Reduction of Substituted Δ^2-Isoxazolines. Synthesis of β-Hydroxy Acid Derivatives

Dennis P. Curran,*[1] Susan A. Scanga,[2] and Christopher J. Fenk

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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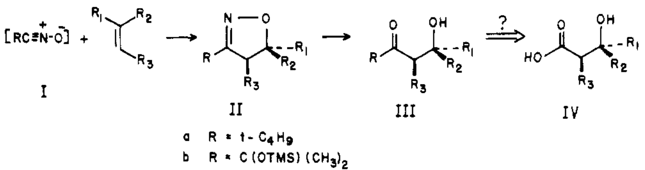
Three separate methods are reported for the formation of β-hydroxy acid derivatives from readily available substituted Δ^2-isoxazolines. Cycloaddition of 2,2-dimethylpropanenitrile oxide with a variety of olefins followed by reductive cleavage produces α'-*tert*-butyl β-hydroxy ketones. These are cleaved to β-hydroxy *tert*-butyl esters by Baeyer–Villiger oxidation with peroxytrifluoroacetic acid. In the second approach, α',β-dihydroxy ketones are generated via cycloaddition of olefins with the nitrile oxide generated from 2-[(trimethylsilyl)oxy]-2-methyl-1-nitropropane followed by reductive ring opening. Standard periodic acid cleavage gives β-hydroxy acids. Finally, 3-methoxy-substituted Δ^2-isoxazolines, readily available via benzenesulfonylcarbonitrile oxide–olefin cycloaddition and methoxide displacement, are directly reduced to β-hydroxy esters.

We have recently completed the first phase of a research program directed toward the development of a general cycloadditive strategy for the assemblage of "aldol"-type adducts (β-hydroxy carbonyls).[3] In many ways, this is complementary to the standard carbonyl addition approach. Summarized in eq 1, the sequence involves (1) well-known cycloaddition of an olefin with an in situ generated nitrile oxide[4] followed by (2) hydrogenolysis–hydrolysis of the resultant Δ^2-isoxazoline (II). Our research thus far has uncovered an exceedingly mild and general hydrogenolysis–hydrolysis procedure (Ra Ni; H_2; $B(OH)_3$; $MeOH/H_2O$)[3a] which suppresses several serious side reactions including over-reduction, epimerization, and retro-aldol reaction.[3] Employing this cycloadditive approach, a large number of β-hydroxy ketones III (R = alkyl, aryl) have been synthesized.[3] Clearly it is important to generalize this approach such that β-hydroxy acids (and esters) IV are also available. Previous fragmentations of Δ^2-isoxazolines in this vein have usually led to β-hydroxy nitriles (R = CO_2H, SO_2Ph, Me_4Si).[5] This is complicated in sensitive systems by the harsh conditions often applied for nitrile hydrolysis. While this work was in progress, several examples of reduction and oxidative cleavage of (hydroxymethyl)-substituted isoxazolines to give β-hydroxy acids were reported by Kozikowski.[5e] More recently, the ability to obtain modest asymmetric induction in a chiral system was also demonstrated.[6]



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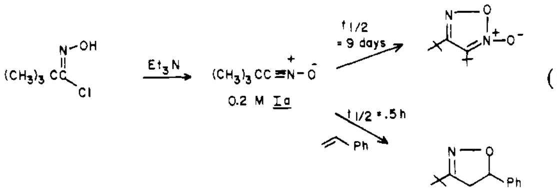
A most direct route to β-hydroxy acids IV involves oxidative cleavage of an appropriately substituted ketone. We chose to investigate sterically congested nitrile oxides since evidence suggests that yields of cycloaddition are maximized with respect to competing dimerization of the nitrile oxide.[4] This is of the utmost importance in intermolecular cycloaddition reactions since dimerization of the nitrile oxide can be a serious side reaction when disubstituted olefins are employed.[7] Although syringe pump addition of reagents to minimize the concentration of the nitrile oxide can be useful, employment of large excesses of olefin is more common. Another important advantage of these conjested nitrile oxides, demonstrated by Martin and Dupre,[8a] is the high regioselectivity observed in cycloaddition with cis-disubstituted olefins. This regiochemical bias is based on the size of the olefin substituents with the nitrile oxide oxygen preferentially bonding to the more hindered site.

Results and Discussion

In the first approach, the known 2,2-dimethylpropanenitrile oxide Ia[8] was generated from the corresponding hydroximic acid chloride[9] via standard dehydrochlorination with triethylamine (eq 2). In contrast to other alkyl-substituted nitrile oxides which dimerize readily to furoxans at room temperature,[4] 2,2-dimethylpropanenitrile oxide exhibits a reasonable stability.[10] In a simple ^1H NMR experiment, 2,2-dimethylpropanenitrile oxide was generated as a 0.2 M solution in C_6D_6 (see Experimental Section). At room temperature, more than 1 month was



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[1] Recipient of a Dreyfus Foundation Award for Young Faculty in Chemistry, 1981–86.

[2] University of Pittsburgh Undergraduate Research Participant.

[3] (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Curran, D. P. *Ibid.* **1982**, *104*, 4024. (c) Curran, D. P. *Tetrahedron Lett.* **1983**, *24*, 3443. (d) β-Dicarbonyls may also be formed. Curran, D. P.; Singleton, D. M. *Ibid.* **1983**, *24*, 2079. (e) Kozikowski, A. P. *Acc. Chem. Res.*, in press.

[4] (a) Grundmann, C.; Grunanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971. (b) Caramella, P. In "1,3-Dipolar Cycloaddition"; Padwa, A., Ed.; Wiley: New York, 1983.

[5] (a) Huisgen, R.; Cristl, M. *Chem. Ber.* **1973**, *106*, 3291. (b) Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209 and 210. (c) Wade, P. M.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. (d) Brandi, A.; DeSarlo, F.; Guarna, A.; Speroni, G. *Synthesis* **1982**, 719. (e) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.

[6] Kozikowski, A. P.; Kitagawa, Y.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1460.

[7] Our experience using near equivalent amounts of olefin has been that while 1,1-disubstituted olefins give good yields, *trans*-olefins usually give moderate yields and *cis*-olefins give very poor yields (<25%). Unactivated trisubstituted olefins are not generally useful in normal intermolecular cycloadditions.

[8] (a) Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337. (b) Scarpati, R.; Speroni, G. *Gazz. Chim. Ital.* **1959**, *89*, 1511. (c) Zinner, G.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 383. (d) Christl, M.; Huisgen, R. *Tetrahedron Lett.* **1968**, 5209. (e) Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251.

[9] Zinner, G.; Gunther, H. *Chem. Ber.* **1965**, *98*, 1353.

[10] 2,2-Dimethylpropanenitrile oxide has been reported to have a mp of 18 °C, a bp of 61 °C (15 mm), and a stability of 2–3 days (neat, 25 °C). See ref 4a, p 17.

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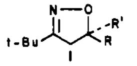
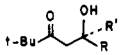
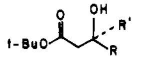
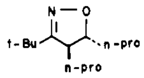
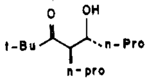
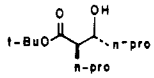
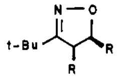
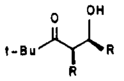
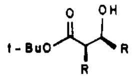
Table I. Baeyer-Villiger Cleavage

entry	cycloadduct[a] olefin, yield, %	β-hydroxy ketone		tert-butyl ester
	 I	 2		 3
a	styrene, 98	78	R = Ph, R′ = H	52
b	1-hexene, 88	92	R = C_4H_9, R′ = H	54
c	methylenecyclohexane, 52	90	R,R′ = $(CH_2)_5$	45
				
d	*trans*-4-octene, 41	75		~0
				
e	cyclopentene, 76	88[c]	R,R = $(CH_2)_3$	40
f	cyclohexene, 52[b]	88	R,R = $(CH_2)_4$	<10
g	*cis*-stilbene, 46	*d*	R = R = Ph	

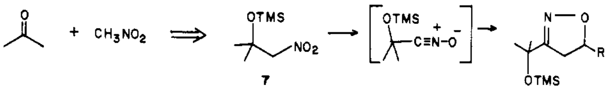
[a] Cycloaddition was conducted in benzene at 40–85 °C depending on the boiling point of the olefin. Two equivalents of olefin were employed. [b] A large excess of cyclohexene was used. The furoxan dimer was also isolated in 32% yield. [c] 87/13 mixture of cis and trans, see text. [d] Retro-aldol fragmentation occurred to give *tert*-butyl benzyl ketone and benzaldehyde.

required for complete disappearance of Ia. The half-life ($t_{1/2}$) of dimerization was found to be about 9 days. Despite this stability, rapid formation of cycloadduct Ia was observed upon addition of styrene ($t_{1/2} \approx 0.5$ h, room temperature). Table I lists the cycloadducts formed by employing 2,2-dimethylpropanenitrile oxide. Disubstituted olefins required heating of the reaction to promote rapid cycloaddition. With use of a modest excess of olefin, reasonable yields of cycloadducts were obtained.[11] The use of less reactive olefins did result in competing dimer formation (entry **1f**). Despite this, the increased utility of sterically conjested nitrile oxides was apparent. For example, generation of Ia by rapid addition (ca. 5 min) of Et_3N to a solution of neopentanal oxime chloride and *cis*-stilbene (see Experimental Section) gave a 1/1 ratio of cycloadduct to dimer while a complementary experiment using *n*-hexanal oxime chloride gave a 1/3.6 ratio of corresponding cycloadduct to dimer.

The overall sequence is completed by Raney nickel mediated cleavage[3a] of the isoxazolines **1a–f** to the α′-*tert*-butyl β-hydroxy ketones **2a–f** and Baeyer–Villiger oxidation to the β-hydroxy *tert*-butyl esters **3a–f**. Several points are worthy of note. As expected, the reduction yields are uniformly high. While entries **1d** and **1f** showed no epimerization, in the cyclopentyl series **2e**, 10–15% loss of stereochemistry was observed. Also, with the *cis*-stilbene adduct **1g**, no β-hydroxy ketone was produced and retro-aldol products were detected. Both of these observations are consistent with our hypothesis that such undesired side reactions occur via the intermediate β-hydroxy imine product by initial Raney nickel mediated N–O bond hydrogenolysis.[3a] The presence of the bulky *tert*-butyl group may depress the hydrolysis rate of the imine and allow reactions such as epimerization and retro-aldol reaction to compete in favorable systems.

The Baeyer–Villiger oxidations were performed with buffered peroxytrifluoroacetic acid.[12] 3,5-Dinitroperoxybenzoic acid[13] and *m*-chloroperoxybenzoic acid were less effective in promoting rapid conversion. Note that the *tert*-butyl ester, a convenient protected form of the acid, is formed directly; however, increasing substitution about the carbonyl decreases the yield dramatically. This is undoubtedly due to the inability of the peracid to add to the ketone. In such cases (entries **d**, **e**, **f**), large amounts of starting material were recovered even after prolonged oxidations in the presence of a stabilizer.

From the above results it is apparent that while the *tert*-butyl substituent allows for reasonable yields in the cycloaddition reaction, it is less than satisfactory for oxidative cleavage. A much more versatile approach relies upon the frequently employed oxidative cleavage of α′,β-dihydroxy ketones.[5e,6] The elegant work of Heathcock and others has demonstrated the utility of this functionality both in promoting stereoselectivity in the aldol reaction and in permitting facile subsequent transformation.[14] In our complementary method, the desired nitrile oxide **1b** was formed from the nitro precursor 2-[(trimethylsilyl)oxy]-2-methyl-1-nitropropane (**7**) readily available via Henry reaction of nitromethane and acetone[15] followed by silylation (eq 3). Using the general method of Mukaiyama,[16] addition of phenyl isocyanate to a refluxing solution of **7**, an olefin (2 equiv), and Et_3N (C_6H_6) produced the cycloadducts **4a–f** in reasonable yields (Table II). The cycloadducts were reduced by using the standard conditions[3a] to produce the α′-(trimethylsilyl)oxy β-hydroxy ketones **5a–f**. In our case, these intermediates **5** were directly cleaved with periodic acid to the β-hydroxy acids **6a–f**. Each yield was determined by subsequent diazomethane treatment and purification (flash chromatography and/or distillation) of the resultant methyl ester. This three-step method of cycloaddition, reduction, and oxidative cleavage should provide a mild and general approach to a wide variety of β-hydroxy acid derivatives. By nucleophilic addition prior to cleavage, β-hydroxy aldeh-



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[11] Two equivalents of olefin were generally employed. These yields are often difficult to compare with literature yields due to the common practice of employment of large excesses of olefin.

[12] Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287.

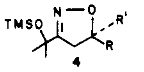
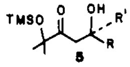
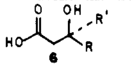
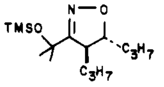
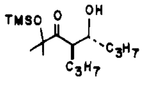
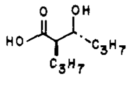
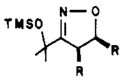
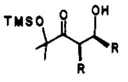
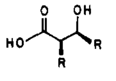
[13] Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

[14] For example, see: Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 295.

[15] Lambert, A.; Lowe, A. *J. Chem. Soc.* **1947**, 1517.

[16] Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

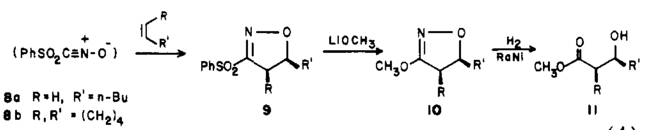
Table II. Periodic Acid Cleavage

entry	cycloadduct^a olefin, yield, %	β-hydroxy ketone		β-hydroxy acid^c
	 4	 5		 6
a	styrene, 75	90	R = Ph, R′ = H	99
b	1-hexene, 84	84	R = C_4H_9, R′ = H	83
c	2-methyl-1-pentene, 83	*a*	R = C_3H_7, R′ = CH_3	42^b
				
d	*trans*-4-octene, 52	*a*		43^b
				
e	cyclopentene, 89	95^e	R = $(CH_2)_3$	79
f	cyclohexene, 52^d	*a*	R = $(CH_2)_4$	65^b

^{a} Product was partially desilylated and used directly in cleavage. ^{b} Yield calculated from cycloadduct 4. ^{c} Based on purified yield of the methyl ester derived via diazomethane treatment. ^{d} PhNCO was added via syringe pump. ^{e} Ratio 87/13; cis to trans, see text.

ydes and ketones should also be available.[14]

Finally, a third approach based on the chemistry of (benzenesulfonyl)-substituted Δ^2-isoxazolines has been explored. Two examples are outlined in eq 4. 3-Methoxy-substituted isoxazolines **10** were generated according to the general two-step procedure of Wade[17] which involves (1) cycloaddition of an olefin with in situ generated benzenesulfonylcarbonitrile oxide **8** to give **9** followed by (2) displacement of benzene sulfinate with lithium methoxide. The resulting alkoxy-substituted isoxazolines **10a,b** were converted directly to the β-hydroxy esters **11a,b** without event by using the standard reduction conditions. Presumably a similar hydrogenolysis-hydrolysis mechanism is operating.[3a] In the case of the cis-fused bicyclic isoxazoline **9b**, no loss of stereochemistry was evident in either the displacement or the reduction. Although only these two examples have been investigated, this promises to be a useful method in view of the ease of formation and versatility of (benzenesulfonyl)-substituted isoxazolines as shown by the extensive investigations of Wade et al.[17]



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In summary, these methods should extend the utility of this cycloadditive strategy as a complement to aldol-type reactions by providing ready access to a variety of β-hydroxy acid type derivatives. Due to the mildness of the reaction conditions at each stage, a wide variety of common functional groups, whether protected or not, should be tolerated. The utility of this sequence will be extended by our recent discovery that nitrile oxide IIb can be readily generated by furoxan dimer thermolysis. A facile cycloaddition procedure which has evolved will be reported in a forthcoming paper.[18]

Experimental Section

General Methods. All melting points and boiling points are uncorrected. Kugelrohr boiling points refer to oven temperature. All reactions were run under nitrogen atmosphere with the exception of the Raney nickel reductions which were conducted under hydrogen. Olefins employed were all commercially available. Reagents and solvents were purified as follows: Et$_3$N, distilled from CaH$_2$; benzene, distilled from sodium; ether, distilled from sodium/benzophenone; trimethylsilyl chloride, distilled from Bu$_3$N; phenyl isocyanate, vacuum distilled. All NMR spectra were run on a Varian EM-390 (90 MHz) spectrometer unless otherwise indicated. Semipreparative HPLC refers to separation on a Waters Prep 500 with a 25-mm steel column packed with Merck silica gel 60 (230–400 mesh).

Generation and Observation of 2,2-Dimethylpropanenitrile Oxide (Ia). To a solution of neopentanal oxime chloride[9] (62 mg, 0.46 mmol) in C$_6$D$_6$ (860 μL containing 1% Me$_4$Si) was added Et$_3$N (77 μL, 0.55 mmol). The reaction was shaken vigorously for ~1 min and centrifuged. The supernatant was decanted into an NMR tube; 90-MHz NMR showed the appearance of a single new *tert*-butyl peak (δ 0.66) which was assigned to 2,2-dimethylpropanenitrile oxide. Gradually, two new singlets attributed to the dimer (3,4-di-*tert*-butylfuroxan, mp 67–69 °C; lit.[8c] mp 67 °C) could be observed at δ 1.18 and 1.22 (see below):

time	% nitrile oxide	% dimer
20 min	>99	<1
2 h	>99	<1
20 h	99	1
2 days	95	5
6 days	60	40
9 days	50	50
16 days	40	60
23 days	15	85
34 days	5	95

General Procedure for Cycloaddition with 2,2-Dimethylpropanenitrile Oxide. Cyclopentene Adduct 1f. To a solution of neopentanal oxime chloride[9] (271 mg, 2 mmol) and cyclopentene (352 μL, 4 mmol) in benzene (5 mL) was added triethylamine (293 μL, 2.1 mmol) in benzene (5 mL) dropwise via addition funnel. An immediate white precipitate was observed. The reaction was heated to 40 °C for 10 h, filtered, and concentrated in vacuo. The residue was distilled (58 °C, 1 mm, Kugelrohr) to give **1f** as a white solid (255 mg, 76%): mp 33–34.5 °C; ^{1}H NMR (CDCl$_3$) δ 5.02 (1 H, m), 3.55 (1 H, m), 2.2–1.5 (6 H, m), 1.22 (9 H, s); IR (CHCl$_3$) 1485, 1365 cm^{-1}; MS, *m/e* 167 (M$^+$), 152, 110. Anal. (C$_{10}$H$_{17}$NO) C, H.

5-Phenyl-3-*tert*-butyl-Δ^2-isoxazoline (1a): reaction time 20 h at 25 °C; solvent, Et$_2$O; ^{1}H NMR (CDCl$_3$) δ 7.35 (5 H, m), 5.54 (1 H, dd, *J* = 10 Hz, 8 Hz), 3.40 (1 H, dd, *J* = 16 Hz, 10 Hz), 2.90 (1 H, dd, *J* = 16 Hz, 8 Hz), 1.23 (9 H, s); IR (CHCl$_3$) 1600 (weak), 1485, 1470, 1450, 1360 cm^{-1}; MS, *m/e* 203 (M$^+$). Anal. (C$_{13}$H$_{17}$NO) C, H.

5-*n*-Butyl-3-*tert*-butyl-Δ^2-isoxazoline (1b): reaction time 20 h at 25 °C; solvent, Et$_2$O; ^{1}H NMR (CDCl$_3$) δ 4.58 (1 H, m), 3.02 (1 H, dd, *J* = 16 Hz, 10 Hz), 2.54 (1 H, dd, *J* = 16 Hz, 8 Hz), 1.8–1.0 (6 H, M$^+$), 1.23 (9 H, s), 0.91 (3 H, br t); IR (CHCl$_3$) 1480,

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(17) Generation of PhSO$_2$CNO and cycloaddition: see ref 5c. Lithium methoxide displacement: Wade, P. A.; Yen, H.-K.; Hardinger, S. A.; Pittay, M. K.; Amin, N. V.; Vail, P. D.; Morrow, S. P. *J. Org. Chem.* **1983**, *48*, 1796.

(18) D. P. Curran and C. J. Fenk, manuscript in preparation.

1460, 1385 cm^{-1}; MS, *m/e* 183 (M$^+$), 168, 126. Anal. ($C_{11}H_{21}NO$) C, H.

Methylenecyclohexane adduct 1c: reaction time 48 h at 25 °C; solvent, benzene; bp 120 °C (18 mm, Kugelrohr); mp 88.5–90 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (2 H, s); 2.1–1.1 (10 H, m), 1.23 (9 H, s); IR ($CHCl_3$) 1480, 1450, 1370 cm^{-1}; MS, *m/e* 195 (M$^+$), 180, 113. Anal. ($C_{12}H_{21}NO$) C, H.

trans-4,5-Di-_n_-propyl-3-_tert_-butyl-Δ^2-isoxazoline (1d): syringe pump addition of Et_3N at 80 °C in benzene over 8 h; total reaction time 20 h; purified by flash chromatography (5% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 4.28 (1 H, m), 2.82 (1 H, m), 2.0–1.4 (8 H, m), 1.24 (9 H, s), 0.92 (6 H, br t); IR ($CHCl_3$) 1480, 1460, 1385 cm^{-1}; MS, *m/e* 211 (M$^+$), 196. Anal. ($C_{13}H_{25}NO$) C, H.

Cyclohexene adduct 1f: reaction time 20 h at reflux in benzene (13% yield) or 20 h at reflux in cyclohexene (52% yield); purified by flash chromatography (8% EtOAc/hexane); mp 54.5–55 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 4.24 (1 H, m), 2.80 (1 H, br m); 2.2–1.0 (8 H, m), 1.23 (9 H, s); IR ($CHCl_3$) 1480, 1460, 1450, 1365 cm^{-1}; MS, *m/e* 181, 166, 124. Anal. ($C_{11}H_{19}NO$) C, H.

trans-4,5-Diphenyl-3-_tert_-butyl-Δ^2-isoxazoline (1g): reaction time 20 h at reflux in benzene; purified by flash chromatograph (10% EtOAc/hexane); mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ ~7.1 (10 H, m), 5.68 (1 H, d, *J* = 8 Hz), 4.30 (1 H, d, *J* = 8 Hz); 1.26 (9 H, s); IR ($CHCl_3$) 1605, 1495, 1480, 1455, 1365 cm^{-1}; MS, *m/e* 279 (M$^+$), 173, 117. Anal. ($C_{19}H_{21}NO$) C, H.

5-Hydroxy-5-phenyl-2,2-dimethyl-3-pentanone (2a). The reductions were all run by using our previously published procedure, method 2:[3a] ^{1}H NMR ($CDCl_3$) δ 7.30 (5 H, m), 5.27 (1 H, t, *J* = 8 Hz), 3.65 (1 H, br s), 1.24 (9 H, s); IR ($CHCl_3$) 3500, 1690 cm^{-1}; MS, *m/e* calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1307.

5-Hydroxy-2,2-dimethyl-3-nonanone (2b): ^{1}H NMR ($CDCl_3$) δ 4.05 (1 H, m), 3.10 (1 H, br s), 2.65 (2 H, m), 1.7–1.2 (6 H, br), 1.27 (9 H, s), 0.90 (3 H, br t); IR ($CHCl_3$) 3500 (br), 1690 cm^{-1}; MS, *m/e* 168 (M – H_2O), 129, 111.

1-(3,3-Dimethyl-2-oxobutyl)cyclohexanol (2c): ^{1}H NMR ($CDCl_3$) δ 4.25 (1 H, s), 2.64 (2 H, s), 2.1–1.0 (10 H, m), 1.24 (9 H, s); IR ($CHCl_3$) 3450 (br), 1690 cm^{-1}; MS, *m/e* 198 (M$^+$), 180, 141, 133. Anal. ($C_{11}H_{22}O_2$) C, H.

(_R_*,_R_*)-5-Hydroxy-4-_n_-propyl-2,2-dimethyl-3-octanone (2d): ^{1}H NMR ($CDCl_3$) δ 3.68 (1 H, m), 2.95 (1 H, m), 2.80 (1 H, br s), 1.8–1.2 (8 H, m), 1.26 (9 H, s), 0.92 (6 H, t); IR ($CHCl_3$) 3450 (br), 1680 cm^{-1}; MS, *m/e* calcd for $C_9H_{17}O_2$ (M – *t*-Bu) 157.1229, found 157.1229.

cis-2-(2,2-Dimethyl-1-oxopropyl)cyclopentanol (2e): 87/13 mixture of erythro/threo; ^{1}H NMR of erythro ($CDCl_3$) δ 4.30 (1 H, br s), 3.81 (1 H, br s), 3.15 (1 H, dt), 2.1–1.5 (6 H, m), 1.27 (9 H, s); IR ($CHCl_3$) 3450 (br), 1690 cm^{-1}; MS, *m/e* calcd for $C_{10}H_{16}O$ (M – H_2O) 152.1201, found 152.1201.

cis-2-(2,2-Dimethyl-1-oxopropyl)cyclohexanol (2f): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.98 (1 H, br d), 2.96 (1 H, br d), 2.0–1.2 (9 H, m), 1.26 (9 H, s); IR ($CHCl_3$) 3450 (br), 1690 cm^{-1}; MS, *m/e* calcd for $C_{11}H_{18}O$ (M – H_2O) 166.1358, found 166.1358.

tert-Butyl 3-Hydroxy-3-phenylpropionate (3a). Solid Na_2HPO_4 (409 mg, 2.88 mmol) was added to a solution of **2a** (74 mg, 0.36 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. Freshly generated peroxytrifluoroacetic acid[12] (1.1 M in CH_2Cl_2, 1.0 mL) was added to the suspension dropwise by pipet through a reflux condenser. During the addition, the reaction began to reflux and was maintained at reflux for 1 h. The reaction was diluted with CH_2Cl_2, washed with water, saturated Na_2HSO_3, and brine, dried over $MgSO_4$, and concentrated in vacuo to give **3a** (41 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (5 H, m), 5.08 (1 H, m), 4.43 (1 H, d), 3.67 (2 H, m), 1.44 (9 H, s) IR ($CHCl_3$) 3500 (br), 1710 cm^{-1}; MS, *m/e* calcd for $C_9H_9O_3$ (M – *t*-Bu) 165.0552, found 165.0551.

tert-Butyl 3-hydroxyheptanoate (3b): purified by flash chromatography (12/1, hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (1 H, m), 3.13 (1 H, d), 1.46 (1 H, dd), 1.33 (1 H, dd), 1.6–1.2 (6 H, m), 1.48 (9 H, s), 0.92 (3 H, br t); IR ($CHCl_3$) 3500 (br), 1710 cm^{-1}; MS, *m/e* 145, 127, 111.

1-(2-_tert_-Butoxy-2-oxoethyl)cyclohexanol (3c): purified by flash chromatography (9/1, hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (1 H, s), 2.37 (2 H, s), 1.8–1.3 (10 H, m), 1.46 (9 H, s); IR ($CHCl_3$) 3500 (br), 1705 cm^{-1}; MS, *m/e* calcd for $C_8H_{14}O_3$ (M – *t*-Bu) 158.0943, found 158.0944.

tert-Butyl _cis_-2-hydroxycyclopentanecarboxylate (3e): purified by medium-pressure liquid chromatography (8% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 4.40 (1 H, br), 3.29 (1 H, br s), 2.60 (1 H, dt), 2.0–1.4 (6 H, m), 1.47 (9 H, s); IR ($CHCl_3$) 3450 (br), 1705 cm^{-1}.

2-[(Trimethylsilyl)oxy]-2-methyl-1-nitropropane (7). Trimethylsilyl chloride (23.0 mL, 0.18 mol) was added slowly to a mixture of 2-hydroxy-2-methyl-1-nitropropane[15] (7.15 g, 0.06 mol) and imidazole (16.4 g, 0.24 mol) in dry DMF (60 mL). The exothermic reaction was cooled with a cold water bath. After being stirred for 14 h at 25 °C, the reaction was poured into water and extracted with Et_2O. The organic phase was washed with water (4×) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled (bp 37–38 °C, 0.3 mm) to give 10.01 g (87%) of **7** as a clear oil; ^{1}H NMR ($CDCl_3$) δ 4.34 (2 H, s), 1.43 (6 H, s), 0.14 (9 H, s).

5-Phenyl-3-[1-[(trimethylsilyl)oxy]-1-methylethyl]-Δ^2-isoxazoline (4a). General Cycloaddition Procedure.[16] A solution of **7** (831 mg, 4.35 mmol), styrene (458 μL, 4.00 mmol), phenyl isocyanate (930 μL, 8.60 mmol), and triethylamine (60 μL) in benzene was refluxed for 20 h. After cooling to room temperature, water (100 μL) was added. The mixture was stirred for 1 h, filtered, diluted with Et_2O, and dried over $MgSO_4$. The resulting solution was filtered and concentrated in vacuo and the residue was purified by semipreparative HPLC (7/1, hexane/EtOAc) to give **4a** (814 mg, 75%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.36 (5 H, m), 5.55 (1 H, dd, *J* = 10 Hz, 8 Hz), 3.48 (1 H, dd, *J* = 16 Hz, 10 Hz), 3.03 (1 H, dd, *J* = 16 Hz, 8 Hz), 1.52 (3 H, s), 1.46 (3 H, s), 0.13 (9 H, s); IR ($CHCl_3$) 1540, 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{14}H_{20}NO_2Si$ (M – CH_3) 262.1263, found 262.1263.

5-_n_-Butyl-3-[1-[(trimethylsilyl)oxy]-1-methylethyl]-Δ^2-isoxazoline (4b): ^{1}H NMR ($CDCl_3$) δ 4.55 (1 H, m), 3.08 (1 H, dd, *J* = 17 Hz, 10 Hz), 2.66 (1 H, dd, *J* = 16 Hz, 8 Hz), 2.0–1.2 (6 H, m), 1.50 (6 H, s), 0.13 (9 H, s); IR ($CHCl_3$) 1470, 1380, 1360 cm^{-1}; MS, *m/e* 242, 214, 200. Anal. ($C_{13}H_{27}NO_2Si$) C, H.

5-Methyl-5-_n_-propyl-3-[1-[(trimethylsilyl)oxy]-1-methylethyl]-Δ^2-isoxazoline (4c). Two equivalents of olefin were employed: purified by semipreparative HPLC (8/1, hexane/EtOAc): bp 100 °C (Kugelrohr, 2 mm); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (1 H, d), 2.73 (1 H, d), ~1.65 (2 H, m), 1.53 (3 H, s), 1.50 (3 H, s), ~1.4 (2 H, m), 1.35 (3 H, s), 0.97 (3 H, t), 0.14 (9 H, s); IR ($CHCl_3$) 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{12}H_{24}NO_2Si$ (M – Me) 242.1576, found 242.1577. Anal. ($C_{13}H_{27}NO_2Si$) C, H.

trans-4,5-Di-_n_-propyl-1-[1-[(trimethylsilyl)oxy]-1-methylethyl]-Δ^2-isoxazoline (4d). Two equivalents of olefin were employed: purified by semipreparative HPLC (3% EtOAc/hexane); bp 100 °C (Kugelrohr, 2 mm); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (1 H, m), 2.93 (1 H, dt), 1.81 (1 H, m), 1.57 (3 H, s), 1.50 (3 H, s), 1.55–1.2 (8 H, m), 0.93 (6 H, t), 0.16 (9 H, s); IR ($CHCl_3$) 1460, 1375, 1355; MS, *m/e* calcd for $C_{14}H_{26}NO_2Si$ (M – Me) 270.1889, found 270.1889. Anal. ($C_{15}H_{29}NO_2Si$) C, H.

Cyclopentene adduct 4e: reaction time 48 h at 40 °C; purified by flash chromatography (8% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.01 (1 H, m), 3.69 (1 H, m), 2.2–1.4 (6 H, m), 1.55 (3 H, s), 1.50 (3 H, s), 0.16 (9 H, s); IR ($CHCl_3$) 1460, 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{11}H_{20}NO_2Si$ (M – CH_3) 226.1263, found 226.1259.

Cyclohexene Adduct 4f. Two equivalents of olefin were employed and PhNCO in benzene was added over 6 h to a refluxing solution of the remaining reactants via syringe pump: purified by semipreparative HPLC (3% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.28 (1 H, m), 2.96 (1 H, m), 2.2–1.2 (8 H, m), 1.55 (3 H, s), 1.51 (3 H, s), 0.13 (9 H, s); IR ($CHCl_3$) 1450, 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{12}H_{22}NO_2Si$ (M – Me) 240.1417, found 240.1420.

Reduction of Cycloadducts 4a–f. This was carried out by employing our previously described reduction conditions, method 2.[3a] In several cases, partial desilylation (10–40%) of the silyl ether occurred. This was of no importance as the crude reduction product was generally directly subjected to oxidative cleavage.

5-Hydroxy-5-phenyl-2-[(trimethylsilyl)oxy]-2-methyl-3-pentanone (5a): ^{1}H NMR ($CDCl_3$) δ 7.45 (5 H, m), 5.12 (1 H, t, *J* = 6 Hz), 3.07 (2 H, d, *J* = 6 Hz), 1.35 (6 H, s), 0.13 (9 H, s);

IR ($CHCl_3$) 3500 (br), 1700 cm^{-1}.

5-Hydroxy-2-[(trimethylsilyl)oxy]-2-methyl-3-nonanone (5b): ^1H NMR ($CDCl_3$) δ 3.98 (1 H, m), 3.05 (1 H, br s), 2.76 (2 H, m), 1.31 (6 H, s), 1.6–1.1 (6 H, m), 0.90 (3 H, br t), 0.14 (9 H, s); IR ($CHCl_3$) 3500 (br), 1700 cm^{-1}.

5-Hydroxy-2-[(trimethylsilyl)oxy]-2,5-dimethyl-3-octanone (5c): ^1H NMR ($CDCl_3$) δ 2.80 (2 H, m), 1.6–1.3 (10 H, m), 1.21 (3 H, s), 0.91 (3 H, br t), 0.17 (9 H, s); IR ($CHCl_3$) 3450 (br), 1700 cm^{-1}.

5-Hydroxy-2-[(trimethylsilyl)oxy]-4-*n*-propyl-2-methyl-3-octanone (5d): ^1H NMR ($CDCl_3$) δ 4.25 (1 H, m), 3.94 (1 H, m), 1.9–1.2 (14 H, m), 0.90 (3 H, br t), 0.17 (9 H, s); IR ($CHCl_3$) 3450 (br), 1705 cm^{-1}.

Hydroxy ketone 5e: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.43 (1 H, q), 3.40 (1 H, dt), 2.0–1.5 (6 H, m), 1.37 (3 H, s), 1.34 (3 H, s), 0.18 (9 H, s); IR ($CHCl_3$) 3450 (br), 1700 cm^{-1}.

Hydroxy ketone 5f: ^1H NMR ($CDCl_3$) δ 4.05 (1 H, m), 3.03 (1 H, m), 2.0–1.4 (14 H, m), 0.19 (9 H, s); IR ($CHCl_3$) 3500 (br), 1700 cm^{-1}.

3-Hydroxy-3-methylhexanoic Acid, Methyl Ester. General Oxidative Cleavage Procedure. Aqueous 0.5 M periodic acid (8.4 mL, 4.2 mmol) was added to a solution of crude **5c** (156 mg, partially desilylated) in methanol (5 mL). After stirring 90 min at 25 °C, the reaction was diluted with water, extracted with EtOAc, dried ($MgSO_4$), and concentrated. The crude acid was directly esterified with diazomethane. The resultant methyl ester was purified by flash chromatography (20% EtOAc/hexane) to give 40 mg of **6c** (42% from **4c**): ^1H NMR ($CDCl_3$, 300 MHz) δ 3.72 (3 H, s), 2.53 (1 H, d), 2.45 (1 H, d), 1.7–1.3 (5 H, m), 1.24 (3 H, s), 0.92 (3 H, t); IR ($CHCl_3$) 3520 (br) 1720 cm^{-1}.

3-Hydroxy-2-*n*-propylhexanoic acid, methyl ester: purified by flash chromatography (20% EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (3 H, s), 3.67 (1 H, m), 2.47 (1 H, m), 1.9–1.2 (9 H, m), 0.92 (6 H, two overlapping t); IR ($CHCl_3$) 3500 (br), 1715 cm^{-1}; MS (of derived trimethylsilyl ether), *m/e* calcd for $C_{10}H_{21}O_3Si$ (M – CH_3) 217.1260, found 217.1260.

Generation and Reduction of Methoxy-Substituted Isoxazolines 10. Addition of benzenesulfonylcarbonitrile oxide and displacement with methoxide were both conducted according to the procedure of Wade.[17] Reduction to **11a,b** was carried out by following the standard reduction procedure (method 2).[3a]

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Registry No. **1a**, 91157-51-6; **1b**, 91157-52-7; **1c**, 91157-53-8; **1d**, 91157-54-9; **1e**, 91157-73-2; **1f**, 91157-55-0; **1g**, 91157-56-1; **2a**, 42052-52-8; **2b**, 91157-57-2; **2c**, 59671-45-3; **2d**, 91157-58-3; *cis*-**2e**, 91157-59-4; *trans*-**2e**, 91157-74-3; **2f**, 91157-60-7; **3a**, 5397-27-3; **3b**, 91157-61-8; **3c**, 5292-13-7; **3e**, 91157-62-9; **4a**, 91157-63-0; **4b**, 91157-64-1; **4c**, 91157-65-2; **4d**, 91157-66-3; **4e**, 91157-67-4; **4f**, 91157-68-5; **5a**, 76777-60-1; **5b**, 76777-62-3; **5c**, 91157-69-6; **5d**, 91157-70-9; **5e**, 91157-71-0; **5f**, 91157-72-1; **6a**, 3480-87-3; **6b**, 17587-29-0; **6c** (methyl ester), 91178-20-0; **6d** (methyl ester), 91157-75-4; **6e**, 17502-28-2; **6f** (methyl ester), 936-03-8; **7**, 55816-65-4; **7** (alcohol), 5447-98-3; Ia, 27143-81-3; Ia (oxime chloride), 3273-26-5; $PhCH{=}CH_2$, 100-42-5; $C_4H_9CH{=}CH_2$, 592-41-6; *trans*-*n*-proCH=CHpro-*n*, 14850-23-8; *cis*-PhCH=CHPh, 645-49-8; $C_3H_7C(CH_3){=}CH_2$, 763-29-1; Me_3SiCl, 75-77-4; PhNCO, 103-71-9; methylenecyclohexane, 1192-37-6; cyclopentene, 142-29-0; cyclohexene, 110-83-8.

Selective Carbon–Carbon Bond Formation at the Oxazole Ring. Cycloadditions and Michael-Type Additions of Ketenes to 1,3-Oxazoles

Alessandro Dondoni,* Giancarlo Fantin, Marco Fogagnolo, Annarosa Mastellari,
Alessandro Medici, and Paola Pedrini

Laboratory of Organic Chemistry, Faculty of Science, University of Ferrara, Ferrara, Italy

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1,3-Oxazole (**1a**) and 4-methyl-1,3-oxazole (**1b**) react with dichloroketene (DCK) affording the 2-(dichloroacetyl)oxazoles **3a** and **3b**, respectively, very likely via the corresponding *N*-acyloxazolium ylides as intermediates. 2-(*N*-Benzyl-*N*-methylamino)-1,3-oxazole (**1c**) and *tert*-butylcyanoketene (TBCK) give the 5-acyl derivative **4c** and a mixture of the diastereomeric 2:1 cycloadducts **5** and **6** constituted by a δ-lactone ring condensed across the former C_4–C_5 bond of **1c**. The 4-methyl derivative **1d** affords the ketone **4d** and the enol ester **7**, whereas the 4,5-dimethyl derivative **1e** undergoes the addition of 2 mol of TBCK and ring fission producing a 2,5-dihydrofuran derivative **8**. Other ketenes, namely diphenyl- (DPK), chlorocyano- (CCK), and dichloroketene (DCK), react with **1c** and **1d** to give the corresponding 5-acyl derivatives **4**, and in the case of DCK only, also the enol ester **11**. Plausible schemes accounting for the formation of products **4**–**11** involve as a common step, the initial attack of the ketene at C_5 of the oxazole ring to give a zwitterion which undergoes different reactions depending on the substitution at C_4 and C_5 of the heterocycle.

The chemistry of 1,3-oxazoles[1] continues to attract interest because of the presence of the oxazole ring in numerous biologically active compounds both natural and synthetic.[2] Oxazole derivatives can be prepared by various cyclization reactions, whereas effective methods for the direct introduction of a functional group in the oxazole ring are rare. In fact, electrophilic substitutions are often accompanied by the same reaction on an aromatic substituent and many nucleophilic substitutions are precluded because of ring scission.[1a] The most synthetically useful reactions of oxazoles are [4 + 2] cycloadditions with olefinic and acetylenic dienophiles.[1a] These reactions give unstable bicyclic systems which undergo fragmentation and rearrangement to pyridine or furan derivatives.[1] The reaction with dimethyl acetylenedicarboxylate is the only one reported[3] to give isolable bicyclic products, however these

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