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The Chemistry of 2-Alkenyl-5(4H)-Oxazolones. VIII Acid-Catalyzed Reaction with Alcohols.

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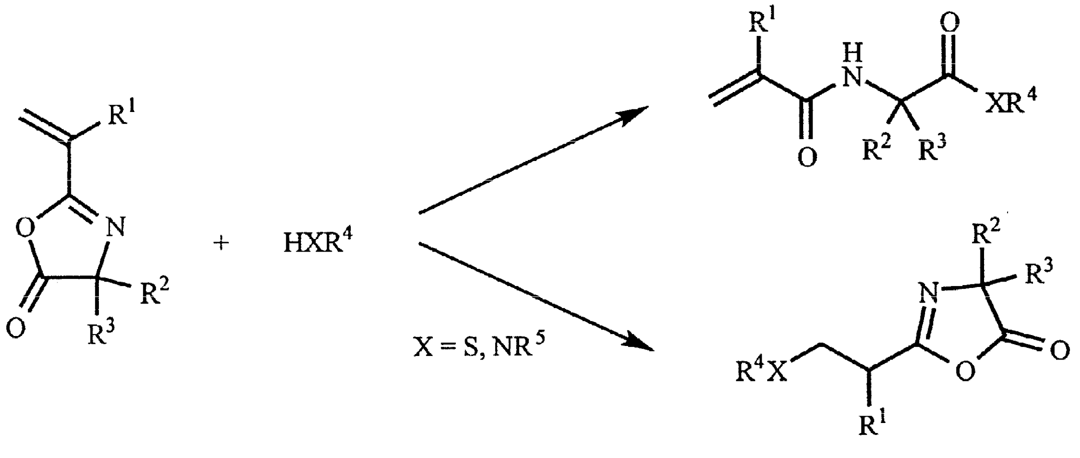
Abstract: *The acid-catalyzed reaction of 4,4-dimethyl-2-vinyl-5(4H)-oxazolone with primary alcohols proceeded with almost equal frequency at both C=C (Michael addition) and C=O (ring opening) groups; reaction with secondary and tertiary alcohols resulted in a modest elevation in Michael addition. Michael addition was not observed in reactions with 4,4-dimethyl-2-isopropenyl-5(4H)-oxazolone.* © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

2-Alkenyl 5(4H)-oxazolones (azlactones or 4,5-dihydro-1,3-oxazol-5-ones) **1** provide multiple electrophilic reaction centers to an attacking nucleophile. In most cases primary amines react exclusively at the carbonyl function resulting in ring opened, acrylamidoacetylated products [equation (1)].[1] On the other hand, secondary amines[2] and thiols[2,3] (especially in the presence of acid) react predominantly at the 2-alkenyl function resulting in Michael-type addition [equation (2)].



(1)

(2)

The C=N group has also been accessed by still other special nucleophiles which are capable of intercepting the normally reversible tetrahedral intermediate by cleavage and ketolization in the case of water[4] or by subsequent reaction of a second nucleophilic group in the case of *ortho*-substituted anilines[5] [equations (3) and (4)].

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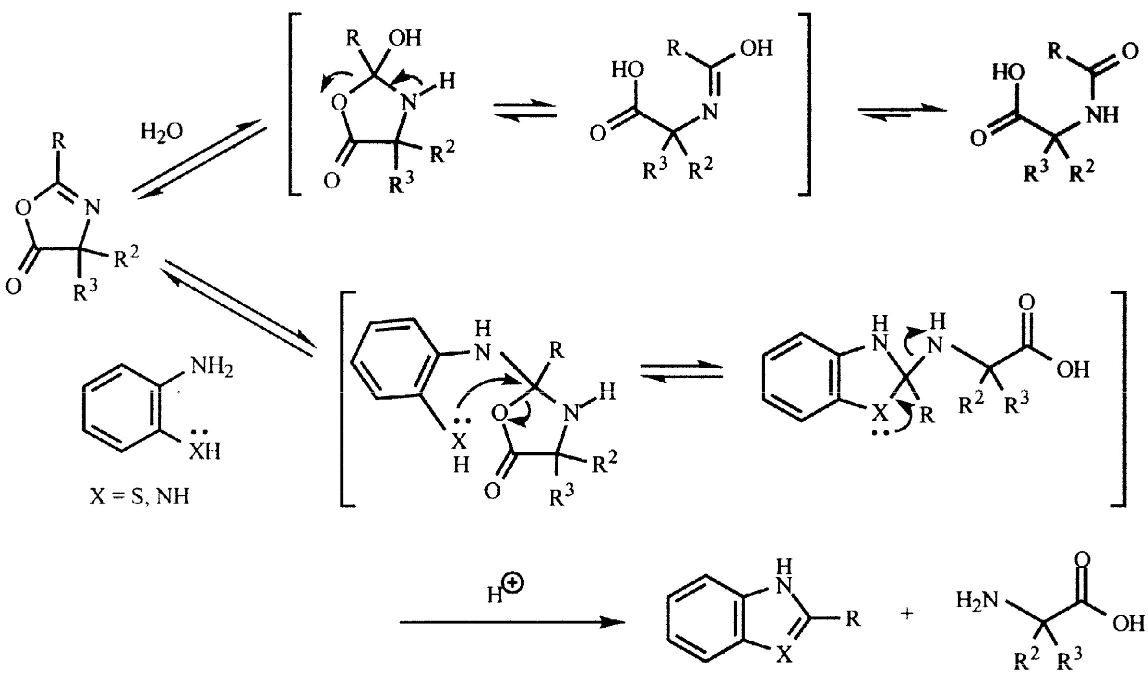


(3)

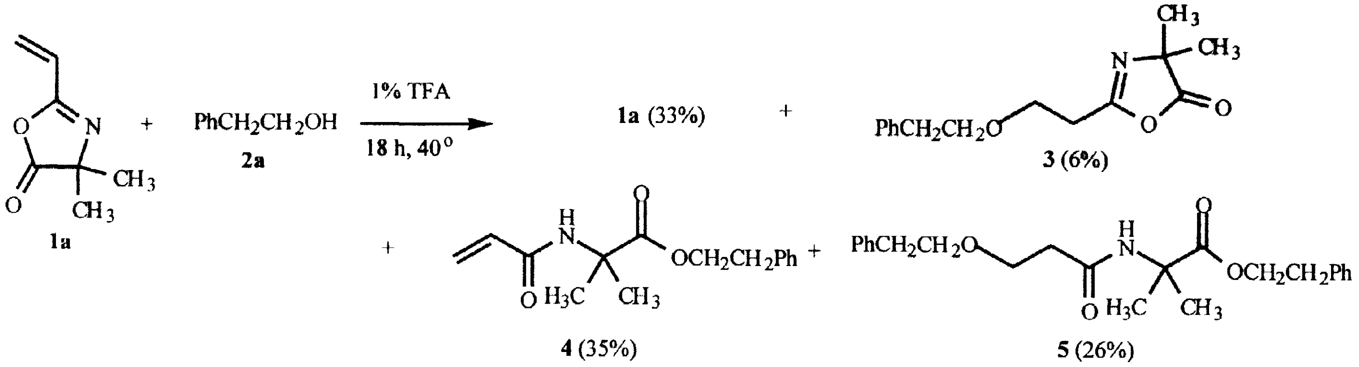
(4)

Reactions of alcohols and 2-alkenyl 5(4H)-oxazolones in the presence of acid catalysts have been briefly described[6] as being complicated by attack occurring at both carbonyl and 2-alkenyl functions. This report describes these reactions in greater detail.

RESULTS AND DISCUSSION

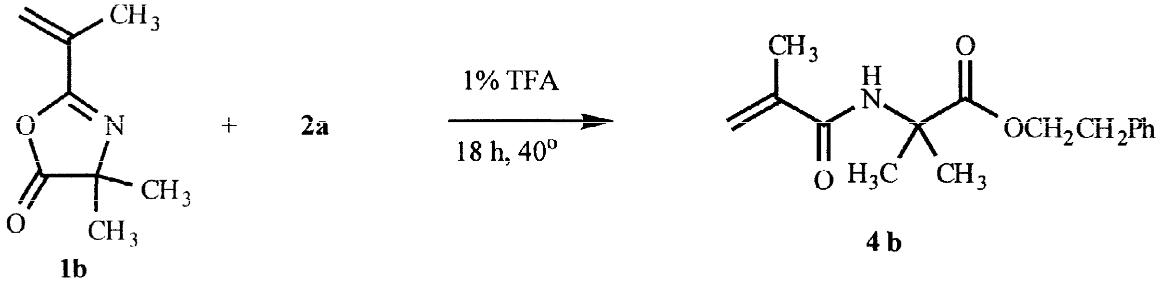
Because of the relative simplicity of the aliphatic region of their ^{1}H-NMR spectra, phenethyl alcohols **2** were selected as alcoholic reactants to be examined with **1**. An additional advantage was that alcohols **2** were liquids at room temperature and provided solutions when mixed with **1** and remained liquid over the entire course of reaction.

Ethanesulfonic acid (2 mol %) was initially examined as catalyst with equimolar quantities of **1a** and **2a**. After 18 hours at 40° C, a highly colored, viscous, rather complex mixture of products resulted, and it was apparent that not only mono- but bis-addition of the alcohol to **1a** had occurred, leaving significant amounts of **1a** in the mixture due to stoichiometric imbalance caused by enhanced depletion of the alcohol. The increase in viscosity was discovered[7] to result from an acid-catalyzed oligomerization of **1a**, somewhat analogous to 2-alkenyl oxazolines under similar conditions.[8] Oligomerization of **1a** was eliminated in the present study by employing the weaker acid trifluoroacetic acid (TFA), and the following reaction products and amounts were identified based on comparison of selected ^{1}H-NMR product resonances with authentic samples: **1a** (33%; methine doublet of doublets at 5.93 ppm), **3** (6%; methylene triplet at 2.73 ppm), **4** (35%; methine doublet of doublets at 5.60 ppm), and **5** (26%; methylene triplet at 2.40 ppm).



Products 3 and 4 clearly indicated that nucleophilic attack was occurring at both C=C and C=O groups of **1a**, respectively. In a separate experiment, bis(adduct) **5** was shown to be formed exclusively from reaction of 3 and **2a**; **4** and **2a** did not react under the conditions. Therefore, including bis(adduct) **5** with the Michael product **3** gave a yield of 32% for products derived from addition to the C=C group, compared to 35% from products due to attack at the C=O group or a ratio of 48:52 of C=C:C=O products. Similar product ratios were observed when a full excess of **2a** was utilized (51:49) and when no acid was employed (55:45; with no bis(adduct) 5 being detected).

Reaction of **2a** and 4,4-dimethyl-2-isopropenyl-5(4H)-oxazolone (**1b**) in the presence of TFA, on the other hand, was quite clean with only ring-opening product **4b** derived from attack at the C=O function being formed.



Two observations concerning reactions of **1** and **2a** deserve additional comment, the first being that the presence of the α-methyl group in **1b** eliminated Michael addition as a competing reaction. A similar influence of the α-methyl group was also observed in Michael additions with analogous acrylate and methacrylate esters. Methacrylates were generally poorer Michael acceptors compared to acrylates, requiring more stringent reaction conditions and providing lower yields of Michael products,[9] with competing 1,2-addition often predominating.[10] As an indication of the relative affinity of an attacking nucleophile for the two respective electrophilic β-carbon atoms, partial charges for the methacrylate and acrylate Michael acceptors were computed.[11] A larger negative charge by 0.23 units was determined for the methacrylate (-0.85 units) relative to the acrylate (-0.62 units) which was reflective of the electron donating inductive effect of the methyl group. Similarly, calculations for protonated **1a** (-0.53 units) and **1b** (-0.88 units) (presumed to be the actual reactants in these acid-catalyzed reactions[12]) gave a larger negative charge by 0.35 for **1b** than **1a**. Therefore, in the absence of other factors[13] the reduced propensity for Michael addition with the α-methyl substituted Michael acceptors resulted primarily from the electron donating inductive effect of the methyl group. The methacrylate and protonated **1b** Michael acceptor systems were less attractive to the attacking alcohol than their non-methylated counterparts and, as a consequence, reaction occurred at the carbonyl.

Application of the ^{13}C-NMR chemical shift computation method of Levin, et al.,[14] was less discriminating. Comparison of the π electron deficiencies of the β carbon atoms of methyl vinyl ketone (9.0%) relative to isopropenyl methyl ketone (8.8%) suggested only a very slightly less electrophilic β carbon atom for the methylated analog.

From the relative amounts of **1a** and **3** present in the product mixture, the second observation was that an azlactone possessing a vinyl group at position-2 was substantially less reactive in a ring opening sense than an azlactone possessing an alkyl group at that position. Differential reactivity had been previously observed in the acid-catalyzed hydrolyses of 4-arylidene-2-methyl- and 4-arylidene-2-phenyl-5(4H)-oxazolones.[4] With these oxazolones addition of water was proposed to take place not at the C=O but the C=N groups, and differences were attributed principally to the greater basicity caused by the larger electron releasing inductive effect of the 2-methyl relative to the 2-phenyl derivative. Basicity differences, however, were concluded to not entirely account for the rather large difference (> 10^5) in hydrolysis rates. Steric problems associated with the 2-phenyl derivative were also proposed to affect hydrolysis. That 4-arylidene substituted oxazolones behaved differently than 4,4-dialkyl substituted oxazolones, however, was apparent when no methyl ester product (resulting from ring opening attack at the carbonyl group) was isolated from the acid-catalyzed reaction of 4-benzylidene-2-methyl-5(4H)-oxazolone with methanol.

To directly ascertain the influence of the 2-substituent on rate of ring opening, a series of individual competitive reactions was conducted of 4,4-dimethyl-2-isopropyl-5(4H)-oxazolone, 2-cyclopropyl-4,4-dimethyl-5(4H)-oxazolone, 2-*t*-butyl-4,4-dimethyl-5(4H)-oxazolone, **1b**[15], and 4,4-dimethyl-2-phenyl-5(4H)-oxazolone versus 4,4-dimethyl-2-ethyl-5(4H)-oxazolone (charged 1:1; each reactant 3 M in d_8-THF) with only one equivalent of **2a**.[16] Analysis of the ratios of the various ring-opened ester products relative to the 2-ethyl derivative product provided insight concerning rate differences. The results are given in Table 1 with the substituents being recorded in order of increasing size.

Table 1. Competitive Reaction Results of 2-Substituted 5(4H)-Oxazolones with **2a**[A]

	Steric Constant		Substituent Constant[19]		Ring-Opening (RO) Product Analysis
2-Substituent	υ[17]	E_S[18]	σ_p	σ_p^+	(%RO_{Sub}/%RO_{Et})
Ethyl	0.56	-1.31	-0.13	-0.30	1.00
Isopropyl	0.76	-1.71	-0.13	-0.28	0.58
Cyclopropyl	1.06	-2.21	-0.21	-0.46	1.86
					1.71[B]
					1.57[C]
t-Butyl	1.24	-2.78	-0.15	-0.26	0.47
Isopropenyl	1.56	----	-0.08[D]	----	0.25
Phenyl	1.66	-3.82	+0.05	-0.18	0.22
					0.41[B]
					0.25[C]

A = Unless otherwise indicated, all reactions were conducted using 2 mol % TFA based on total oxazolone.
B = Stoichiometric TFA was utilized.
C = Ethanesulfonic acid (2 mol %) was utilized as catalyst.
D = No value was reported for isopropenyl; value indicated is for vinyl.

The above results suggested that both steric and electronic factors were important. In a series in which size increased substantially and electronic factors were constant, the descending order of reactivity of Et > Pr^i > Bu^t clearly indicated an important steric influence of the 2-substituent with regard to attack at the carbonyl at position-5. The observed sensitivity to seemingly remote steric effects might have been enhanced with 4,4-dimethyl-5(4H)-oxazolones because of the flanking *gem*-dimethyl group at position-4. In addition to a relatively small size, electron donating ability of the 2-substituent was shown to be perhaps more important than steric factors by the substantially increased reactivity of the larger, more electron donating 2-cyclopropyl derivative relative to 2-ethyl. An electron donating 2-substituent should have a base strengthening effect on the oxazolone ring nitrogen. Product ratios therefore might have been affected by varying degrees of protonation across the series; this hypothesis was also supported by the lack of bis(adduct) **5** being formed in the uncatalyzed reaction. While modest endorsement for the importance of bascity differences was obtained when more strongly acidic conditions, i.e., ethanesulfonic acid and stoichiometric TFA, were employed, cyclopropyl/ethyl product ratios of 1.86 (catalytic TFA), 1.71 (stoichiometric TFA), and 1.57 (ethanesulfonic acid) and corresponding phenyl/ethyl ratios of 0.22, 0.41, and 0.25 did not indicate substantial leveling in reactivity between the two oxazolones as would be expected if protonation was substantially rate and product determining.

Reaction of **1a** with a series of more sterically encumbered phenethyl alcohols was also examined (Table 2) to ascertain the influence of steric factors in the attacking alcohol. Reactions were conducted in the absence of solvent as before except that an additional equivalent of the alcohol was employed to enhance product yields.

Table 2. C=C vs. C=O Reactivity for a Series of Phenethyl Alcohols with **1a**

	$PhC(R^aR^b)C(R^cR^d)OH$				Product Ratio^A	
	R^a	R^b	R^c	R^d	C=C	C=O
2a	H	H	H	H	51	49
2b	H	Me	H	H	47	53
2c	Me	Me	H	H	53	47
2d	H	H	Me	H	54	46
t-Butanol (36% reaction)					70	30

A = Products were identified by integrated areas for the =CH- resonance at 5.6 ppm resulting from ring opening attack at C=O compared to $-CH_2CONH-$ at 2.4 ppm from Michael addition to C=C.

At best, the results showed a modest preference for Michael addition as the steric encumberment of **2** increased. The lack of influence of alkyl substitution in the attacking alcohol was somewhat surprising since secondary amines had earlier been observed to provide predominant Michael addition products with 2-alkenyl-4,4-dimethyl-5(4H)-oxazolones.[2] This resulted presumably because of steric problems associated with the secondary amine nitrogen and its two alkyl groups. That even t-butanol in the present study engaged in significant reaction (30%) at the C=O was indicative that a monoalkyl substituted heteroatom nucleophile such as an alcohol could behave differently and align its alkyl substituent in such a manner as to not seriously crowd the transition state for ring opening. Such alignment of secondary amines is not possible; at least one of the alkyl groups would always cause crowding in the transition state. A previous result[2] in concert with this explanation was the reaction of **1a** and t-butylamine in which a 62:38 ratio for C=C vs. C=O attack was observed which closely paralleled the above result with t-butanol.

CONCLUSIONS

A common practical application of the reaction of alcohols and 2-alkenyl-5(4H)-oxazolones is often concerned with polymer chemistry and, more specifically, polymer modification. An alcohol which contains functionalities desirable for modifying polymer properties can generally be appended to a polymer using oxazolone chemistry in one of two ways: 1) directly through generation of an acrylamide monomer, i.e., ring opening addition by the alcohol, followed by copolymerization; or 2) indirectly by copolymerization of the alkenyl oxazolone followed by ring opening of the polymer bound oxazolone groups by the alcohol. The results of this study using acid catalysts clearly indicate in terms of eliminating side reactions (and perhaps improving reaction efficiency of the resultant 2-alkyl substituted (albeit polymeric) oxazolones) that the indirect, two step method is certainly preferred for 2-vinyl oxazolone derivatives. Methacrylamides resulting from ring opening of 2-isopropenyl oxazolones and alcohols, on the other hand, are formed without side products and can be polymerized directly.

Regarding the observation of the reactivity differences that exist between 2-alkenyl and 2-alkyl substituted 5(4H)-oxazolones, clear answers as to the influence of electronic factors associated with the 2-substituent on reactivity at the carbonyl at position-5 await additional investigation.

EXPERIMENTAL SECTION

Melting points were conducted using a Thomas Hoover Capillary Melting Point Apparatus and were not calibrated. IR spectra were obtained using a Bomem FT Infrared Spectrophotometer on films between KBr plates or as KBr pellets. ^{1}H- and ^{13}C-NMR spectra were recorded using either a Varian Unity 500 or a Varian Inova 400 instrument. Chemical shifts were given as δ values with reference to tetramethylsilane as an internal reference. High resolution mass spectra were performed using a VG ZabSpec 008 Mass Spectrometer. Elemental analyses were performed using a Leco CHNS-932 Elemental Analyzer. 4,4-Dimethyl-2-vinyl-5(4H)-oxazolone (**1a**) was purchased from SNPE, Inc. (Princeton, NJ) and used without further purification. Phenethyl alcohol (**2a**), 1-phenyl-1-propanol (**2b**), 1-phenyl-2-propanol (**2d**), t-butyl alcohol, ethanesulfonic acid, trifluoroacetic acid, β-propiolactone, and 2-aminoisobutyric acid were purchased from Aldrich Chemical Co. and used without further purification. 4,4-Dimethyl-2-isopropenyl-5(4H)-oxazolone (**1b**)[20], 4,4-dimethyl-2-isopropyl-5(4H)-oxazolone[21], 4,4-dimethyl-2-ethyl-5(4H)-oxazolone[22], 4,4-dimethyl-2-phenyl-5(4H)-oxazolone[23], and 2-methyl-2-phenyl-1-propanol (**2c**)[24] were synthesized according to published procedures.

3-(Phenethyloxy)propanoic acid: β-Propiolactone (73.14 grams; 1.016 moles) was added dropwise with stirring to 2-phenethyl alcohol (744 grams; 6.096 moles) at 65° C. The addition was accompanied by a moderate exothermic reaction (to 73° C); the resulting solution was stirred at 65° for 16 hours. The excess phenethyl alcohol was removed by vacuum fractional distillation with the fraction distilling at 100-145° @

0.15 Torr. being retained for re-distillation; this fraction weighed 127 grams. Upon redistillation, a slighly viscous, colorless liquid weighing 87.3 grams (39% yield) and distilling at 118-122° @ 0.12 Torr was collected. IR (neat): 3.72 (OH stretch) and 5.81 (C=O stretch) microns. ^{1}H-NMR ($CDCl_3$): δ 2.62 (t, J = 6.5 Hz, 2H), 2.89 (t, J = 6.5 Hz, 2H), 3.7 (m, 4H), 7.23 (s, 5H) and 11.20 (s, 1H). ^{13}C-NMR: 34.9, 36.1, 65.7, 72.0, 126.1, 128.3, 128.9, 138.5, and 177.4 ppm. Analysis for $C_{11}H_{14}O_3$: Calcd. C, 68.0%; H, 7.3%. Found C, 67.9%; H, 7.0%.

2-Methyl-2-{[3-(phenethyloxy)propanolyl]amino}propanoic Acid: 3-(2-Phenylethoxy)propanoic acid (19.4 grams; 0.10 mole), thionyl chloride (24.6 grams; 0.207 mole), and benzene (40 mL) were mixed together without incident. A drop of pyridine was added and the solution was warmed to 50° for 24 hours. Gas evolution occurred as the solution was warming. The benzene and excess thionyl chloride were removed using a rotary evaporator, and the colorless 3-(2-phenylethoxy)propionyl chloride was used without further purification.

The acid chloride (0.1 mole) dissolved in methylene chloride (35 mL) was added dropwise, with simultaneous dropwise addition of a NaOH solution (4 grams in 10 mL of water), to a solution of 2-aminoisobutyric acid (10.3 grams; 0.10 mole), sodium hydroxide (4.0 grams; 0.10 mole), and water (35 mL). The dropwise additons were conducted such that the temperature of the well stirred reaction was maintained between 0-5° by external cooling with an isopropanol-dry ice bath. After the addition the reaction was stirred and cooled in an ice water bath for one hour. The mixture was allowed to warm with stirring to room temperature for an additional two hours before acidification to pH 2 with con. HCl. Separation of the organic layer and removal of the methylene chloride solvent at reduced pressure produced 100 grams of a white solid. Recrystallization from toluene provided 41.1 grams (43% yield) of white needles melting at 141-142°. IR (KBr pellet): 3.03 (NH stretch), 3.96 (OH stretch), 5.85 (acid C=O), 6.20 (amide C=O), and 6.45 (amide II) microns. ^{1}H-NMR ($CDCl_3$): δ 1.46 (s, 6H), 2.49 (t, J = 5.5 Hz, 2H), 2.90 (t, J = 5.5 Hz, 2H), 3.72 (m, 4H), 6.98 (s, 1H), 7.24 (m, 5H), and 11.28 (s, 1H). ^{13}C-NMR: 24.0, 35.1, 36.1, 55.0, 65.9, 70.7, 125.2, 127.5, 127.9, 137.9, 169.7, and 175.2 ppm. Mass Spectrum: for $C_{15}H_{21}NO_4$, calcd. 280.1549; found 280.1555.

4,4-Dimethyl-2-[2-(phenethyloxy)ethyl)]-5(4H)-oxazolone (**3**): 2-3-(N-(2-Phenylethoxy]propionyl)-aminoisobutyric acid (19.53 grams; 0.070 mole) was suspended in methylene chloride (150 mL). A solution of dicyclohexylcarbodiimide (13.80 grams; 0.067 mole) dissolved in methylene chloride (100 mL) was added dropwise over a 90 minute period; the addition was accompanied by a mild exothermic reaction in which the temperature increased to about 25°. The mixture was stirred for two days at room temperature before filtration, removal of methylene chloride *in vacuo*, dissolution in pentane (100 mL), filtration, and removal of the pentane provided 17.33 grams (99% yield) of a clear, colorless liquid. Repeated attempts to vacuum distil the material were unsuccessful as significant retro-Michael addition occurred. The sample was quite pure in the undistilled form, however, as judged by the absence of extraneous renonances in the NMR spectra. IR (neat): 5.49 (oxazolone C=O) and 5.94 (C=N) microns. ^{1}H-NMR ($CDCl_3$): δ 1.38 (s, 6H), 2.73 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.75 (m, 4H), and 7.22 (s, 5H). ^{13}C-NMR: 24.5, 29.9, 35.9, 65.0, 65.5, 71.6, 125.9, 128.1, 128.9, 138.4, 161.1, and 180.8 ppm.

Phenylethyl 2-(Acryloylamino)-2-methylpropanoate (**4**): 2-Phenethyl alcohol (3.06 grams; 0.025 mole), 4,4-dimethyl-2-vinyl-5(4H)-oxazolone (**1a**) (3.49 grams; 0.025 mole), and 4-dimethylaminopyridine (1.22 grams; 0.01 mole) were placed in a dry sealed flask and warmed to 40°. After 120 hours, reaction was about 80% complete as judged by IR. The mixture was chromatographed using a Waters 500A Prep/LC System and chloroform-ethyl acetate mixtures as eluting solvents. A colorless oil weighing 4.59 grams (70% yield) was obtained. IR (neat): 3.02 (NH stretch), 5. 72 (ester C=O), 6.00 (amide C=O), 6.12 (C=C), and 6.47 (amide II) microns. ^{1}H-NMR ($CDCl_3$): δ 1.55 (s, 6H), 2.95 (t, J = 7 Hz, 2H), 4.37 (t, J = 7 Hz, 2H), 5.60 (d of d, J = 3 & 9 Hz, 1H), 6.15 (m, 2H), 6.46 (s, 1H), and 7.24 (s, 5H). ^{13}C-NMR: 20.8, 34.5, 55.8, 65.1, 125.5, 125.9, 127.9, 128.3, 130.5, 137.2, 164.4, and 173.4. Mass Spectrum: for $C_{15}H_{19}NO_3$; 261.1365 calcd., 261.1360 found.

Phenethyl 2-Methyl-2-{[3-(phenethyloxy)propanoyl]amino}propanoate (**5**): 4,4-Dimethyl-2-(2-phenylethoxyethyl)-5(4H)-oxazolone (**3**) (2.47 grams; 0.01 mole) and phenethyl alcohol (1.15 grams; 0.01 mole) were mixed without incident. Ethanesulfonic acid (0.01 gram) was added and within 90 minutes reaction was complete. The product was a clear, colorless oil. IR (neat): 2.98 (NH stretch), 5.70 (ester C=O), 6.00 (amide C=O), 6.50 (amide II) microns. ^{1}H-NMR ($CDCl_3$): δ 1.41 (s, 6H), 2.40 (t, J = 6 Hz, 2H), 2.93 (m, 4H), 3.68 (m, 4H), 4.35 (t, J = 6 Hz, 2H), 6.76 (s, 1H), and 7.24 (m, 10H). ^{13}C-NMR: 24.5, 34.3, 35.5, 36.1, 55.3, 64.7, 66.1, 71.6, 125.4, 125.7, 127.6, 128.2, 137.0, 138.0, 170.0, and 173.0 ppm.

Reactions of 2-Alkenyl-4,4-dimethyl-5(4H)-oxazolones with Phenethyl Alcohols (**2**):

1a and **2a** [1:1 stoichiometry]: Reactions were conducted in dried, 4 dram glass vials. Equimolar quantities of **1a** and **2a**, either with TFA (2 mol %) or not, were heated at 40°. ^{1}H-NMR analysis of $CDCl_3$ solutions of aliquots indicated the following compounds to be present: (Uncatalyzed Result; after 120 hours): **1a** - 82%; **2a** - 82%; **3** - 8%; and **4** -10% (TFA Result; after 18 hours): **1a** - 33%; **3** - 6%; **4** - 35%; and **5** - 26%.

1b and **2a**: A dry glass vial was charged with **2a** (3.52 grams; 0.029 mole) and TFA (0.10 gram; 0.0009 mole). 4,4-Dimethyl-2-isopropenyl-5(4H)-oxazolone (**1b**) (4.41 grams; 0.029 mole) was added, and the vial was placed in an oven at 40° for 18 hours. ^{1}H-NMR showed the initially colorless liquid product to be essentially pure **4b**. m.p. = 79-80° C (EtOH-H_2O); IR (KBr) = 3.05 (NH), 5.75 (ester C=O), 6.06 (amide C=O), and 6.54 (amide II) microns. ^{1}H-NMR (DMSO-d_6): δ 1.33 (s, 6H), 1.81 (s, 3H), 2.84 (t, J = 6.6 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 5.35 (s, 1H), 5.66 (s, 1H), 7.24 (m, 5H), and 8.02 (s, 1H). ^{13}C-NMR: 18.62, 24.83, 34.37, 55.24, 64.70, 119.55, 126.28, 128.27, 128.87, 167.32, and 173.83 ppm. Mass Spectrum: for $C_{16}H_{22}NO_3$; 276.1594 calcd., 276.1594 found.

1a and **2** [1:2 stoichiometry]: Product ratios were determined by careful integration of either amide NH resonances at 6.5 (for 4) and 6.65 (for **5**) or corresponding =CH- and -$\underline{CH_2}$CONH resonances at 5.4 and 5.6 ppm, respectively. **2a:** When a similar reaction as described above was conducted except that an additional equivalent of **2a** was utilized, the product solution contained in addition to excess **2a** only products **4** and **5** in a 49:51 molar ratio. **2b:** Michael:ring opening product ratio of 47:53. **2c:** Product ratios of 53:47. **2d:** Product ratios of 54:46. **Bu^{t}OH:** (36% reaction) Product ratio of 70:30 for Michael:ring opening.

Preparation of 2-alkyl-4,4-dimethyl-5(4H)-oxazolones:

2-(N-Cyclopropanecarbonyl)amino-2-methylpropanoic acid: To a rapidly stirred solution of 2-amino-2-methylpropanoic acid (51.5 g; 0.50 mole), sodium hydroxide (20 g; 0.50 mole), and water (150 mL) cooled to -10° C were added from separate dropping funnels cyclopropanecarbonyl chloride (52 g; 0.50 mole) and aqueous sodium hydroxide (20 g; 0.50 mole dissolved in 50 mL of water). The simultaneous addition was conducted such that the reaction temperature did not exceed 0° C. After the addition, the cooling bath was removed, and the reaction was stirred and allowed to warm to room temperature over 4h. Concentrated HCl (60 mL) was added and the white solid which formed was filtered, washed with water, and dried at 50° C/< 1 Torr. overnight. The white solid weighed 68.6 grams (80% yield) and melted sharply at 197-197.5° C. IR

(KBr): 3.00 (NH), 5.80 (acid C=O), and 6.13 (amide C=O) microns. ^{1}H-NMR (DMSO-d_6): δ 0.61 (m, 4H), 1.32 (s, 6H), 1.60 (m, 1H), and 8.30 (s, 1H). ^{13}C-NMR: 6.2, 13.4, 25.0, 54.7, 171.9, and 175.6 ppm. Mass Spectrum: for $C_8H_{13}NO_3$; 171.0889 calcd.; 171.0885 found.

2-Cyclopropyl-4,4-dimethyl-5(4H)-oxazolone: To a slurry of the above amidoacid (68 g; 0.40 mole), triethylamine (40.4 g; 0.40 mole), and acetone (400 mL) was added ethyl chloroformate (40.7 g; 0.38 mole) dropwise such that the reaction temperature did not exceed -5° C. After 3h, gas evolution had ceased, and the slurry was filtered and the acetone/triethylamine removed on the rotary evaporator leaving an almost colorless liquid residue. Vacuum fractional distillation provided a water white liquid boiling at 55-57° C/3.2 Torr. and weighing 49.6 g (85% yield). IR (neat): 5.49 (C=O) and 5.99 (C=N) microns. ^{1}H-NMR (CDCl$_3$): δ 1.10 (m, 4H), 1.40 (s, 6H), and 1.78 (m, 1H). ^{13}C-NMR: 6.9, 8.9, 24.2, 64.7, 164.0, and 180.6 ppm. Mass Spectrum: for $C_8H_{11}NO_2$; 153.0784 calcd.; 153.0789 found.

2-Methyl-2-(N-pivaloyl)aminopropanoic acid: Attempted preparation via the acid chloride and sodium salt of the aminoacid did not work well; the pivaloyl chloride was largely hydrolyzed under the conditions. A variation of our earlier procedure[25] was employed in that pivaloyl chloride was substituted for acryloyl chloride as the acylating agent for 2-amino-2-methylpropionitrile. Upon acidification and heating, 74.0 grams (44% yield) of a white solid was collected. The solid melted at 178-180° C. IR (KBr): 2.97 (NH), 5.82 (acid C=O), 6.18 (amide C=O), and 6.52 (amide II) microns. ^{1}H-NMR (DMSO-d_6): δ 1.08 (s, 9H), 1.34 (s, 6H), 7.26 (s, 1H), and 11.96 (s, 1H). ^{13}C-NMR: 24.9, 27.3, 37.9, 54.9, 175.8, and 176.8 ppm. Mass Spectrum: for $C_9H_{17}NO_3$, 187.1204 calcd.; 187.1203 found.

2-t-Butyl-4,4-dimethyl-5(4H)-oxazolone: Employing a procedure very similar to that described above for the 2-cyclopropyl derivative, there was obtained 45.7 grams (71% yield) upon Kugelrohr distillation of a colorless material which solidified on standing. The material was recrystallized from hexane to provide large crystals melting at 33-34° C. IR(Neat): 5.49 (C=O) and 5.98 (C=N) microns. ^{1}H-NMR (DMSO-d_6): δ 1.23 (s, 9H) and 1.33 (s, 6H). ^{13}C-NMR: 24.1, 26.3, 33.4, 64.8, 168.2, and 181.3 microns. Mass Spectrum: for $C_9H_{15}NO_2$, 169.1102 calcd.; 169.1098 found.

Competitive Reactions of 4,4-Dimethyl-2-substituted-5(4H)-oxazolones versus 4,4-Dimethyl-2-ethyl-5(4H)-oxazolone with **2a**: All competitive reactions were conducted using a (1:1:1) molar ratio of the two oxazolones and **2a**. The reactants were carefully weighed into a dry glass vial and enough THF-d_8 was added to achieve a concentration of 3 M for each reactant. Then, TFA (2 mol %, based on total oxazolone) was added, the vial was capped, and placed into an oven at 40° C for 18h. ^{1}H-NMR was utilized to analyze the corresponding ring opened products from the 2-substituted- relative to the 2-ethyloxazolone.

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11. Fractional atomic charges were computed using the the Gaussian 94 for Windows (revision E.1) Program and an Intel Pentium 200 MHz Personal Computer. The computations were unconstrained and the geometries were true minima.
12. The base stength of the oxazolone nitrogen has not been reported in terms of the pK_A of its conjugate acid. Reference 4, however, provided data in support of a value < 5. Furthermore, the value of 5.59 reported for an analogous oxazoline (Weinberger, M.A.; Green halgh, R. *Can. J. Chem.* **1963**, *41*, 1038-1041) would support a value in the range of 3-5 pK units. Clearly, acids such as ethanesulfonic acid and TFA should be sufficiently strong to protonate the oxazolone.
13. There were no remarkable differences in the IR spectra of **1a** and **1b** suggestive of a lack of coplanarity of the alkenyl and C=N units.
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15. **1a** was not examined in this study because of competitive Michael addition.
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