Pergamon

Tetrahedron, Vol. 52, No. 46, pp. 14475-14486, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00902-7

Mechanism of SeO_2 Promoted Oxidative Rearrangement of 2-Substituted Oxazolines to Dihydrooxazinones: Isotopic Labeling and Kinetic Studies

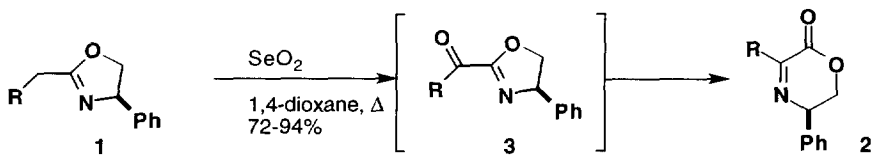
Cynthia M. Shafer, Daniel I. Morse and Tadeusz F. Molinski*

Department of Chemistry, University of California
Davis, California 95616, U.S.A.

Abstract: The mechanism of the recently reported[1] SeO_2 promoted oxidative rearrangement of 2-alkyl oxazolines was investigated. ^{13}C labeling studies with **1a**-2-^{13}C showed that rearrangement proceeds by fission and migration of the C=N bond, not the C-C bond as first proposed. Oxidation-rearrangement of **1** proceeds by rapid SeO_2 promoted oxidation to 2-acyloxazoline **3** followed by slower rearrangement of **3** to oxazinone **2**. The *second order* rate constant for the oxidation step for 2,4-diphenyloxazoline **1b** in 1,4-dioxane at 40° C was $k_1 = 2.85 \pm 0.62 \times 10^{-2}$ $M^{-1}\cdot s^{-1}$. The second and rate limiting rearrangement step (**3b**→**2b**) had a *first order* rate constant of $k_2 = 1.15 \pm 0.09 \times 10^{-3}$ s^{-1} while the relatively low *apparent* energy of activation E_A of 4.2 ± 1.6 kcal·mol^{-1} in the presence of 2.0 equiv of SeO_2 suggests heterogeneous catalysis. The reaction is catalyzed by Lewis acids, including SeO_2 or small amounts of H_2O. A plausible mechanism is proposed involving Lewis acid activation and nucleophilic catalysis with H_2O. Copyright © 1996 Elsevier Science Ltd

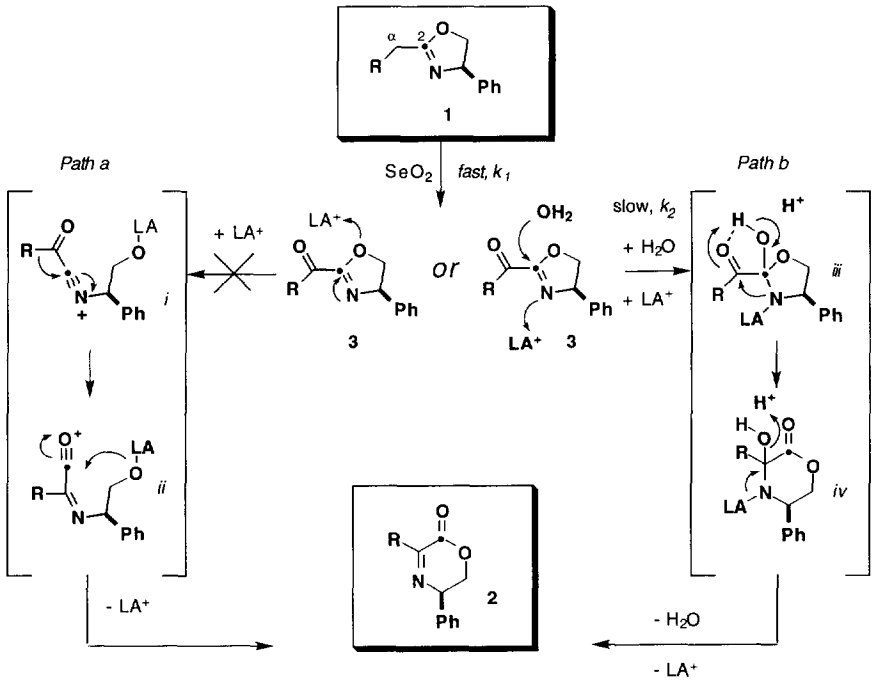
Introduction.

The oxidative rearrangement of 2-alkyloxazolines **1** with SeO_2[1] in 1,4-dioxane (dioxane) provides a convenient entry to 5,6-dihydro-2*H*-1,4-oxazin-2-ones **2** (referred to hereafter in this paper as 'oxazinones') and also affords the *only known route* to simple 3-*unsubstituted* dihydrooxazinones.



Oxazinones are useful precursors for the synthesis of α-amino acids,[2-6] however, 3-unsubstituted oxazinones (**2**, R=H) have added versatility as chiral electrophilic glycine equivalents. The yields of the oxidation-rearrangement were highest for 2-methyl- (**1**, R=H), benzyl- (**1**, R=Ph) and neopentyl-oxazolines (**1**, R=*t*-Bu), but the reaction failed completely with 2-ethyloxazoline (**1**, R=Me). The latter observations, together with other data[1] suggested a possible mechanism involving carbon-carbon bond migration and correlation of reaction efficiency with migratory aptitude of the group attached at the α-position of the 2-oxazoline. A mechanism was advanced[1] to explain the events leading to heterocyclic product **2** which involved oxidation to the putative acyl intermediate **3** followed by ring opening and a 'nitrilium-acylium' ion rearrangement (Scheme 1, *path a*). High migratory aptitude of R in the nitrilium ion *i* would promote rearrangement to the acylium ion *ii*. Because of the synthetic

utility of this reaction, we were interested in examining the mechanism in more detail. This paper reports isotopic labeling experiments and kinetic studies that prove the mechanism does, indeed, proceed through the intermediate **3** but *without* subsequent carbon-carbon bond cleavage. Instead, new evidence supports a mechanism involving Lewis acid catalyzed ring opening of **1** followed by C-N bond cleavage, migration and elimination to give **2** (Scheme 1, *path b*). Additionally, we provide data that the rate of the rearrangement is accelerated by Lewis acids or H_2O and that this rearrangement step is rate limiting.



Scheme 1: Possible mechanisms of SeO_2 promoted oxidation-rearrangement of oxazoline **1** to dihydrooxazinone **2**. Steps in *Path b* may be under heteregeneous catalytic control and may or may not be concerted • = ^{13}C label, LA = Lewis acid.

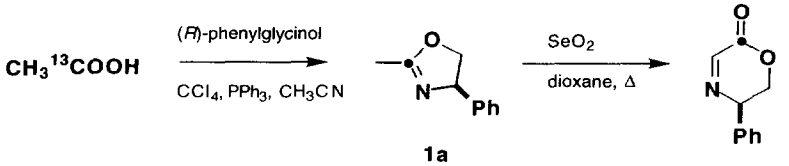
Results:

a) Labeling Studies: Rearrangement of (R)-2-methyl-4-phenyloxazoline-2-^{13}C , **1a**.

The most useful examples of the SeO_2 promoted oxidation-rearrangement are provided by reaction of the 2-methyloxazolines to give 3-unsubstituted oxazinones.† The mechanism shown in Scheme 1 *path a* predicts that the oxidation state of C2 will be exchanged with that of the α-carbon (the 2-formyl group) in the putative oxazoline intermediate **3**. The latter hypothesis is easily testable by ^{13}C labeling. [2-^{13}C]-Oxazoline **1a** (50 atom %) was synthesized by

† Benzoxazinones ('azacoumarins') are known in the literature. Synthetic methods for fused-ring oxazinone syntheses include condensation of glyoxylic acid with 2-aminophenols[7,8] and a novel NaOMe promoted ring expansion of α,α-dichloromethylbenzoxazole,[9] however, neither method has been applied to make simple monocyclic 3-unsubstituted oxazinones **2**.

condensation of acetic acid-1-^{13}C with *R*-(-)-phenylglycinol using the one step procedure of Vorbrüggen and Krolikiewicz[10] (CCl_4, Ph_3P, CH_3CN, 17%).



1a **2a**

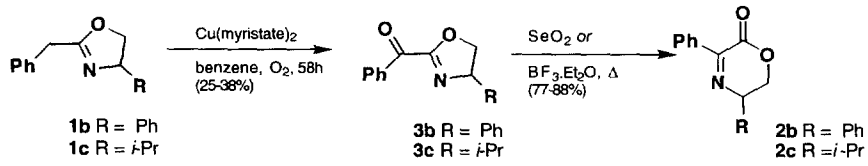
Treatment of a **1a** with 2.2 equiv SeO_2 under standard conditions gave **2a** (61%) after chromatography. A unimolecular rearrangement was evident because EIMS analysis of **2a** showed retention of label (44±5 atom %, no inter-molecular exchange of label). Examination of the ^{13}C NMR spectrum of **2a** revealed that the enhanced signal was C2 (carboxyl), instead of C3 as expected from the mechanism in Scheme 1, *path a*. The chemical shift of the C2 signal was unambiguously assigned in earlier work[1] from DEPT and 2D heteronuclear correlation spectroscopy. This labeling pattern is consistent, not with C-C bond fission and migration, but with retention of ^{13}C label at the carboxylate and preservation of the oxidation state of oxazoline C2. A mechanism that is consistent with this finding must invoke fission of the C=N bond in oxazoline **1a**, and subsequent migration of N to the formyl carbon in presumed **3** (R=H).

b) Oxidative Rearrangement (**1** → **2**)*: Intermediacy of 2-acyloxazoline* **3**.

The oxidation-rearrangement proceeds well for a variety of oxazolines, but we chose to investigate the kinetics of conversion of **1b** to **2b** because under the reported standard conditions (100°, 2.2 equiv SeO_2, anhydrous dioxane) the yield is high (94%) and both starting material and product could be followed conveniently using HPLC with UV detection (λ 254 nm). Previous experiments under standard conditions (100°C) failed to detect intermediate **3**, even after only a few minutes. However, when the reaction temperature was lowered to 40°C, a less polar intermediate appeared rapidly and increased in concentration at the expense of **1b**. When the reaction was run again on larger scale and stopped after 26 min, a less-polar intermediate was isolated by HPLC (9%) and determined to be the 2-acyloxazoline **3b** by spectroscopic means. The formula of **3b**, $C_{16}H_{13}NO_2$, isomeric with product **2b**, was secured from EIHRMS. The UV spectrum of **3b** showed a strong chromophore (λ_{max} 258, ε 10,200) associated with a substituted acetophenone. The ^{13}C NMR spectrum revealed that the α-methylene carbon found in **1b** was replaced in **3b** by a signal due to a conjugated C=O (δ 183.4 ppm, s). Finally, the structure was confirmed by independent synthesis of **3b** by autoxidation of **1b** (O_2, Cu(myristate)$_2$, benzene, 17% isolated, 25% based on recovered starting material).

Heating **3b** in dioxane at reflux (100°C) in the absence of SeO_2 for 19 hours produced no change, however, when the reaction was repeated with 2 equiv SeO_2 rapid conversion to **2b** was observed. While SeO_2 is required for the oxidation of **1b** to **3b**, the function of SeO_2 in the rearrangement of **3b** to **2b** appears to be that of a Lewis acid catalyst. Efficient conversion of **3b** to **2b** was catalyzed by the presence of 2 equiv or less of SeO_2 (see below), while 2-acyloxazoline **3c**,

prepared by autoxidation of oxazoline **1c** (38%), could be smoothly converted to **2c** by 0.15 equiv of either SeO_2 (77%) or freshly distilled $BF_3 \bullet Et_2O$ (88%) in refluxing dioxane.



1b R = Ph
1c R = *i*-Pr

3b R = Ph
3c R = *i*-Pr

2b R = Ph
2c R = *i*-Pr

Thus, SeO_2 serves the dual roles of oxidant and Lewis acid catalyst in the oxazoline-oxazinone conversion.* While $BF_3 \bullet Et_2O$ catalyzed rearrangement was most intriguing, we restricted further kinetic studies to the SeO_2 catalyzed reaction because it was most relevant to the rearrangement step in **1** → **2**.

c) Kinetics of Oxazoline-Oxazinone Rearrangement (**3**→**2**)

Assuming that the mechanism is the same for 2-acyl derivatives **3** (R=alkyl, aryl, etc) other than **3a** we examined the mechanism in more detail by measuring kinetics of the both oxidation and rearrangement steps using **3b**. Oxidation-rearrangement of **1b** at lower temperature (40°C) afforded us the opportunity to study the course of the reaction in some detail as the disappearance of starting material and appearance of both the acyl intermediate **3b** and the final product **2b** were slow enough to be easily monitored by HPLC. Reactions were initiated under N_2 atmosphere at controlled temperature (oil bath) by adding solutions of **1** in anhydrous dioxane to rapidly stirred mixtures of SeO_2 in the same solvent (final concentration of **1**, 0.060-0.061 M). Aliquots of the reaction mixture were sampled at various time intervals after initiation and analyzed by HPLC (Dynamax 8μ silica, EtOAc:*n*-hexane). Concentrations of **1b**, **2b** and **3b** in each sample were determined by integration of peak areas in the respective chromatograms and comparison with standard curves or by standards addition to individual samples. Both analytical methods gave comparable results. Calculations of initial rates were done using only the first four time points (≤ 10 min), and rate constants k were calculated from integrated rate equations (Table 1).[11]

Appreciable conversion of **1b** to **3b** was observed within the first minute of the reaction at 40°C with little or no apparent induction period (Figure 1). Prolonged reaction was accompanied by a decline in the concentration of **1b**, followed by an initial rise in **3b**, the appearance of **2** and a concomitant decrease in the concentration of **3b** as **1b** was depleted. Consumption of **1b** was shown to be second order with respect to SeO_2 and **1b**, and the second order rate constant k_1 of the first step (oxidation of **1b** → **3b**) was estimated from the rate of

* When less than 2.2 equivalents were used (eg. 1.0 equiv.) incomplete reaction was observed. It is therefore clear that a minimum of 2 equivalents of SeO_2 are required for complete conversion as expected from the required stoichiometry of the SeO_2 oxidation step. The excess over the stoichiometric amount used in standard reaction conditions (0.2 equiv) ensures Lewis acid is always present, even at completion of oxidation, however, we cannot exclude the possibility that unidentified reduced Se containing byproducts also catalyze the reaction.

consumption of **1** to be $k_1 = 2.85 \times 10^{-2}\ M^{-1}\cdot s^{-1}$ at 40°C.† The rate constant for conversion of **3b**→**2b** could not be reliably measured from this time course data for two reasons. First, the rate of appearance of **2b** was dependent upon the concentration of **3b**, which in turn was dependent upon the amount of conversion of **1b**→**3b**. Second, the rearrangement step (**3b**→**2b**, rate constant k_2) was found to be catalyzed by SeO_2 (see below), the concentration of which also varied with time. Instead, we calculated k_2 by carrying out separate experiments in which pure **3b** was subjected to the same reaction conditions, but in the presence of a fixed SeO_2 concentration (2.0 equiv, ~0.11 M).

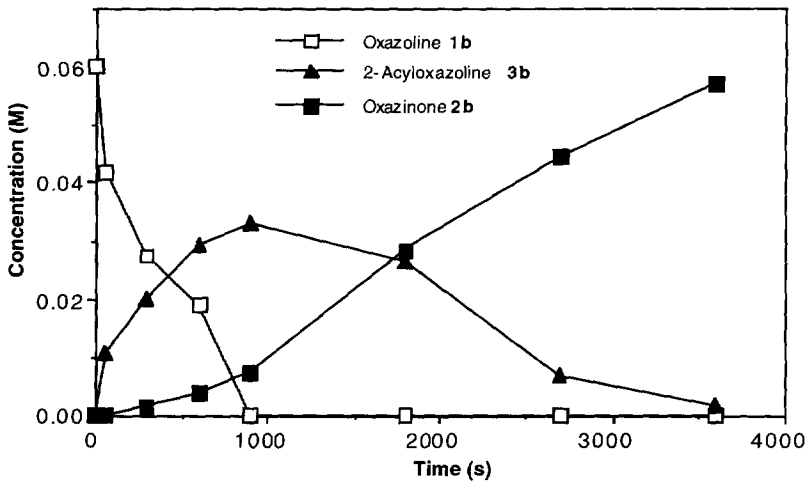


Figure 1: Time course of SeO_2 promoted oxidation-rearrangement of oxazoline **1b** to oxazinone **2b** in 1,4-dioxane. Initial [SeO_2] ~ 0.11 M, T = 40° C.

The *first order* rate constant of the rearrangement step **3b**→**2b** was calculated as $k_2 = 1.15 \times 10^{-3}\ s^{-1}$ (40° C and 0.11 M SeO_2) and, therefore, must be the slower, rate limiting step of oxidation-rearrangement. As no other intermediates could be detected under these reactions conditions, we propose that the simplest sequence of events is rapid SeO_2 promoted oxidation of **1** to 2-acyloxazoline **3** followed by a slower rearrangement of **3** to oxazinone **2**.

d) Effect of SeO_2

SeO_2 is an appreciable Lewis acid and catalyzes the conversion of **3b** to **2b**. The dependence of k_2 upon [SeO_2] was examined in reaction time courses conducted in the presence of varying amounts of SeO_2. Rearrangement of **3b** was promoted by 1.0 equiv of SeO_2 ($k_2 = 7.7 \times 10^{-4}\ s^{-1}$ at 40°C) while 2.0 equiv SeO_2 almost doubled the rate ($k_2 = 1.15 \times 10^{-3}\ s^{-1}$) under otherwise identical conditions. It is not clear whether second order kinetics or 'saturation kinetics' characteristic of catalysis are followed in the latter case because of the heterogeneous

† Strictly, this may be *pseudo second order* because at high SeO_2 concentrations **1b**→ **2b**, **3b** is a heterogeneous reaction.

nature of the reaction - SeO_2 is only sparingly soluble in anhydrous dioxane and does not appear to dissolve completely at higher concentrations.

e) Effect of Temperature

The effect of temperature of the rearrangement of **3b** to **2b** was investigated by carrying out the reaction at different temperatures (Figure 2). Predictably, the reaction was slowest at room temperature 26°C ($k_2 = 1.1 \times 10^{-3}$ s^{-1}) and fastest at 100°C ($k_2 = 3.9 \times 10^{-3}$ s^{-1}). A simple Arrhenius plot[11] of rate constants, k_2 measured at different temperatures provided an *apparent* Arrhenius activation energy of $E_A = 4.2 \pm 1.6$ kcal·mol^{-1} for the rearrangement step in the presence of 2.0 equiv SeO_2.

Entry	Starting Material and initial conc. (M)		Product	Equiv H_2O	Equiv SeO_2	Temp. (°C)	Initial Rate, ($M \cdot s^{-1}$)	Rate constants k (± uncert.) (s^{-1})
1	**1b**	0.060	**2b, 3b**	-	2.2	40	9.6×10^{-5}	2.85^a $(0.62) \times 10^{-2}$
2	**3b**	0.053	**2b**	-	1.0	40	2.2×10^{-5}	7.70 $(0.93) \times 10^{-4}$
3	**3b**	0.053	**2b**	-	2.0	26	2.9×10^{-5}	1.10 $(0.12) \times 10^{-3}$
4	**3b**	0.053	**2b**	-	2.0	40	3.3×10^{-5}	1.15 $(0.09) \times 10^{-3}$
5	**3b**	0.053	**2b**	-	2.0	58	4.8×10^{-5}	1.60 $(0.26) \times 10^{-3}$
6	**3b**	0.053	**2b**	-	2.0	79	8.1×10^{-5}	3.21 $(0.31) \times 10^{-3}$
7	**3b**	0.053	**2b**	-	2.0	100	8.1×10^{-5}	3.90 $(0.24) \times 10^{-3}$
8	**3b**	0.055	**2b**	1.0	2.0	40	6.9×10^{-5}	3.40 $(0.78) \times 10^{-3}$
9	**1b**	0.061	**2b, 3b**	1.0	2.2	40	2.2×10^{-4}	8.13^a $(-)^b \times 10^{-2}$

Table 1: Compilation of initial rates of reaction and rate constants for SeO_2 promoted reactions of **1b** or **3b** in anhydrous dioxane. Rates were calculated based on consumption of **1** or **3**. Initial rates were *estimated* from slope (d[**x**]/dt where **x** is **1b** or **3b**) over the first 10 minutes of reaction. Rate constants are first order for **3b**→**2b** and second order for **1b**→**3b**. Rate constants, *k*'s, and uncertainties were determined as described in the Experimental. [a] k_1 second order rate constant, units $M^{-1} \cdot s^{-1}$; [b] Estimate only, N=3 data points.

f) Effect of added H_2O

The rearrangement of 2-acyl oxazolines appears to require Lewis acid catalyzed ring opening with the possibility that the two oxygen atoms in the starting material are preserved in product (unimolecular reaction). In the absence of evidence for the involvement of an incipient nitrilium ion *i* (Scheme 1, *path a*), the possibility was considered that H_2O or a nucleophilic Se byproduct might be involved in an addition-elimination at the same time as ring opening. Although the reaction was carried out with anhydrous solvent, it is conceivable that H_2O may be generated by disproportionation or elimination of the 'H_2SeO' equivalent formed during the oxidation step. The effect of small amounts of added water would be

expected to accelerate the reaction, and, indeed, the rate constant increased when the rearrangement of **3b**→**2b** was carried out in the presence of 2.0 equivalents of SeO_2 and 1.0 equiv of added H_2O ($k_2 = 3.4 \times 10^{-3}$ s^{-1}). Nucleophilic catalysis with H_2O is necessary and sufficient to account for this rate increase, however, SeO_2 may also undergo hydration in the presence of H_2O. The product, H_2SeO_3, is an appreciable Brønsted acid (pKa_1 2.62, pKa_2 8.32[12]) and may also participate in general acid catalysis of the reaction. While the initial rate of appearance of **2** was enhanced by added H_2O, prolonged reaction times resulted in loss of product and starting material, presumably due to competing irreversible hydrolytic ring opening of the H_2O-sensitive oxazoline and oxazinone.

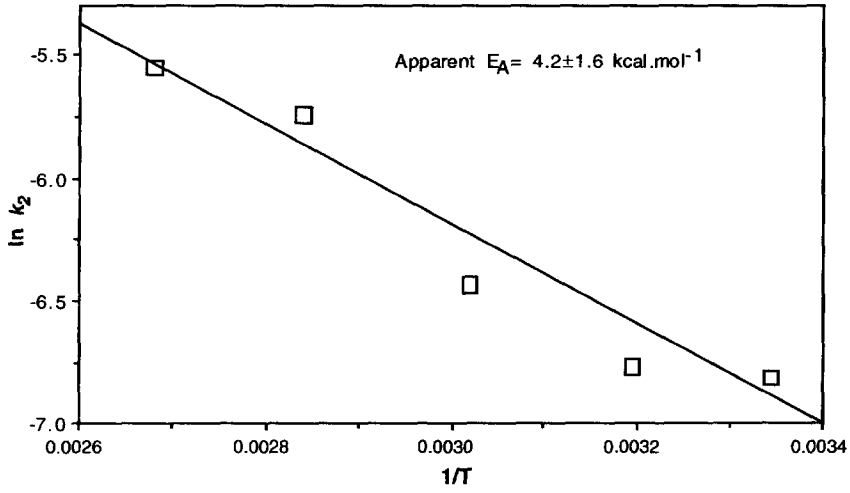


Figure 2: Temperature dependence of the first order rate constant k_2 for rearrangement **3b** → **2b** in 1,4-dioxane in the presence of 2.0 equiv of SeO_2.

Discussion.

The mechanism of SeO_2 promoted oxidative rearrangement of 2-oxazolines involves oxidation of the α-carbon to carbonyl followed by Lewis acid catalyzed ring opening and migration of the nitrogen to the newly formed α-carbonyl. Formally, this must involve fragmentation of the oxazoline ring to an ester by departure of an amino group rather than conventional leaving group OR. The relatively low *apparent* activation energy of E_A = 4.2 kcal·mol^{-1} (Figure 2) strongly suggests a mechanism limited by one or more transport processes (diffusion, chemiadsorption, desorption, etc.) as is typically found in some heterogeneous catalytic reactions.[13,14] While this points to a catalytic mechanism that could be occurring on the surface of SeO_2, we cannot conclude more without additional experiments. Nevertheless, at 40° C the rate constants (Figure 1 and Table 1) show the rate limiting step under these conditions is intramolecular rearrangement **3b**→**2b**, but the observed rate enhancement with H_2O also militates for simultaneous nucleophilic catalysis.

A possible sequence of elementary reactions for the rearrangement that is consistent with these observations is presented in Scheme 1, *path b*. Some or all of these reactions may occur at

the surface of solid phase SeO_2. Activation of the nitrogen on the oxazoline ring by Lewis acid (SeO_2) is followed by addition of trace H_2O (for example, adsorbed on hygroscopic SeO_2) at C2 of oxazoline, generating a tetrahedral intermediate, *ortho*-amide *iii* that collapses by protonation of the α-carbonyl and migration of N to the α-carbonyl giving aminal *iv*. The latter intermediate eliminates H_2O to provide the final product **2**.

Essentially the proposed sequence in Scheme 1 *path b* is Schiff base formation between the newly created carbonyl group and an amino group liberated by cleavage of the oxazoline ring. The latter appears to be initiated by nucleophilic attack by trace H_2O. Displacement of the amino group rather than hydroxyl is the usual path for cleavage of oxazolines by aqueous acid (55 M H_2O)[15] or under certain conditions with strong nucleophiles[16] although this may not be so under anhydrous conditions with other Lewis acids. In the conversion of **3b** to **2b**, under *almost* anhydrous conditions the weak nucleophile H_2O apparently still prevails, again with displacement of the amino group. Several factors probably contribute to this preference, for example preferential Lewis acid activtion of the more basic nitrogen, ring-strain relief by opening of the oxazoline and facile 1,2 nitrogen migration-elimination, assisted by intramolecular H-bonding in *iii* to produce the stable conjugated heterocycle **2**.

The intermediates *iii* and *iv* are not observed in solution during the time frame of the present experiments. If *path b* is correct, the intermediates may be transient or bound (covalently or non-covalently) at the surface of solid SeO_2. Trapping experiments may help to resolve this issue, however, at this point we cannot divine further aspects of the mechanism. An attractive experiment that would clarify the mechanism would utilize as starting material **3b** labeled with ^{18}O in the acyl group. Loss of ^{18}O label would support *path b*, whereas retention of label would argue against the H_2O elimination step *iv*→**2b**. Alternatively, monitoring the reaction in the presence of $H_2{}^{18}O$ by appearance of ^{18}O label in **2b** may further elucidate the possible role of water catalysis.

Conclusion.

We have shown that the SeO_2 promoted oxidation-rearrangement of oxazolines proceeds *via* Lewis acid catalyzed ring opening and C=N bond fission and migration rather than the earlier proposed C-C bond cleavage. The intermediacy of 2-acyloxazoline **3** is proven while Lewis acid activation of the oxazoline nitrogen followed by nucleophilic catalysis in ring opening is invoked to explain observed trends in reaction rates and the outcome of ^{13}C labeling. The low apparent energy of activation E_A (4.2 kcal.mol^{-1}) suggests that the rearrangement of **3** to **2** is under control of heterogeneous catalysis by solid SeO_2 and the rate is limited by transport processes.

Experimental Procedure.

General

All solvents were distilled before use. In particular, 1,4-dioxane (dioxane) was distilled immediately before use from Na-benzophenone ketyl. Silica chromatography was carried out using 43-60 μ silica (EM Merck), TLC was conducted on 0.2 mm plates coated with silica impregnated with a fluorescent indicator. ^{1}H and ^{13}C NMR measurements made at 300 MHz and 75 MHz, respectively, and the spectra referenced to internal residual solvent signals $CHCl_3$ (δ 7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C). ^{13}C signal multiplicities were determined from DEPT experiments and are listed as CH_3, CH_2, CH or C (quaternary). Class A analytical volumetric flasks were used in the kinetic studies.

(4R)-2-Methyl-4-phenyl-4,5-dihydrooxazole-2-^{13}C (**1a**)

Triphenylphosphine (2.58 g, 9.84 mmol) was added to a solution of acetic acid (0.1 ml, 1.75 mmol), [1-^{13}C]acetic acid (99 atom%, 0.1 ml, 1.72 mmol) and acetonitrile (7.5 ml). The reaction solution was cooled to 0°C, and CCl_4 (3.2 ml, 33.2 mmol) was added dropwise. After stirring for 2h at 0°C, a solution of (*R*)-(-)-2-phenylglycinol (0.4019 g, 2.93 mmol), Et_3N (1.6 ml, 11.5 mmol) and acetonitrile (12.5 ml) was added dropwise. After 20 min, the ice bath was removed, and the reaction stirred at room temperature for 14 h. The reaction mixture was filtered, and the filter pad washed with EtOAc. The solvent was removed under reduced pressure leaving a brown solid which was purified by column chromatography (2.5 × 30 cm; 1:5 EtOAc:*n*-hexane to 2:3 EtOAc:*n*-hexane) to give **1a** as a yellow oil (0.0812 g, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3 H), 4.07 (m, 1 H), 4.59 (m, 1 H), 5.16 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3, $^{1}J_{C\text{-}C}$ = 58.6 Hz), 69.6 (CH), 74.5 (CH_2), 126.4 (CH), 127.4 (CH), 128.6 (CH), 142.3 (C), 165.6 (C × 68 times enhanced intensity). The nominal isotopic purity, determined from dilution of acetic acid-^{13}C was ~50 atom % [2-^{13}C].

(5R)-5-Phenyl-5,6-dihydro-2H-1,4-oxazin-2-one-2-^{13}C (**2a**)

A solution of (4*R*)-2-methyl-4-phenyl-4,5-dihydrooxazole-2-^{13}C (**1a**, 0.0379 g) in dioxane (3 ml) was added to SeO_2 (0.0623 g, 0.56 mmol) in 2 ml of dioxane. The mixture was stirred under reflux for 45 min, cooled, and filtered through silica gel with 1:1 EtOAc:*n*-hexane. The solvent was removed under reduced pressure to give a red oil (0.0340 g) with some red precipitate. The crude material was purified by HPLC (silica, Dynamax, 3:7 EtOAc:*n*-hexane; 3 ml·min^{-1}) to provide pure **2a** (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (m, 1 H), 4.59 (m, 1 H), 4.92 (m, 1 H), 7.37 (m, 5 H), 8.06 (dd, 1 H, *J* = 3.0 Hz, $^{2}J_{C\text{-}H}$ = 14.6 Hz); ^{13}C NMR ($CDCl_3$) δ 59.9 (CH, $^{3}J_{C\text{-}C}$ = 10.0 Hz), 71.0 (CH_2), 127.0 (CH), 128.5 (CH), 129.0 (CH), 136.0 (C), 153.2 (CH, $^{1}J_{C\text{-}C}$ = 59.1 Hz), 154.0 (C × 21 enhanced intensity, $^{1}J_{C\text{-}C}$ = 59.1 Hz, C2); LRCIMS found *m/z* 177.15 (MH+1, 53%), 176.20 (MH^+, 47%) $C_{10}H_{10}NO_2$, $^{13}C_1C_9H_{10}NO_2$. ^{13}C isotopic purity estimated from MS (44±5 atom %).

(±)-2-Benzoyl-4-phenyl-4,5-dihydrooxazole (**3b**)

Method A: A solution of (±)-2-benzyl-4-phenyl-4,5-dihydrooxazole (**1b**,[1] 0.5001 g, 2.14 mmol) in dioxane (5 ml) was added to SeO_2 (0.5157 g, 4.65 mmol) in 16 ml of dioxane. The mixture was

heated at 40°C for 26 min, cooled, and filtered through silica gel with 1:1 EtOAc:hexane. The solvent was removed under reduced pressure to give 0.3649 g of a yellow oil with red precipitate. The crude material was dissolved in EtOAc:*n*-hexane, centrifuged and the supernatant separated by HPLC (silica Dynamax 3:7 EtOAc:*n*-hexane, 3.0 ml·min^{-1}) to obtain **3b** (9%), recovered starting material **1b** and oxazinone **2b**. Method B: To a rapidly stirred solution of oxazoline **1b** (0.5000 g, 2.22 mmol) in benzene (50 ml) was added copper (II) myristate (0.0462 g, 0.089 mmol). The flask was repetitively evacuated and purged with O_2 and left under one atmosphere of O_2 for 58 h with continuous stirring. Removal of the solvent under reduced pressure and purification of the crude product by column chromatography (silica gel; 1:4 methyl *t*-butyl ether:*n*-hexane) provided **3b** (oil, 93.8 mg, 17% total, 25% based on recovered starting material) and starting material. UV (CH_3CN) λ 258 (ε 10,200); IR (NaCl, neat) 1737 (PhC=O), 1668 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (dd, 1 H, *J* = 8.8, 8.5 Hz), 4.83 (dd, 1 H, *J* = 10.5, 8.8 Hz), 5.53 (dd, 1 H, *J* = 10.5, 8.5 Hz), 7.40 (m, 7 H), 7.61 (m, 1 H), 8.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 70.9 (CH), 74.4 (CH_2), 126.7 (2 x CH), 128.4 (CH), 128.9 (2 x CH), 130.6 (2 x CH), 134.3 (2 x CH), 134.7 (C), 140.7 (C), 160.1 (C), 183.4 (C); HREIMS found *m/z* 251.0940 (M^+), $C_{16}H_{13}NO_2$ requires 251.0946.

(4S)-2-(Benzoyl)-4-(1-isopropyl)-4,5-dihydrooxazole (**3c**)

The title compound **3c** was prepared by autoxidation (Method B, above) of **1c**[1] (38%). $[\alpha]_D$ = -57.1° (c 1.89, $CHCl_3$); UV (CH_3CN) λ 221 (ε 2420), 257 (ε 11100), 339 (ε 110); IR (NaCl, neat) 1678 (PhC=O), 1634 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3 H, *J* = 6.7 Hz), 1.06 (d, 3 H, *J* = 6.7 Hz), 1.94 (dq, 1 H, *J* = 6.7 Hz), 4.21 (m, 2 H), 4.46 (dd, 1 H, *J* = 9.2, 7.8 Hz), 7.48 (m, 2 H), 7.62 (m, 1 H), 8.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3), 18.9 (CH_3), 32.6 (CH), 70.1 (CH_2), 73.6 (CH), 128.4 (CH), 130.6 (CH), 134.1 (CH), 134.8 (C), 159.1 (C); HREIMS found *m/z* 217.1101 (M^+), $C_{13}H_{15}NO_2$ requires 217.1103.

Preparative Synthesis of **2c** *by Rearrangement of* **3c** *with Catalytic Lewis Acid* Method A: A solution of **3c** (26.5 mg, 0.122 mmol) in dioxane (1 ml) was added to SeO_2 (2.0 mg, 0.018 mmol, 0.15 equiv) in dioxane (1 ml). The mixture heated to reflux for 1 h, cooled and centrifuged. The yellow supernatant was filtered through a plug of silica gel, and concentrated under reduced pressure to a yellow oil of pure **2c** (20.5 mg, 77%), identical by ^{1}H and ^{13}C NMR with authentic material.[1]

Method B: A solution prepared by diluting BF_3•Et_2O in anhydrous dioxane (final conc. BF_3 conc. 1.63 M, 13 μl) was added to a stirred solution of **3c** (30.4 mg, 0.140 mmol) in dioxane (1.5 ml). The mixture was heated to reflux for 1.5 h, cooled, and treated with pyridine (5 μl). After stirring for 15 min, the mixture was filtered through silica gel and concentrated under reduced pressure to give a yellow oil of **2c** (26.8 mg, 88%).

Copper (II) myristate, $Cu(C_{13}H_{27}COO)_2$

Potassium hydroxide (10 mmol) was added to a solution of myristic acid (tetradecanoic acid, 10 mmol) in ethanol (50 ml) and poured slowly into an aqueous solution of $CuSO_4$ (20 mmol) in

H_2O with constant stirring. The resultant gelatinous precipitate was filtered, air dried under suction then dried under high vacuum at 56°C overnight, and the product $Cu(C_{13}H_{27}COO)_2$, a light blue powder, was used without further purification.

Kinetic Studies: Standard Reaction Conditions and Analytical Methods

Concentrations of **1b**, **2b**, and **3b** were assayed using HPLC with UV detection using a Rainin Rabbit HP pump (25 ml·min^{-1} pump head) coupled to a Dynamax silica column (8μ, 250 × 10 mm), EtOAc:*n*-hexane mobile phase (3.0 ml·min^{-1}) and an ISCO UA-5 detector (λ 254 nm filter). For analysis of **2b** and **3b**, solvent A (3:7 EtOAc:*n*-hexane) was used, while analysis of **1b** was carried out using solvent B (1:1 EtOAc:*n*-hexane). Peak areas were measured using a Hewlett Packard HP 3394 integrator. HPLC injections (50 μL) were made with a Hamilton 100 μL syringe such that the maximum absorbance was ≤ 1.0 AU. Retention times of the relevant compounds are listed as follows: Compound (retention time in solvent A, min ; retention time in solvent B, min): **1b** (18.52; 10.62), **2b** (8.47; 6.81), **3b** (9.58; 7.28). The following control experiment is representative of standard reaction conditions and analysis of the reaction time course. A dry 15 ml two neck round bottom flask, fitted with a reflux condensor and a rubber septum, was purged with dry nitrogen and charged with anhydrous dioxane (6.0 ml) and SeO_2 (0.1035 g, 0.933 mmol). The mixture was equilibrated with stirring for 10 min at 40°C (oil bath) followed by addition of a standard solution of 2-benzyl-4-phenyl-4,5-dihydrooxazole (**1b**, 0.423 M, 1.00 ml, 0.423 mmol, final conc. 0.060 M) in dioxane. The color of the reaction mixture immediately change to an opaque orange. Aliquots (0.100 ml) of the mixture were removed with a calibrated syringe at the following time points: t = 1, 5, 10, 15, 30, 45 and 60 min. Each aliquot was immediately eluted through a small pipet column containing silica gel (height ~ 1 cm) with dioxane and the eluate made up to 2.00 ml in a volumetric flask. The samples were analyzed by HPLC as described above. The initial concentration of **1b** (0.060 M, t=0) was calculated from dilution of the standard solution at initiation of reaction. Concentrations in the reaction mixture at subsequent time points were determined by comparison of peak areas from sample HPLC chromatograms (see above) with those of standard curves prepared for **1b**-**3b** and corrected for dilution (see Table 1). In one run, use of the standards addition method to monitor oxidation of **1b** at 40° C gave essentially the same results.

Assignment of second and first reaction orders were made by linear fit to plots of 0.5× [**1b**]$^{-1}$ *vs.* t (factor of 0.5 accomodates 1:2 stoichiometry of **1b**:SeO_2) and ln [**3b**] *vs.* t, respectively (N = 6-7 sample points, correlation coefficient R ≥ 0.95).[11,17] Rate constants were calculated from the slopes of the corresponding linear regression plots and uncertainties were derived from standard deviations of linear regression[18] (1.94-2.0 σ, student t distribution,[19] 90% confidence).

i. Rearrangement of **3b** *to* **2b**. *Standard Conditions, T° Dependence and* E_A.
Reaction time course was followed as above, only the starting materials were 2-benzoyl-4-phenyl-4,5-dihydrooxazole (**3b**, 0.0399 g, 0.159 mmol) in 1,4 dioxane (total 3.00 ml, initial concentration of **3b**, 0.053 M) and SeO_2 at 40°C (oil bath). The reaction mixture remained clear

throughout the time course and aliquots (0.100 ml) were sampled as described above. Kinetic measurements were repeated at 26°, 58°, 79° and 100°C (see Table 1) and the *apparent* Arrhenius activation energy $E_A = 4.2 \pm 1.6$ kcal.mol^{-1} calculated from the slope of ln k_2 vs T^{-1}.[17]

ii. Effect of H_2O

A stirred mixture of dioxane (2.00 ml) and SeO_2 (0.0368 g, 0.332 mmol, 2.2 equ) was equilibrated in an oil bath at 40°C under N_2. After 10 min, **1b** (0.0417 g, 0.1661 mmol) in dioxane (1.00 ml) and 3.0 µl of H_2O (0.17 mmol) were added simultaneously (initial concentration of **1b**, 0.055 M). The reaction mixture remained clear throughout the reaction. Aliquots (0.100 ml) of the reaction mixture were sampled and measured as described above (see Table 1).

iii. Effect of SeO_2 Concentration

Reaction time course of **3b**→**2b** was monitored under the same conditions as before, only with the addition of 1.0 or 2.0 equivalents of SeO_2 (see Table 1).

Acknowledgments:

We'd like to thank Dr. Don Land, Dr. Jim Swinehart and Mr. Kirk Green, Chemistry Department, UC Davis for valuable discussions and an anonymous reviewer for pointing out reference 15. This work was supported in part by the NIH (AI 31660) and the UC Davis Committee on Research. TFM gratefully acknowledges an American Cyanamid Faculty Award.

References:

(1) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 2044-2050.
(2) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079-6082.
(3) Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916-3926.
(4) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989, pp 410.
(5) Williams, D.; McClymont, E. L. *Tetrahedron Lett.* **1993**, *34*, 7705-7708.
(6) Williams, C. E.; Harwood, L. M., *American Chemical Society 209th National Meeting*, Anaheim, 1995, Abstract #: 290.
(7) Sengupta, S. K.; Trites, D. H.; Madhavarao, M. S.; Beltz, W. R. *J. Med. Chem.* **1979**, *22*, 797-802.
(8) Yasuo, O.; Tanaka, T.; Nishi, T.; Kuwahara, K.; Fugisawa, S.; Takasu, K.; Wada, Y. Japan. Patent WO 9602508, 1996; *Chem. Abstr.* **1996**, *124*, 345360
(9) Gauss, W.; Heitzer, H. *Liebigs Ann. Chem.* **1970**, *733*, 59-69.
(10) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353-9372.
(11) Moore, W. J. *Physical Chemistry*; 5th ed.; Prentice Hall: New Jersey, 1972, pp 977.
(12) Perrin, D. B. *Ionization Constants of Inorganic Acids and Bases in Aqueous Solution*; Pergamon: Oxford, 1982.
(13) Augustine, R. L. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1996, pp 647.
(14) Hsien-Cheng, Y.; Emmett, P. H. *J. Am. Chem. Soc.* **1959**, *81*, 4125-4132.
(15) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575-1578.
(16) Kaloustian, M. K.; Aguilar-Laurents de Gutierrez, M. I.; Nader, R. B. *J. Org. Chem.* **1979**, *44*, 666-668.
(17) Levine, I. N. *Physical Chemistry*; 3rd ed.; McGraw-Hill: New York, 1988, pp 920.
(18) Higbie, J. *Am. J. Phys.* **1991**, *59*, 184-185.
(19) Shoemaker, D. P.; Garland, C. W.; Nibler, J. W. *Experiments in Physical Chemistry*; 5th ed.; McGraw-Hill: New York, 1989.

(*Received in USA* 16 *August* 1996; *revised* 5 *September* 1996; *accepted* 30 *September* 1996)