dependent on the number of attached protons as well as the time delay (τ) in data acquisition. Thus the intensity of quaternary carbon resonances show no time (τ) dependence, whereas the methylene (CH_2) exhibits a varying positive intensity. The methyl (CH_3) and methine (CH) resonances are differentiated by their

varying negative peak intensity after longer delay (τ) times. The methyl resonances show a much stronger time dependence (τ) than the methine resonances. Due to the close proximity of the ^{13}C resonances in the isoxazolidines 3b and 3c, the more commonly used off-resonance decoupling technique was not useful for peak assignments. The assignments (based on ^{13}C-DND-NMR experiments) for the bicyclic isoxazolidines are as follows: **3b**: ^{13}C-NMR ($CDCl_3$) δ 23.7 (CH_3), 29.4 (CH_3), 29.9 (C-6, CH_2), 38.5 (-N-CH_3), 38.8 (C-7, $-CH_2-$), 40.4 (C-5, -C-), 51.8 (-OCH_3), 63.4 (C-4, -C-H), 68.0 (-CH_2-O), 173.1 (C=O). **3c**: ^{13}C-NMR ($CDCl_3$) δ 20.58 (C-5, $-CH_2-$), 21.64 (C-6, CH_2), 24.50 (C-7, $-CH_2$), 26.12 (C-8, $-CH_2-$), 38.62 (-N-CH_3), 42.73 (-C-H, 52.15 (-OCH_3), 69.47 (-CH_2-O), 174.95 (-C=O).

7) N.A. LeBel and E.G. Banucci, J. Org. Chem., 1971, 36, 2440-8.

8) W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923-5.

9) The α-nitrone ester 2b underwent a slow conversion into the isoxazolidine 3b in $CDCl_3$ solution (0.01M) at 35°C (t 1/2 ≃ 4 days). After 18 days at 35°C, the integration of the -CH_3 resonances (^1H-NMR) indicated that the ratio of 3b to 2b was 20:1.

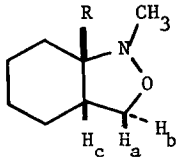
10) General procedure for the preparation of the γ-hydroxy-α-aminoesters (4a-c):[13] A solution of 5 mmole of the isoxazolidine (3a-c) in 100 mL of absolute methanol was shaken with 200 mg of 5% rhodium on carbon (Strem Chemical Co.) under 50 psi of hydrogen. After 5h (3 days for the sterically congested isoxazolidine 3b), the mixture was filtered and concentrated under reduced pressure. The hydroxyaminoesters were purified by either recrystallization, evaporative distillation at 0.05mm, or flash chromatography[8] through a short column of silica gel. **4a**: Rf = .16 (1:9:10, MeOH/EtOAc/CH_2Cl_2); ^1H-NMR (CCl_4) δ 1.6-2.0 (m, 5H), 2.0-2.3 (m, 1H), 2.25 (s, 3H), 2.6-2.8 (m, 3H), 3.55 (m, 2H), 3.6 (s, 3H); IR (CCl_4) 3400, 1730, 1450, 1435, 1250 cm^{-1}. **4b**: mp 58°C (hexane) Rf.3 (1:9:10 MeOH/EtOAc/CH_2Cl_2); ^1H-NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.06 (s, 3H), 1.6 (dd, 2H, J_1 = 6 Hz, J_2 = 8 Hz), 1.75-1.95 (m, 2H), 2.2-2.3 (m, 1H), 2.27 (s, 3H), 2.45 (br m, 2H), 3.60-3.70 (dd, 1H, J_1 = 4.5 Hz, J_2 = 11 Hz), 3.7 (s, 3H), 3.8-3.9 (dd, 1H, J_1 = 9 Hz, J_2 = 11 Hz); IR (CCl_4) 3500, 1730, 1465, 1438, 1270, 1250 cm^{-1}. **4c**: Rf= 0.22 (1:9:10, MeOH/EtOAc/CH_2Cl_2); ^1H-NMR (CCl_4) δ 0.9-2.1 (br m, 8H), 2.3 (s, 3H), 2.5-2.7 (m, 2H), 3.5 (m, 1H), 3.7 (s, 3H); IR (CCl_4) 3400, 1735, 1450, 1430 cm^{-1}.

11) Lithium aluminum hydride reduction of isoxazolidine 3b according to the procedure described in L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, p 584-5 afforded the aminodiol[13] **5** (83%): ^1H-NMR (CCl_4) δ 0.9 (s, 3H), 1.1 (s, 3H), 1.15-1.9 (m, 5H), 2.3 (s, 3H), 3.0 (d, 1H, J = 11 Hz), 3.4-3.7 (m, 2H), 3.7 (d, 1H, J = 11 Hz), 4.3 (br m, 3H); IR (CCl_4) 3300, 1460, 1370 cm^{-1}.

12) T. Prangé, M.-A. Billion, M. Vuilhorgne, C. Pascard, and J. Polonsky, Tetrahedron Lett., 1981, 1977-80.

13) All new compounds described in this communication gave correct C,H analyses.

14) The bicyclic isoxazolidine 3c is the only bicyclic addition product we have investigated capable of having trans stereochemistry. The cis stereochemistry of 3c was assigned on the basis of comparison of the splitting patterns of the isoxazolidine ring protons (H_a, H_b and H_c) of 3c with the bicyclic isoxazolidine 3e[7] of established stereochemistry.



3c: R = CO_2CH_3

3e: R = CH_3

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