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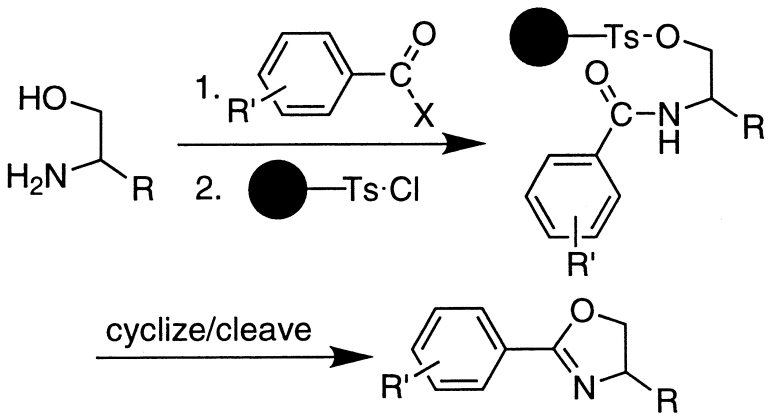

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Oxazoline Synthesis from Hydroxyamides by Resin Capture and Ring-Forming Release

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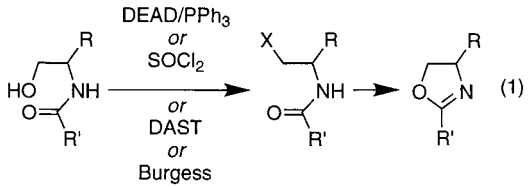
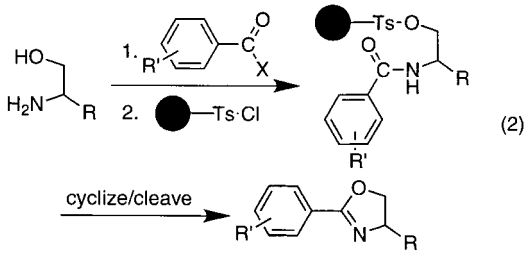
Polymer-bound tosyl chloride was used to capture hydroxyamides (prepared from amino alcohols and acid chlorides) from the reaction mixtures in which they were formed. The resulting support-bound amide/sulfonates undergo ring-forming cleavage from the polymer on treatment with weak base, forming oxazolines and oxazines in generally good yield and high purity. Low temperature is required in the polymer-loading step to slow the cleavage process and achieve high efficiency in the execution of the method.

Oxazolines, along with their oxidized oxazole relatives, are present in a wide variety of biologically active natural products, including siderophores and postsynthetically modified, nonribosomal polypeptides.[1,2] They also contribute to the flavors of a variety of foods.[3] They have played an important part in the development of synthetic methods[4] and are commonly present in ligands for asymmetric catalysis.[5] Hydrophilic polymers can also be made by ring-opening polymerization of oxazolines. Oxazolines can be prepared from hydroxyamides by activation of the hydroxyl group through conversion to a good leaving group (eq 1). The R group can be alkyl, acyl, or H. Several reagents have been used to promote this reaction, including PPh_3/DEAD,[6] $SOCl_2$,[7] DAST,[8] and the Burgess reagent.[9] The latter currently appears to be the reagent of choice for this transformation.



Polymer-bound reagents and scavengers have become increasingly important in solution-phase high-throughput organic synthesis. Their most common use is in scavenging the excess of one or more reagents after a synthetic step.[10] A less common, though more useful, utilization of polymers is "catch-and-release" purification, which involves the capture of a desired product by a resin followed by a wash step that removes excess reagents and starting material. The product is then cleaved from the resin, leaving it free of impurities.

The goal of this work was to apply a polymer-bound reagent to high-throughput oxazoline synthesis. The diversity inputs are hydroxyamines and acylating agents, and the method provides the targets without any need for intermediate or final purification. Our rationale was that an initial N-acylation product could be captured onto a polymer support, eliminating purification in the first step. The oxazoline ring could be formed and this product released into solution if the support also encompasses a good leaving group. This strategy exploits a valuable concept when using support-bound intermediates in a synthetic sequence: simultaneous cyclization/cleavage.[11,12] When the final step of a designed reaction sequence forms a ring bond as it also releases molecules from the support, only those molecules that have successfully completed each step in the sequence are removed. Any intermediate failure products are retained on the support or removed in earlier wash steps and cannot contaminate the product. High product purity is therefore generally observed, even when the efficiency of intermediate steps is less than quantitative. Polymer-bound tosyl chloride[13] is frequently used as a scavenger resin for amines, and occasionally for alcohols. We envisioned a reaction sequence in which this resin captures an alcohol (eq 2), forming the resin-bound tosylate. Ring-forming release to form the oxazoline should be possible using a volatile, non-nucleophilic base.[14]



Because of our interest in oxazoline hydroxamate antibacterial agents,[15] an initial focus was oxazolines prepared from serine derivatives. With these substrates, β-elimination can be a major reaction competing with cyclization. In 1956, Wilson reported the effects of leaving group, substrate, and solvent on the reaction of hydroxyamides with dehydrating agents.[16] He found two factors that affect the partitioning between cyclization and elimination. The acidity of the α-proton is important, as elimination was the main process observed when R was an ester, while cyclization was the

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Table 1

reaction conditions	oxazoline (**3**):dehydroalanine (**3**)
DCM/Et_3N (10:1)	1:1.5
MeOH/Et_3N (10:1)	no product
THF/Et_3N (10:1)	3:1
THF/KOAc	40:1
THF/pyridine (1:1)	40:1
THF/pyridine (10:1)	∞

main process observed when R was an amide. Solvent is also important, with polar solvents such as methanol and THF promoting cyclization, while less polar solvents such as dichloromethane promote elimination.

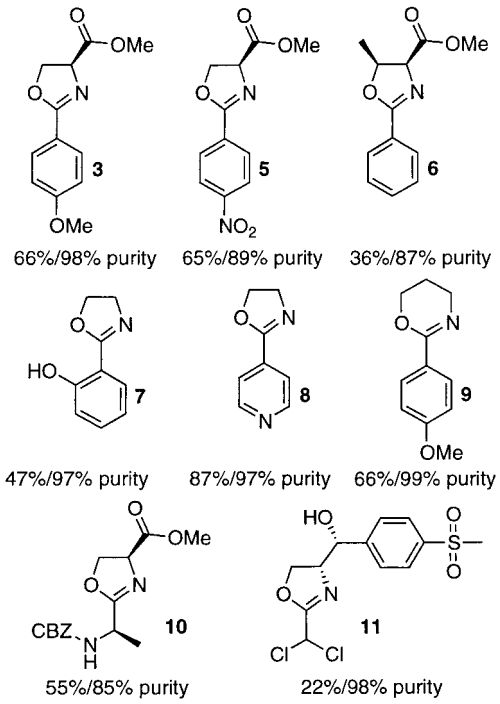
Results

A model acylated serine was used to initially address the issue of controlling cyclization versus elimination without concern for the acylation step. Compound **1** was treated with the tosyl chloride resin in pyridine at room temperature to form **2**, which was subjected to a variety of reaction conditions with product analysis by ^{1}H NMR. Results are summarized in Table 1. They generally agree with the observations of Wilson. The use of a weak base with THF as solvent practically abolishes the elimination product for this particular starting material. Pyridine is preferable to KOAc because excess base can be removed by evaporation. While the product ratio we were able to obtain was gratifying, the yield was quite low, sometimes less than 10%. This problem was traced to the loading of the resin. Because loading and cyclization are both base promoted, a significant fraction of **2** was being lost from the resin during the loading step. At room temperature, both reactions occur at roughly the same rate, meaning that the alcohol is tosylated and quickly cyclized, cleaving it from the resin. Although this means that the polymer-bound tosyl chloride could be used as a solid-phase reagent, the advantages of resin capture chemistry would be lost.

It proved possible to separate the loading step from the cyclization step kinetically. Below 0 °C, tosylation is still fast, while cleavage takes place much more slowly. Using low-temperature loading, we were able to achieve up to 70% capture of alcohol **1** (0.09 M) by tosyl chloride resin.[17] This was assayed by depletion of the alcohol from the resin filtrate (NMR, internal standard). Cleavage of **2** using the optimized conditions from the first study (pyridine/THF, room temperature) gives the oxazoline **3** in 66% yield and very high purity (98% by HPLC). No purification is needed other than filtration and evaporation of solvent.

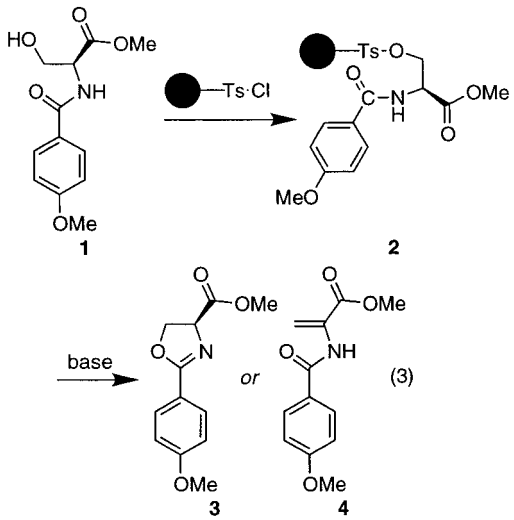
The scope of the reaction was determined using these loading and cleavage conditions.[18] The oxazolines produced from their cognate hydroxyamides are collected in Table 2 and show that significant chemical diversity can be tolerated in the method. It is notable that serine *p*-nitrobenzamide can be converted to **5** in good yield because this substrate should be very prone to elimination, due to the enhanced acidity of the α-proton as compared to **1**, as well as reduced electron density at the carbonyl oxygen. Steric hindrance at the site of displacement/ring closure inhibits the reaction, as shown by low efficiency in the production of **6** and the selective generation of **11** (without a trace of oxazoline from closure

Table 2



at the benzylic position). The conversion of the Z-Ala-Ser-OMe dipeptide to oxazoline **10** is significant, as the conversion of serine and threonine dipeptides to oxazolines has been important in the synthesis of several marine natural products.[19] It was established by chiral HPLC that no racemization is observed in the conversion of the L-serine amide to **3**.[20] The method can also be applied to γ-hydroxyamides to produce oxazines, as shown by **9**. As expected for a ring-forming release method, generally high purities are observed for the reaction products.

The examples in Table 2 do not exploit the resin capture purification method that was the ultimate goal of this work. The plan was to N-acylate amino alcohols with activated acid derivatives in solution and subsequently load the crude product onto the tosyl chloride resin. Base-promoted cleavage should release only the target from the resin (eq 3). The



examples in Figure 1 demonstrate this reaction with four

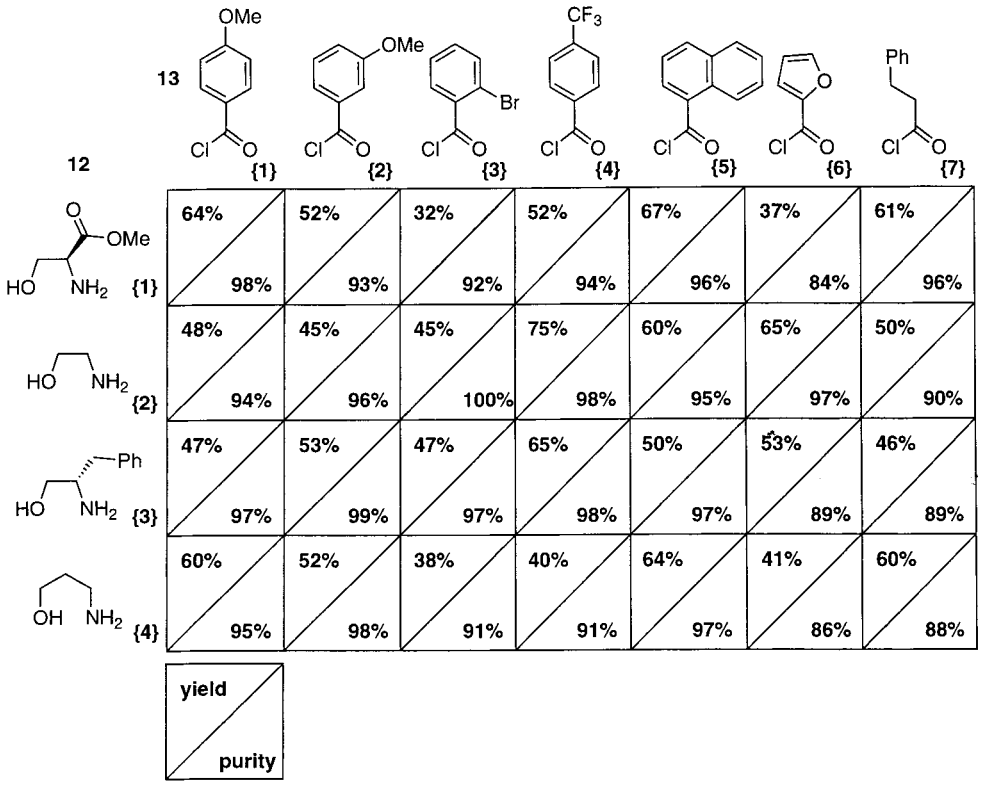


Figure 1. A library of 28 N,O-heterocycles was prepared in an average yield of 52% and average crude HPLC purity of 94%.

amino alcohols **12**{*1*−*4*} and seven acid chlorides **13**{*1*−7}. Very reliable results are obtained using diverse amino alcohols containing alkyl and electron-withdrawing groups. A variety of aromatic, heteroaromatic, and alkyl acid chlorides are tolerated as well. The average overall yield in the preparation of these 28 compounds is 52%. The average purity (determined by HPLC) of the products is 94%.

Discussion

The reaction sequence developed in this work should be a useful tool in the solid-phase or solution-phase synthesis of oxazoline-containing products. The resin capture purification aspect of this reaction makes it particularly useful in multistep solution-phase parallel syntheses. Since Reitz has shown that polymer-bound tosylates are stable to a wide variety of reaction conditions including Suzuki couplings, reductive aminations, and acylations,[21] it may be possible to use a resin-bound tosylate in a multistep solid-phase synthesis ending with an acylation and ring-forming cleavage reaction to form an oxazoline. Analogous ring-forming cleavage reactions can be envisioned to make other three-, five-, and six-membered heterocycles such as aziridines, epoxides, tetrahydrothiophenes, and tetrahydrofurans. Some of these reactions are being further investigated in our labs.

Experimental Section

General. (Polystyrene)tosyl chloride resin was obtained from Argonaut Technology, lot numbers 00864 and 00531. THF for the cleavage reaction was inhibited with 50 ppm BHT.[22] HPLC analysis was performed with a Hewlett-Packard series 1100 HPLC using an Econosphere C18 5U column (4.6 × 250 mm).[23] NMR analysis was performed using a Varian INOVA 300 MHz instrument. GCMS analysis was performed on an HP 5988A using chemical ionization (NH_3).

Methyl *N*-(4-Methoxybenzoyl)serinate (1). *p*-Anisic acid (24 mmol, 3.65 g), L-serine methyl ester hydrochloride (24 mmol, 3.73 g), EDC (26.4 mmol, 5.06 g), and *N*-methyl morpholine (24 mmol, 2.64 mL) were stirred for 2 days in CH_2Cl_2. The solution was washed with saturated sodium bicarbonate, 5% citric acid, and brine. The solution was dried over $MgSO_4$, filtered, and evaporated to give 4.35 g of white solid (71%). ^{1}H NMR ($CDCl_3$) δ 7.81 (2H, d, J = 9 Hz), 6.97 (1H, bs, J = 7.5 Hz), 6.94 (2H, d, J = 9 Hz), 4.87 (1H, dt, J = 6.9, 3.6 Hz), 4.06 (2H, d, J = 3.6 Hz), 3.86 (3H, s), 3.84 (3H, s). GCMS (M + H): 254.

Resin 2. Alcohol **1** (0.323 mmol, 87 mg) was dissolved in 3.5 mL of freshly distilled pyridine. The solution was slowly added to a peptide synthesis vessel containing 0.4 g (0.97 mmol) of **(**polystyrene)tosyl chloride resin. After allowing the resin to swell for 3 min, the vessel was sealed and placed in a freezer (−15 °C) for 48 h. The resin was washed twice with CH_2Cl_2:MeOH (1:1), three times with DMSO, and four times with CH_2Cl_2:MeOH (1:1).

Methyl 2-(4-Methoxyphenyl)-4,5-dihydro-oxazole-4-carboxylate (3). Resin **2** was shaken at room temperature for 24 h in THF:pyridine (10:1). The resin was filtered and washed twice with CH_2Cl_2:MeOH (1:1). The filtrate was evaporated to give 50 mg (66%) of a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 9 Hz), 6.90 (2H, d, J = 9 Hz), 4.92 (1H, dd, J = 7.8, 10.5 Hz), 4.66 (1H, dd, J = 8.1, 8.7 Hz), 4.56 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s), 3.81 (3H, s). GCMS (M + H): 236.

Methyl *N*-(4-Methoxybenzoyl)dehydroalaninate (4). This compound is isolated when resin **2** is shaken with 10:1 Et_3N:CH_2Cl_2. ^1H NMR ($CDCl_3$) δ 8.46 (1H, bs), 7.80 (2H, d, J = 9 Hz), 6.95 (2H, d, J = 9 Hz), 6.76 (1H, d, J = 1.2 Hz), 5.95 (1H, d, J = 1.2 Hz), 3.88 (3H, s), 3.86 (3H, s). GCMS (M + H): 236.

Methyl *N*-(4-Nitrobenzoyl)serinate. This compound was made analogously to compound **1**. Yield: 71%. ^1H NMR ($CDCl_3$) δ 8.31 (2H, d, J = 8.7 Hz), 8.01 (2H, d, J = 8.4 Hz), 7.13 (1H, bd, J = 5.7 Hz), 4.89 (1H, dt, J = 7.2, 3.6 Hz), 4.20−4.04 (2H, m), 3.86 (3H, s), 2.19 (1H, bt, J = 6 Hz). GCMS (M + H): 269.

Methyl 2-(4-Nitrophenyl)-4,5-dihydro-oxazole-4-carboxylate (5). This compound was made analogously to compound **3**. Yield: 65%. ^1H NMR ($CDCl_3$) δ 8.26 (2H, d, J = 9 Hz), 8.17 (2H, d, J = 9 Hz), 5.01 (1H, dd, J = 8.4, 10.8 Hz), 4.77 (1H, dd, J = 8.1, 8.7 Hz), 4.66 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s). GCMS (M + H): 269.

Methyl 2-Phenyl-4,5-dihydro-5-methyl-oxazole-4-carboxylate (6). This compound was made analogously to compound **3**, giving 26 mg (36%) of a dark oil. ^1H NMR ($CDCl_3$) δ 8.01−7.97 (2H, m), 7.50−7.41 (3H, m), 5.08−5.01 (1H, m), 5.00 (1H, d, J = 10.2 Hz), 3.78 (3H, s), 1.41 (3H, t, J = 7.5 Hz). GCMS (M + H): 220.

2-(2-Hydroxyphenyl)-4,5-dihydro-oxazole (7). This compound was made analogously to compound **3** with the exception of the cleavage, which was performed in THF:EtOH:Et_3N (8:1:1), giving 74 mg (47%) of a white solid. ^1H NMR ($CDCl_3$) δ 12.17 (1H, bs), 7.65 (1H, dd, J = 1.5, 7.8 Hz), 7.36 (1H, dt, J = 1.5, 7.5 Hz), 7.00 (1H, d, J = 8.1 Hz), 6.87 (1H, t, J = 7.2 Hz), 4.43 (2H, t, J = 9.3 Hz), 4.10 (2H, t, J = 9.3 Hz). GCMS (M + H): 164.

2-(4-Pyridyl)-4,5-dihydro-oxazole (8). This compound was made analogously to compound **3** with the exception of the cleavage, which was performed in THF:EtOH:Et_3N (8:1:1), giving 42 mg (87%) of a white solid. ^1H NMR ($CDCl_3$) δ 8.70 (2H, d, J = 4.5 Hz), 7.77 (2H, d, J = 4.5 Hz), 4.47 (2H, t, J = 9.6 Hz), 4.09 (2H, t, J = 9.9 Hz). GCMS (M + H): 149.

***N*-(4-Methoxybenzoyl)-3-amino-1-propanol.** This compound was made analogously to compound **1**. Yield: 35%. ^1H NMR ($CDCl_3$) δ 7.73 (2H, d, J = 8.7 Hz), 6.90 (2H, d, J = 8.7 Hz), 6.75 (1H, bs), 3.84 (3H, s), 3.70 (2H, t, J = 5.1 Hz), 3.61 (2H, q, J = 6 Hz), 3.45 (1H, bs), 1.81−1.74 (2H, m). GCMS (M + H): 210.

2-(4-Methoxyphenyl)-5,6-dihydro-4*H*-[1,3]-oxazine (9). *N*-(4-Methoxybenzoyl)-3-amino-1-propanol (0.323 mmol) was dissolved in 4 mL of 1:1 pyridine/CH_2Cl_2. The solution was slowly added to a peptide vessel containing 0.4 g (0.97 mmol) of polystyrene-bound tosyl chloride. The vessel was then sealed and shaken for 1 h at room temperature. The resin was filtered and washed twice with CH_2Cl_2:MeOH (1:1), three times with DMSO, and four times with CH_2Cl_2:MeOH (1:1). The resin was treated with 10 mL of THF:EtOH:Et_3N (8:1:1) and shaken at room temperature for 24 h. The resin was filtered and washed twice with CH_2Cl_2:MeOH (1:1). The filtrate was evaporated to give 42 mg (68%) of **9** as a clear oil. ^1H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 9 Hz), 6.90 (2H, d, J = 9 Hz), 4.92 (1H, dd, J = 7.8, 10.5 Hz), 4.66 (1H, dd, J = 8.1, 8.7 Hz), 4.56 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s), 3.81(3H, s). GCMS (M + H): 192.

Methyl 2-(*N*-(Benzyloxycarbonyl)-1-aminoethyl)-4,5-dihydro-oxazole-4-carboxylate (10). This compound was made analogously to compound **3**, giving 54 mg (55%) of an oil. ^1H NMR ($CDCl_3$) δ 7.38−7.26 (5H, m), 5.48 (1H, bd, J = 9 Hz), 5.12 (1H, d, J = 12.3 Hz), 5.09 (1H, d, J = 12.3 Hz), 4.75 (1H, t, J = 8.4 Hz), 4.58−4.44 (3H, m), 3.78 (3H, s), 1.44 (3H, d, J = 6.9 Hz). GCMS (M + H): 307.

2-Dichloromethyl-4-[(4-methanesulfonyl-phenyl)-methanol]-4,5-dihydro-oxazole (11). This compound was made analogously to compound **3** with the exception of the cleavage, which was performed in THF:EtOH:Et_3N (8:1:1), giving 24 mg (22%) of an oil. ^1H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.4 Hz), 6.21 (1H, s), 4.82 (1H, d, J = 5.7 Hz), 4.61−4.54 (1H, m), 4.40 (1H, dt, 20.1, 8.7 Hz), 3.03 (3H, s). GCMS (M + H): 338.

General Procedures for the Synthesis of Compounds in Table 2. 14{*1,1*−*7*}. Amino alcohol **12**{*1*} (HCl salt, 0.323 mmol) and Et_3N (0.84 mmol, 118 μL) were stirred in 5 mL of CH_2Cl_2. Acid chloride **13**{*1*−*7*} (0.36 mmol) was added, and the solution was stirred for 3 h. The solvent was removed. The crude mixture was loaded and cleaved from the resin in the same manner as compound **1** to give the desired oxazoline products.

14{*2,1*−*7*}. Amino alcohol **12**{*2*} (0.323 mmol) and Et_3N (0.42 mmol, 59 μL) were stirred in 5 mL of CH_2Cl_2. Acid chloride **13**{*1*−*7*} (0.36 mmol) was added, and the solution was stirred for 3 h. The solvent was removed. The crude mixture was loaded and cleaved from the resin in the same manner as compound **8** to give the desired oxazoline products.

14{*3,1*−*7*}. Amino alcohol **12**{*3*} (0.323 mmol) and Et_3N (0.42 mmol, 59 μL) were stirred in 5 mL of CH_2Cl_2. Acid chloride **13**{*1*−*7*} (0.36 mmol) was added, and the solution was stirred for 3 h. The solvent was removed. The crude product was loaded onto the resin in 3.5 mL of 25% Et_3N in CH_2Cl_2 at −15 °C for 1.5 h. After washing the resin as previously described, the product was cleaved from the resin by shaking for 24 h at room temperature in 10% Et_3N in THF. The resin was filtered and washed twice with CH_2Cl_2:MeOH (1:1). The filtrate was evaporated to give the desired oxazoline products.

14{*4,1*−*7*}. Amino alcohol **12**{*4*} (0.323 mmol) and Et_3N (0.42 mmol, 59 μL) were stirred in 5 mL of CH_2Cl_2. Acid chloride **13**{*1*−*7*} (0.36 mmol) was added, and the solution was stirred for 3 h. The solvent was removed. The crude mixture was loaded and cleaved from the resin in the same manner as compound **9** to give the desired 1,3-oxazine products.

Spectral Data for 14{*1*−*4,1*−*7*}. Methyl 2-(4-Methoxy-phenyl)-4,5-dihydro-oxazole-4-carboxylate (14{*1,1*}). ^1H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 9 Hz), 6.90 (2H, d, J = 9 Hz), 4.92 (1H, J = 7.8, dd, 10.5 Hz), 4.66 (1H, dd, J = 8.1, 8.7 Hz), 4.56 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s), 3.81(3H, s). GCMS (M + H): 236.

Methyl 2-(3-Methoxy-phenyl)-4,5-dihydro-oxazole-4-carboxylate (14{*1,2*}). ^1H NMR ($CDCl_3$) δ 7.57−7.50 (2H,

m), 7.29 (1H, dd, J = 8.1, 15.9 Hz), 7.04 (1H, dd, J = 2.7, 8.1 Hz), 4.95 (1H, dd, J = 7.8, 10.5 Hz), 4.69 (1H, t, J = 8.7 Hz), 4.59 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s), 3.82 (3H, s). GCMS (M + H): 236.

Methyl 2-(2-Bromo-phenyl)-4,5-dihydro-oxazole-4-carboxylate (14{*1,3*}). ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, dd, J = 6.9, 2.4 Hz), 7.64 (1H, dd, J = 6.9, 1.5 Hz), 7.37−2.76 (2H, m), 5.00 (1H, dd, J = 8.1, 10.5 Hz), 4.73 (1H, t, J = 8.7 Hz), 4.63 (1H, dd, J = 8.7, 10.8 Hz), 3.83 (3H, s). GCMS (M + H): 284.

Methyl 2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-oxazole-4-carboxylate (14{*1,4*}). ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, s), 8.17 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J = 7.2 Hz), 7.55 (1H, t, J = 7.2 Hz), 4.99 (1H, dd, J = 7.8, 10.5 Hz), 4.75 (1H, t, J = 8.4 Hz), 4.64 (1H, dd, J = 8.4, 10.2 Hz), 3.84 (3H, s). GCMS (M + H): 274.

Methyl 2-Naphthalen-1-yl-4,5-dihydro-oxazole-4-carboxylate (14{*1,5*}). ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, s), 8.05 (1H, dd, J = 1.8, 8.7 Hz), 7.92−7.85 (3H, m), 7.57−7.50 (2H, m), 5.02 (1H, dd, J = 8.1, 10.5 Hz), 4.76 (1H, dd, J = 8.1, 8.7 Hz), 4.66 (1H, dd, J = 8.7, 10.5 Hz), 3.84 (3H, s). GCMS (M + H): 256.

Methyl 2-Furan-2-yl-4,5-dihydro-oxazole-4-carboxylate (14{*1,6*}). ^{1}H NMR ($CDCl_3$) δ 7.55 (1H, dd, J = 0.6, 1.8 Hz), 7.03 (1H, dd, J = 0.6, 3.3 Hz), 6.49 (1H, dd, J = 1.8, 3.6 Hz), 4.94 (1H, dd, J = 7.8, 10.5 Hz), 4.67 (1H, dd, J = 7.8, 8.7 Hz), 4.56 (1H, dd, J = 8.7, 10.5 Hz), 3.80 (3H, s). GCMS (M + H): 196.

Methyl 2-Phenethyl-4,5-dihydro-oxazole-4-carboxylate (14{*1,7*}). ^{1}H NMR ($CDCl_3$) δ 7.31−7.17 (5H, m), 4.73 (1H, dd, J = 7.8, 10.8 Hz), 4.50 (1H, t, J = 8.7 Hz), 4.39 (1H, dd, J = 8.7, 10.5 Hz), 3.78 (3H, s), 2.98 (2H, t, J = 6.9 Hz), 2.64 (2H, t, J = 6.9 Hz). GCMS (M + H): 234.

2-(4-Methoxy-phenyl)-4,5-dihydro-oxazole (14{*2,1*}). ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, J = 6.9 Hz), 6.91 (2H, d, J = 6.9 Hz), 4.41 (2H, t, J = 9.3 Hz), 4.03 (2H, t, J = 9.3 Hz), 3.84 (3H, s). GCMS (M + H): 178.

2-(3-Methoxy-phenyl)-4,5-dihydro-oxazole (14{*2,2*}). ^{1}H NMR ($CDCl_3$) δ 7.54−7.48 (2H, m), 7.30 (1H, dd, J = 8.4, 15.9 Hz), 7.02 (1H, dd, J = 2.4, 8.1 Hz), 4.44 (2H, t, J = 9.3 Hz), 4.06 (2H, t, J = 9.3 Hz), 3.84 (3H, s). GCMS (M + H): 178.

2-(2-Bromo-phenyl)-4,5-dihydro-oxazole (14{*2,3*}). ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, dd, J = 1.5, 7.5 Hz), 7.65 (1H, dd, J = 1.5, 7.5 Hz), 7.37−7.25 (2H, m), 4.45 (2H, t, J = 9.6 Hz), 4.12 (2H, t, J = 9.6 Hz). GCMS (M + H): 226.

2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-oxazole (14{*2,4*}). ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, s), 8.12 (1H, d, J = 7.8 Hz), 7.72 (1H, d, J = 7.8 Hz), 7.54 (1H, t, J = 7.8 Hz), 4.47 (2H, t, J = 9.6 Hz), 4.09 (2H, t, J = 9.6 Hz). GCMS (M + H): 216.

2-Naphthalen-1-yl-4,5-dihydro-oxazole (14{*2,5*}). ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, s), 8.04 (1H, dd, J = 1.8, 8.7 Hz), 7.92−7.85 (3H, m), 7.57−7.49 (2H, m), 4.50 (2H, t, J = 9.6 Hz), 4.13 (2H, t, J = 9.3 Hz). GCMS (M + H): 198.

2-Furan-2-yl-4,5-dihydro-oxazole (14{*2,6*}). ^{1}H NMR ($CDCl_3$) δ 7.54 (1H, dd, J = 1.2, 1.8 Hz), 6.95 (1H, d, J = 3 Hz), 6.48 (1H, dd, J = 1.8, 3.3 Hz), 4.41 (2H, t, J = 9.3 Hz), 4.06 (2H, t, J = 9.3 Hz). GCMS (M + H): 138.

2-Phenethyl-4,5-dihydro-oxazole (14{*2,7*}). ^{1}H NMR ($CDCl_3$) δ 7.31−7.19 (5H, m), 4.23 (2H, t, J = 9.6 Hz), 3.83 (2H, t, J = 9.3 Hz), 2.96 (2H, t, J = 8.1 Hz), 2.59 (2H, t, J = 8.1 Hz). GCMS (M + H): 176.

4-Benzyl-2-(4-methoxy-phenyl)-4,5-dihydro-oxazole (14{*3,1*}). ^{1}H NMR ($CDCl_3$) δ 7.90 (2H, d, J = 9 Hz), 7.33−7.20 (5H, m), 6.91 (2H, d, J = 9 Hz), 4.61−4.49 (1H, m), 4.32 (1H, t, J = 8.7 Hz), 4.12 (1H, dd, J = 7.2, 8.4 Hz), 3.85 (3H, s), 3.25 (1H, dd, J = 4.8, 13.8 Hz), 2.72 (1H, dd, J = 9, 13.5 Hz). GCMS (M + H): 268.

4-Benzyl-2-(3-methoxy-phenyl)-4,5-dihydro-oxazole (14{*3,2*}). ^{1}H NMR ($CDCl_3$) δ 7.53 (1H, dt, J = 8.1, 1.5 Hz), 7.48 (1H, dd, J = 1.5, 2.4 Hz), 7.35−7.20 (6H, m), 7.03 (1H, ddd, J = 1.2, 2.4, 8.1 Hz), 4.64−4.53 (1H, m), 4.35 (1H, dd, J = 8.4, 9.3 Hz), 4.14 (1H, dd, J = 7.5, 8.4 Hz), 3.85 (3H, s), 3.26 (3H, s), 3.26 (1H, dd, J = 5.1, 13.8 Hz), 2.73 (1H, dd, J = 9. 13.5 Hz). GCMS (M + H): 268.

4-Benzyl-2-(2-bromo-phenyl)-4,5-dihydro-oxazole (14{*3,3*}). ^{1}H NMR ($CDCl_3$) δ 7.67−7.62 (2H, m), 7.37−7.23 (7H, m), 4.69−4.60 (1H, m), 4.38 (1H, dd, J = 8.4, 9 Hz), 4.18 (1H, dd, J = 7.5, 8.4 Hz), 3.25 (1H, dd, J = 5.1, 13.8 Hz), 2.81 (1H, dd, J = 8.4, 13.8 Hz). GCMS (M + H): 316.

4-Benzyl-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-oxazole (14{*3,4*}). ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, s), 8.13 (1H, d, J = 7.8 Hz), 7.73 (1H, d, J = 7.8 Hz), 7.54 (1H, t, J = 7.8 Hz), 7.35−7.20 (5H, m), 4.67−4.57 (1H, m), 4.39 (1H, dd, J = 8.7, 9.3 Hz), 4.18 (1H, dd, J = 7.8, 8.7 Hz), 3.25 (1H, dd, J = 5.1, 13.8 Hz), 2.76 (1H, dd, J = 8.7, 13.8 Hz). GCMS (M + H): 306.

4-Benzyl-2-naphthalen-1-yl-4,5-dihydro-oxazole (14{*3,5*}). ^{1}H NMR ($CDCl_3$) δ 8.45 (1H, s), 8.06 (1H, dd, J = 1.5, 8.4 Hz), 7.93−7.85 (3H, m), 7.58 (2H, m), 7.35−7.24 (5H, m), 4.71−4.61 (1H, m), 4.43 (1H, t, J = 8.4 Hz), 4.22 (1H, dd, J = 7.5, 8.4 Hz), 3.31 (1H, dd, J = 5.1, 13.8 Hz), 2.80 (1H, dd, J = 8.7, 13.8 Hz). GCMS (M + H): 288.

4-Benzyl-2-furan-2-yl-4,5-dihydro-oxazole (14{*3,6*}). ^{1}H NMR ($CDCl_3$) δ 7.55 (1H, dd, J = 0.9, 1.8 Hz), 7.31−7.23 (5H, m), 6.97 (1H, d, J = 3.3 Hz), 6.50−6.48 (1H, m), 4.65−4.55 (1H, m), 4.33 (1H, t, J = 8.4 Hz), 4.12 (1H, t, J = 8.4 Hz), 3.28 (1H, dd, J = 4.8, 13.8 Hz), 2.73 (1H, dd, J = 9, 13.8 Hz). GCMS (M + H): 228.

4-Benzyl-2-phenethyl-4,5-dihydro-oxazole (14{*3,7*}). ^{1}H NMR ($CDCl_3$) δ 7.38−7.17 (10H, m), 4.42−4.32 (1H, m), 4.17 (1H, t, J = 8.4 Hz), 3.95 (1H, dd, J = 6.9, 8.4 Hz), 3.07 (1H, dd, J = 5.1, 13.5 Hz), 2.96 (2H, t, J = 7.5 Hz), 2.65−2.55 (3H, m). GCMS (M + H): 266.

2-(4-Methoxy-phenyl)-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,1*}). ^{1}H NMR ($CDCl_3$) δ 7.85 (2H, d, J = 9.3 Hz), 6.87 (2H, d, J = 9.3 Hz), 4.35 (2H, t, J = 5.4 Hz), 3.82 (3H, s), 3.59 (2H, t, J = 5.7 Hz), 1.98 (2H, quintet, J = 5.7 Hz). GCMS (M + H): 192.

2-(3-Methoxy-phenyl)-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,2*}). ^{1}H NMR ($CDCl_3$) δ 7.49−7.44 (2H, m), 7.26 (1H, t, J = 7.8 Hz), 6.96 (1H, ddd, J = 0.9, 2.7, 8.1 Hz), 4.36 (2H, t, J = 5.4 Hz), 3.83 (3H, s), 3.61 (2H, t, J = 5.7 Hz), 1.98 (2H, quintet, J = 5.7 Hz). GCMS (M + H): 192.

2-(2-Bromo-phenyl)-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,3*}). ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, dd, J = 1.2, 8.1 Hz), 7.47 (1H, dd, J = 2.1, 7.5 Hz), 7.30 (1H, dt, J = 1.5, 7.5

Hz), 7.21 (1H, ddd, $J = 1.8$, 7.2, 8.1 Hz), 4.37 (2H, t, $J = 5.7$ Hz), 3.61 (2H, t, $J = 6$ Hz), 2.03 (2H, quintet, $J = 5.7$ Hz). GCMS (M + H): 240.

2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,4*}). ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, s), 8.08 (1H, d, $J = 7.8$ Hz), 7.65 (1H, d, $J = 9$ Hz), 7.47 (1H, t, $J = 8.1$ Hz), 4.39 (2H, t, $J = 5.4$ Hz), 3.63 (2H, t, $J = 5.7$ Hz), 2.00 (2H, quintet, $J = 5.7$ Hz). GCMS (M + H): 230.

2-Naphthalen-1-yl-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,5*}). ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, s), 8.02 (1H, dd, $J =$ 1.8. 8.7 Hz), 7.83−7.81 (3H, m), 7.51−7.48 (2H, m), 4.43 (2H, t, $J = 5.7$ Hz), 3.68 (2H, t, $J = 6$ Hz), 2.03 (2H, quintet, $J = 5.7$ Hz). GCMS (M + H): 212.

2-Furan-2-yl-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,6*}). ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, dd, $J = 0.9$, 1.8 Hz), 6.80 (1H, d, $J = 3.6$ Hz), 6.42 (1H, dd, $J = 1.8$, 3.6 Hz), 4.32 (2H, t, $J = 5.4$ Hz), 3.59 (2H, t, $J = 5.7$ Hz), 1.99 (2H, quintet, $J = 5.7$ Hz). GCMS (M + H): 152.

2-Phenethyl-5,6-dihydro-4*H*-[1,3]oxazine (14{*4,7*}). ^{1}H NMR ($CDCl_3$) δ 7.33−7.18 (5H, m), 4.14 (2H, t, $J = 5.7$ Hz), 3.35 (2H, t, $J = 5.7$ Hz), 2.89 (2H, t, $J = 8.4$ Hz), 2.44 (2H, t, $J = 8.4$ Hz), 1.85 (2H, quintet, $J = 5.7$ Hz). GCMS (M + H): 190.

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