Chapter 12

Synthesis and Properties of Oxazole Heterocycles

Communication.

In our search to develop new DNA recognition elements, a variety of heterocyclic ring systems have been synthesized.[1-4] Yet, due to unanticipated electronic properties, these ring systems have not been successfully incorporated into existing polyamide/oligomer technology. Of particular interest is the series of oxazole isomers: O-oxazole (**Oo**), N-oxazole (**No**), and hydroxyisoxazole (**Hi**). **Oo** and **No** were envisioned to be formal imidazole (**Im**) mimics, by placing a long pair of electrons to the DNA minor groove.[5] **Hi** was envisioned to be a hydroxypyrrole (**Hp**) mimic, projecting

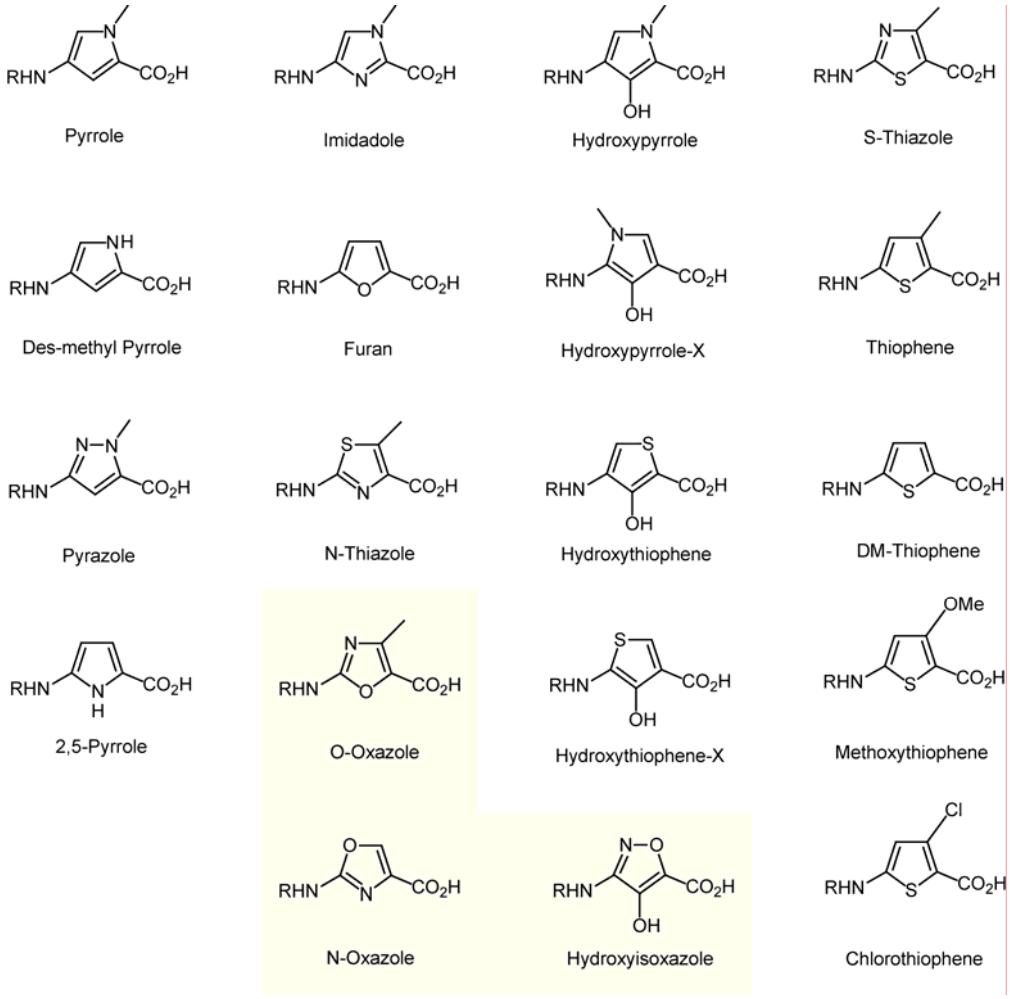


Figure 12.1. Library of synthesized 5-membered heterocyclic carboxamides. O-Oxazole (Oo), N-Oxazole (No) and Hydroxyisoxazole (Hi) are shaded.

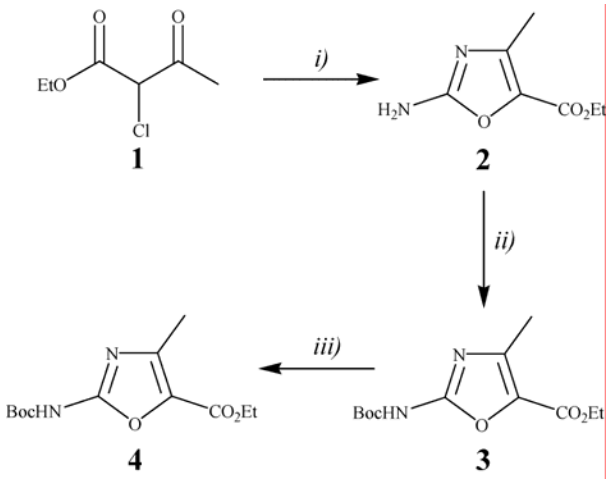


Figure 12.2. O-Oxazole synthesis. i) CON_2H_4, EtOH, reflux; ii) $(Boc)_2O$, DMF, DIEA, DMAP, 40 °C; iii) 1N NaOH, MeOH, 35 °C.

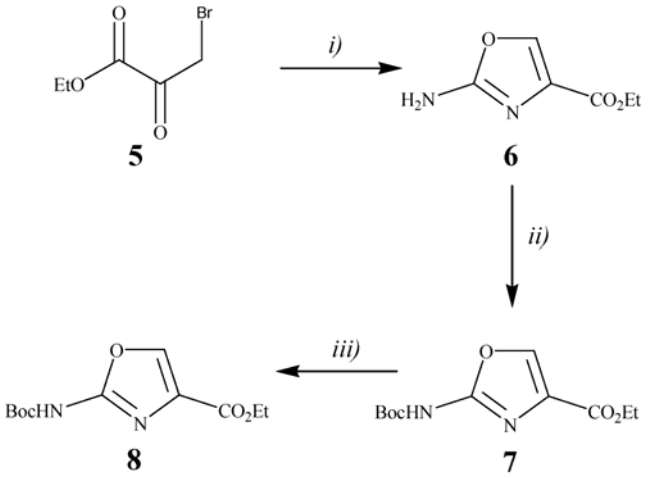


Figure 12.3. N-Oxazole synthesis. i) CON_2H_4, EtOH, reflux; ii) $(Boc)_2O$, DMF, DIEA, DMAP, 40 °C; iii) 1N NaOH, MeOH, 35 °C.

the exocyclic hydroxyl group into the asymmetric T●A base pair cleft.[6, 7]

Heterocycle Synthesis.

O-Oxazole (Oo). (**1**) was refluxed with urea in ethanol to cyclize directly to the amino-ester (**2**). Boc-protection of (**2**) was accomplished using a mixture of Boc-anhydride and DMAP. Due to the poor nucleophilicity of the aryl amine, DMAP is absolutely necessary for the acylation to occur. Saponification was accomplished with sodium hydroxide to provide the final monomeric unit (**4**) (Figure 12.2).

N-Oxazole (No). Ethyl bromopyruvate (**5**) was condensed with urea in ethanol at reflux to provide (**6**). Boc-protection followed by saponification gave (**8**). Similar to the O-oxazole system, the aryl amine of N-oxazole is also a very

poor nucleophile, necessitating the use of DMAP as a trans-acylation catalyst (Figure 12.3).

Oxazole Fragmentation.

After several attempts at incorporating oxazole compounds **Oo** and **No** into polyamides using solid phase synthesis protocols,[8] it was determined that both oxazole compounds were susceptible to nucleophilic fragmentation. The conditions that are normally used for cleaving polyamides from resin involve the use of highly nucleophilic reagents such as dimethylaminopropylamine (Dp) at elevated temperatures. These conditions are not compatible with the oxazole heterocycles. It seems that the majority of

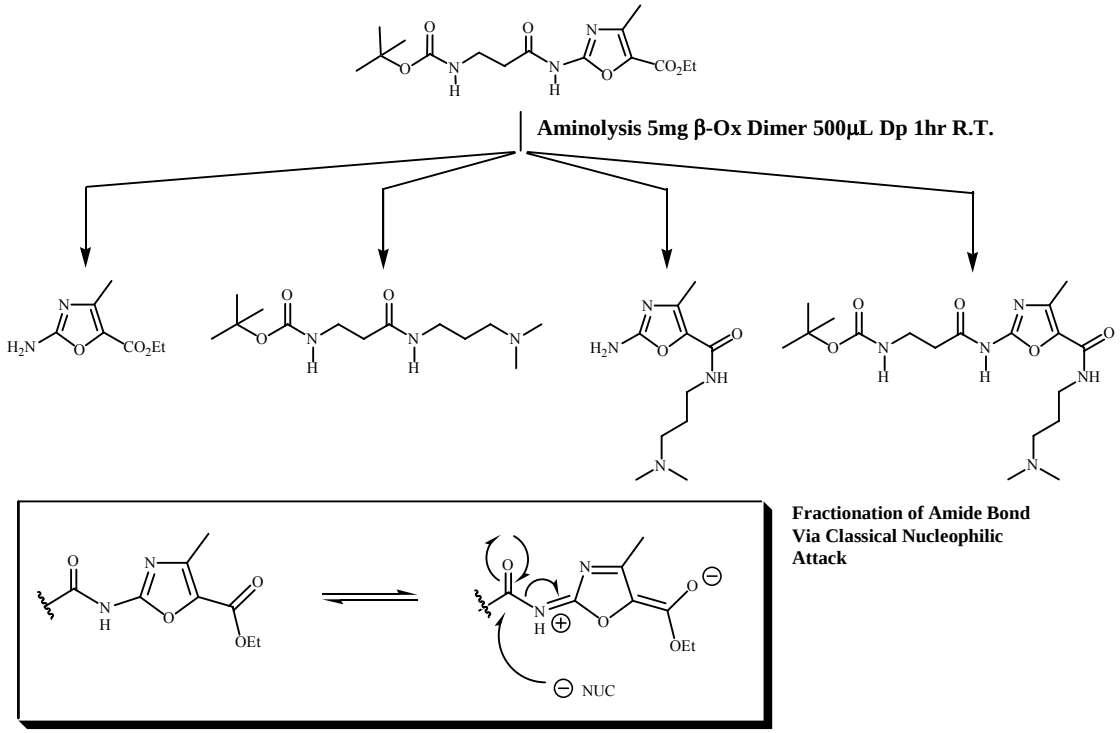


Figure 12.4. Nucleophilic induced fragmentation of the oxazole carboxamide bond.

electron density from the aryl amine is delocalized into the oxazole ring, making the amide carbonyl susceptible to nucleophilic attack. To determine the mechanism of the degradation, Boc-β-alanine-oxazole (Boc-**β**-**Oo**-OH and Boc-**β**-**No**-OH) dimers were

synthesized using the symmetrical anhydride of Boc-β-Ala and DMAP as a transacylation catalyst. Protocols for generating and using the symmetric anhydrides

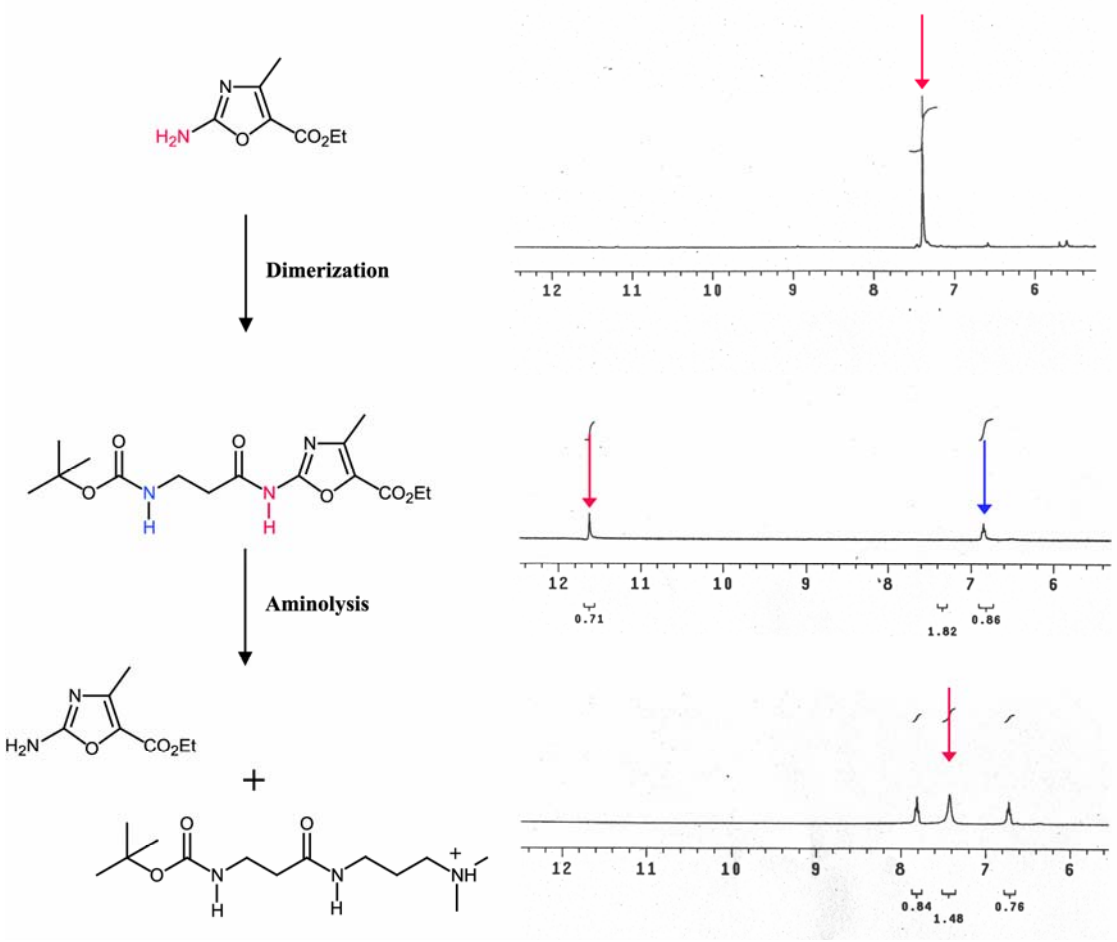
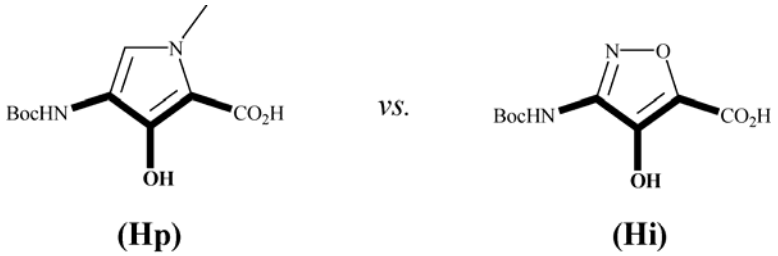


Figure 12.5. Determination of oxazole decomposition by H^1 NMR.

have previously been described.[1] As a test reaction, Boc-**β-Oo**-OH was subjected to aminolysis with dimethylaminopropylamine (Dp) (Figure 12.4). Fragmentation products were characterized using mass spectroscopy and ^{1}H NMR (Figure 12.5).

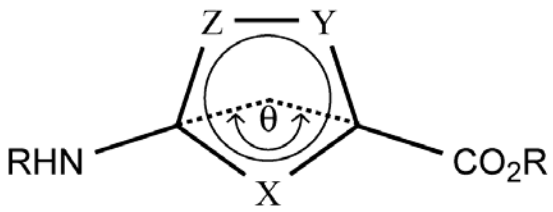
The Search for a Hydroxypyrrole (Hp) Replacement.

While the discovery of the hydroxypyrrole/pyrrole (**Hp**/**Py**) pairing was seminal in the sense that it broke the A,T degeneracy and allowed for the coding of all four Watson-Crick bases,[9, 10] hairpins containing **Hp** bind the DNA with a mildly lower affinity.[6, 11-13] Furthermore, hairpins containing the **Hp** ring systems tend to degrade in mildly acidic aqueous solutions.[3] In an effort to address these issues, a search for hydroxypyrrole mimics was initiated. One of the first synthetic targets proposed was the hydroxyisoxazole (**Hi**) ring system. The **Hi** ring system is able to mimic the recognition face of **Hp**, and present the same atomic composition to the DNA minor groove (Figure 12.6). The **Hi** ring system was also of particular interest due to its substantially different electronic and geometric profile (Figure 12.7). It has previously been demonstrated that Py-Im polyamides are over-curved with respect to the DNA helix, limiting the



(Hp) **(Hi)**

Figure 12.6. Comparison of hydroxypyrrole (Hp) with hydroxyisoxazole (Hi). Recognition face presented to the DNA minor groove is shown in bold.



Ring	X	Y	Z	θ (*degrees*)	Charge on X (*e*)
Fu	O	C-H	C-H	*126*	*-0.31*
Ht	O-H	S	C-H	*133*	*+0.40*
Nh	N-H	C-H	C-H	*136*	*+0.34*
Im	N	N-Me	C-H	*137*	*-0.71*
Ny	N-OH	C-H	C-H	*139*	*+0.51*
Hm	N-OH	N-Me	C-H	*143*	*+0.55*
Py	C-H	N-Me	C-H	*146*	*+0.21*
Hp	O-H	N-Me	C-H	*148*	*+0.50*
Tn	S	C-Me	C-H	*149*	*-0.21*
Pz	C-H	N-Me	N	*151*	*+0.23*
Dt	S	C-H	C-H	*152*	*-0.21*
Th	S	C-Me	N	*153*	*-0.25*
Hi	O-H	O	N	*157*	*+0.49*

Figure 12.7. Geometry and electronics of 5-membered heterocyclic carboxamides. **Hi** is indicated by a shaded box.

contiguous number of Watson-Crick bases that can be coded for.[14] By substitution of the heterocyclic backbone with two small heteroatoms, the overall curvature of the ring system is significantly altered, making the ring much less curved and possibly allowing for the targeting of a longer DNA sequence.[1]

(Hi) Heterocycle Synthesis.

The general synthesis for hydroxyisoxazole is shown in Figure 12.8. A

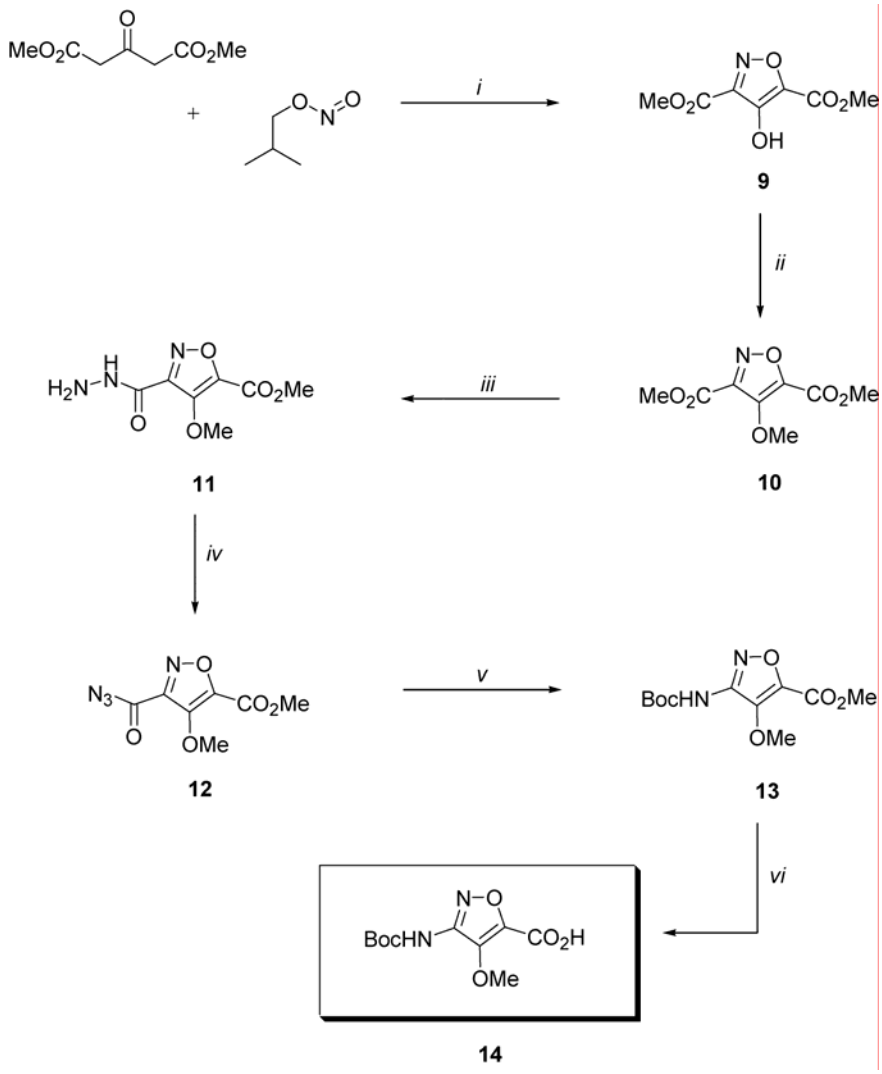


Figure 12.8. Synthesis of **Hi**. i) 2M HCl in Et_2O, pet Et_2O, r.t.; ii) DIEA, DMS, MeOH, Ph; iii) H_4N_2, THF, -40 ^oC; iv) $NaNO_2$ 1N HCl; v) t-BuOH, Ph; vi) 1N NaOH, MeOH

cyclocondensation between 1,3-acetonedicarboxylate and isoamylnitrite afforded the dicarboxy-isoxazole ring system (**9**) in good yield. Protection of the aryl ether was

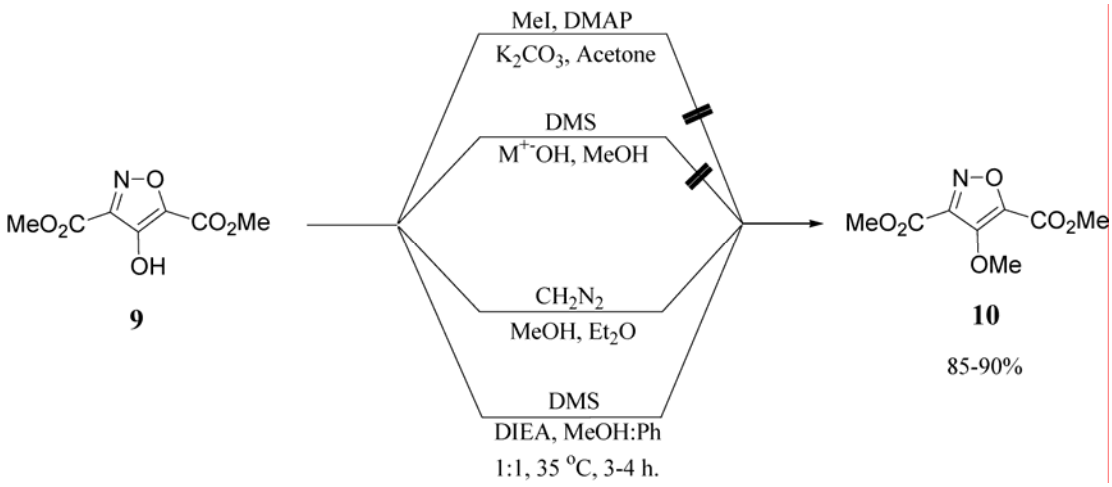


Figure 12.9. Alkylation of hydroxyisoxazole aryl ether.

accomplished using a mixture of DMS and DIEA in methanol and benzene to provide **10**. This system was determined to be more efficient than the commonly employed alkylation mixture of potassium carbonate and methyl iodide (Figure 12.9). Differentiation of the

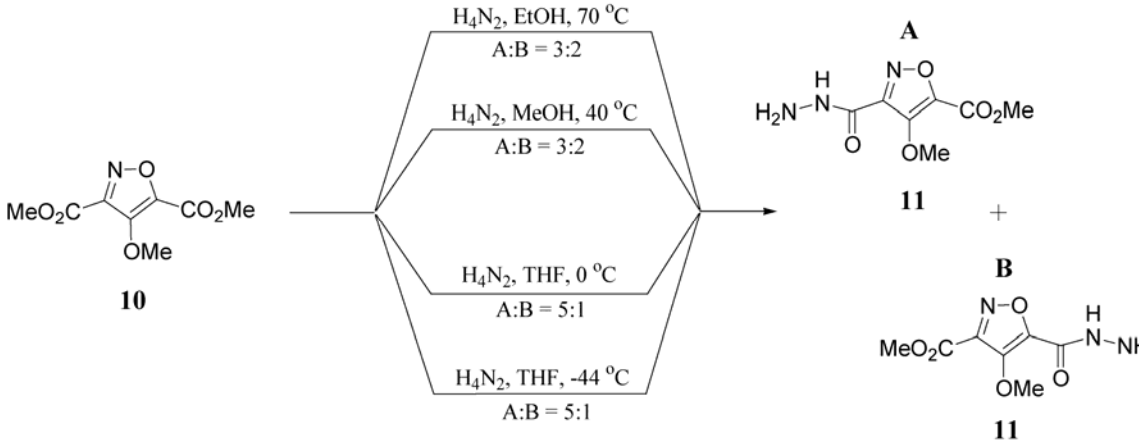


Figure 12.10. Differentiation of carboxy esters using hydrazine at low temperature.

two carboxy esters was difficult but reasonably successful using a mixture of hydrazine and THF at low temperature to give **11** as the major isomer (Figure 12.10). Isomers are

separable by preparatory HPLC at all stages of the synthesis. It is most efficient to remove the isomeric impurity after the last step of the synthesis by HPLC (Figure 12.11). Oxidation of the hydrazine group using sodium nitrite, followed by rearrangement in the presence of t-butanol gave the Boc-protected ester (**13**) cleanly. Saponification of **13** was

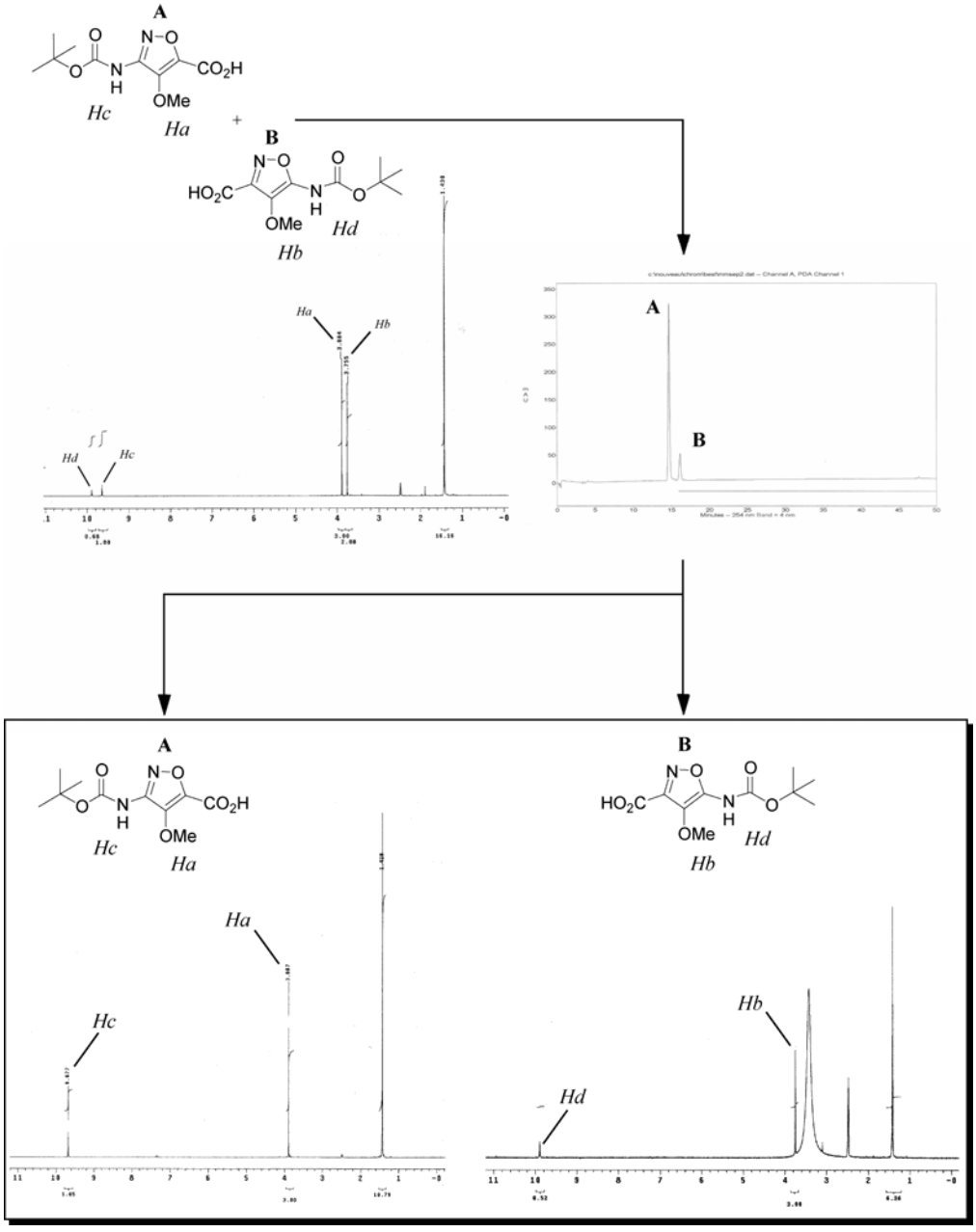


Figure 12.11. Final separation of hydroxyisoxazole (Hi) constitutional isomers.

accomplished using sodium hydroxide and methanol to provide **14**.

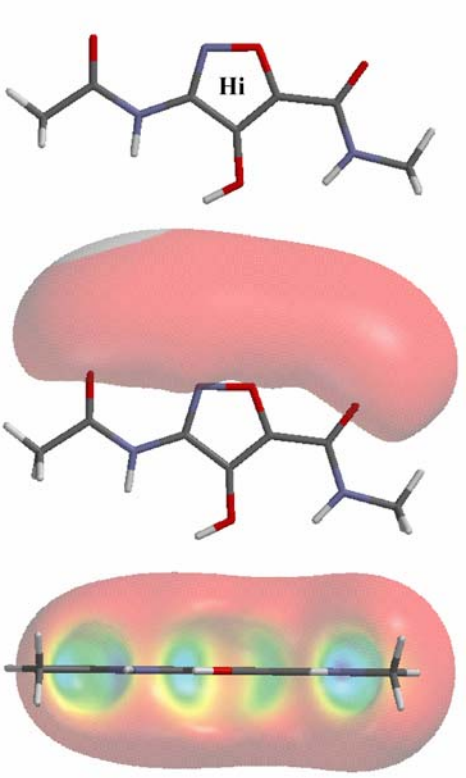


Figure 12.12. Isopotential surface for the hydroxyisoxazole (Hi) ring system. A large negative potential on the backbone of the ring system is indicated in red.

Upon completion of the synthesis and separation of the two constitutional isomers, both ring systems were unsuccessfully incorporated into an 8-ring hairpin structure. Coupling of the **Hi** ring system onto the resin appeared to proceed according to standard protocols. However, coupling further residues onto the **Hi** ring system was unsuccessful. It is likely that the aryl amine of the **Hi** ring system is similar in reactivity to the other oxazoles described (**Oo** and **No**) earlier in this chapter. Fragmentation of the hydroxyisoxazole carboxamide bond is also a likely possibility. Finally, molecular modeling of the **Hi** ring system electronic structure indicated a large negative isopotential surface on the back side of the ring system (Figure 12.12). The large electron cloud, resulting from the nitrogen and oxygen lone pair electrons would likely have destabilizing electronic interactions with the negatively charged phosphate backbone of the DNA, resulting in an unfavorable recognition profile. It has previously been shown that negatively charged groups on the backbone of the heterocycle can result in markedly lower affinities.[1, 15]

Experimental.

General. N,N-dimethylformamide (DMF), N,N-diisopropylethylamine (DIEA), thiophenol (PhSH), N,N-diethylamine, N,N-dimethylaminopropylamine (Dp), Triethylamine (TEA), and ethyl bromopyruvate were purchased from Aldrich. Compound **1** was purchased from Fluka. Boc-β-alanine-(4-carbonylaminomethyl)-benzyl-ester-copoly(styrene-divinylbenzene)resin (Boc-β-Pam-resin), dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBt), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N,N-dimethylaminopyridine (DMAP), and Boc-β-alanine were purchased from NOVA Biochem. Trifluoroacetic acid (TFA) was purchased from Halocarbon. All other solvents were reagent grade from EM. All reagents were used without further purification.

NMR spectra were recorded on a Varian spectrometer at 300 MHz in DMSO-*d6* or $CDCl_3$ with chemical shifts reported in parts per million relative to residual solvent. UV spectra were measured on a Hewlett-Packard Model 8452A diode array spectrophotometer. High resolution FAB and EI mass spectra were recorded at the Mass Spectroscopy Laboratory at the California Institute of Technology or the Mass Spectroscopy Laboratory at the University of California at Los Angeles. Matrix-assisted, laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) was conducted at the Protein and Peptide Microanalytical Facility at the California Institute of Technology.

Heterocycle Synthesis. Synthetic Procedures for the Synthesis of Boc-Oo-OH (**4**), Boc-No-OH (**8**), and Boc-Hi-OH (**14**).

Methyl 2-amino-4-methyl-1,3-oxazole-5-carboxylate **(2).** Commercially available (**1**), (10 g, 60.7 mmol) and urea (3.65 g, 60.7 mmol) were dissolved in ethanol (40 mL) and refluxed for 12 h. The reaction was cooled to 0 ^{o}C at which time a crystalline white solid precipitated out of solution. The precipitate was collected by vacuum filtration and washed with hexanes to provide (**2**) (6.97 g) in 67% yield. TLC (5:2 hexanes/ethyl acetate) R_f 0.2; ^{1}H NMR (DMSO-d_6) δ 7.42 (s, 2H), 3.69 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.7, 158.9, 149.6, 130.2, 51.6, 14.2; EI-MS m/e 170.069 (M^+ calcd. for 170.069 $C_7H_{10}N_2O_3$).

Methyl 2-[(tert-butoxy)carbonylamino]-4-methyl-1,3-oxazole-5-carboxylate **(3).** A mixture of (**2**) (1 g, 5.8 mmol), Boc anhydride (1.92 g, 8.8 mmol), DIEA (835 mg, 1.12 ml, 6.4 mmol), DMAP (190 mg, 1.4 mmol) and DMF (10 mL) was stirred at 40 ^{o}C overnight. The DMF was removed in vacuo and the residue taken up in ethyl acetate (150 mL). The reaction was washed with brine (2 x 100 mL), saturated sodium bicarbonate (100 mL), (0.01M HCl 100 mL), and dried over sodium sulfate. Removal of the organics provided (**3**) (1.11 g) as an oily solid in 71% yield. (5:2 hexanes/ethyl acetate) R_f 0.5; ^{1}H NMR (DMSO-d_6) δ 11.22 (s, 1H), 3.76 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.2, 154.8, 147.1, 132.9, 81.2, 51.4, 28.5, 14.1; EI-MS m/e 270.122 (M^+ calcd. for 270.122 $C_{12}H_{18}N_2O_5$).

2-[(tert-butoxy)carbonylamino]-4-methyl-1,3-oxazole-5-carboxylic acid **(4).** A mixture of (**3**) (1.1 g, 4 mmol), 1N NaOH (15 mL) and methanol (5 mL) was stirred at

35 ^{o}C. The reaction was determined to be complete by TLC after 4 h. The methanol was removed in vacuo and the aqueous layer carefully adjusted to pH 2 with 1N HCl at which time a crystalline white solid precipitated out of solution. Filtration of the solid gave (**4**) (0.92 g) in 93% yield. TLC (5:2 hexanes/ethyl acetate, 10% acetic acid) R_f 0.55; ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1H), 2.71 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 159.7, 154.7, 150.7, 146.2, 133.8, 81.7, 28.5, 14.0; EI-MS m/e 242.091 (M^{+} calcd. for 242.090 $C_{10}H_{14}N_2O_5$).

Methyl 2-amino-1,3-oxazole-4-carboxylate **(6).** A mixture of ethyl bromopyruvate (**5**) (10 g, 51 mmol) and urea (3.08 g, 51 mmol) was refluxed in ethanol for 12 h. The reaction was cooled to 0 ^{o}C at which time a crystalline white solid precipitated out of solution. The precipitate was collected by vacuum filtration and washed with hexanes to provide (**6**) (4.61 g) in 58% yield. TLC (ethyl acetate) R_f 0.7; ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H), 6.92 (s, 2H), 4.16 (q, J = 6.9 Hz, 2H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 162.1, 161.9, 138.4, 132.6, 60.6, 14.9; EI-MS m/e 156.053 (M^{+} calcd. for 156.053 $C_6H_8N_2O_3$).

Methyl 2-[(tert-butoxy)carbonylamino]-1,3-oxazole-4-carboxylate **(7).** A mixture of (**6**) (2 g, 12.8 mmol), Boc anhydride (4.19 g, 19.2 mmol), DIEA (1.82 g, 2.45 ml, 14 mmol), DMAP (413 mg, 3.2 mmol) and DMF (15 mL) was stirred at 40 ^{o}C overnight. The DMF was removed in vacuo and the residue taken up in ethyl acetate (150 mL). The reaction was washed with brine (2 x 100 mL), saturated sodium bicarbonate (100 mL), (0.01M HCl 100 mL), and dried over sodium sulfate. Removal of the organics provided (**7**) (1.96 g) as an oily solid in 60% yield. (5:2 hexanes/ethyl acetate) R_f 0.5; ^{1}H NMR (DMSO-d_6) δ 10.92 (s, 1H), 8.90 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.38 (s, 9H), 1.27 (t, J

= 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 163.1, 155.1, 152.0, 147.3, 143.1, 81.6, 59.4, 28.5, 14.2; EI-MS m/e 256.106 (M^+ calcd. for 256.106 $C_{11}H_{16}N_2O_5$).

2-[(tert-butoxy)carbonylamino]-1,3-oxazole-4-carboxylic acid **(8).** A mixture of (**7**) (1.0 g, 3.9 mmol), 1N NaOH (10 mL) and methanol (3 mL) was stirred at 35 ^{o}C. The reaction was determined to be complete by TLC after 4 h. The methanol was removed in vacuo and the aqueous layer carefully adjusted to pH 2 with 1N HCl at which time a crystalline white solid precipitated out of solution. Filtration of the solid gave (**8**) (0.81 g) in 91% yield. TLC (5:2 hexanes/ ethyl acetate, 10% acetic acid) R_f 0.50; ^{1}H NMR (DMSO-d_6) δ 10.86 (s, 1H), 8.42 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 162.5, 159.0, 154.0, 151.3, 141.8, 81.5, 28.5; EI-MS m/e 228.075 (M^+ calcd. for 228.075 $C_9H_{12}N_2O_5$).

(OMe-**Hi**(OH)-OMe: **9**) To a mixture of dimethyl 1,3-acetonedicarboxylate (10 g, 8.43 mL, 57.4 mmol) and isoamyl nitrite (21.9 g, 25.1 mL, 0.19 mol) in petroleum ether (25 mL) at room temperature, was added 2M HCl in diethyl ether (2.8 mL, 5.7 mmol) dropwise with stirring. The mixture was stirred for 3-4 h upon which time a pale yellow fibrous precipitate formed. The precipitate was collected by vacuum filtration and washed with cold petroleum ether to provide **9** (9.92 g) in 86% yield. TLC (5:2 hexanes/ethyl acetate) R_f 0.4; ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 3.88 (s 3H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.4, 157.2, 150.1, 144.3, 143.2, 53.6, 53.0; EI-MS m/e 201.027 (M^+ calcd. for 201.027 $C_7H_7NO_6$).

(OMe-**Hi**(OMe)-OMe: **10**) To a mixture of **9** (5 g, 24.8 mmol) in methanol (25 mL) and benzene (25 mL) was added DIEA (3.53 g, 4.76 mL, 27.3 mmol) and DMS (6.25 g, 4.69 mL, 49.6 mmol). The reaction was stirred at 50 ^{o}C and determined to be

complete by TLC in 4 h. The solvent was then removed in vacuo to provide a fibrous white solid. The solid was collected, washed with cold hexanes and dried under high vacuum to provide **10** (4.96 g) in 93% yield. TLC (5:2 hexanes/ethyl acetate) R_f 0.75; ^{1}H NMR (DMSO-d_6) δ 3.94 (s, 3H), 3.90 (s 3H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 158.1, 155.7, 150.6, 148.2, 144.3, 63.0, 53.0, 52.8; EI-MS m/e 215.043 (M^+ calcd. for 215.043 $C_8H_9NO_6$).

(H_2NNH-**Hi**(OMe)-OMe: **11**) A solution of **10** (4g, 18.5 mmol) in THF (370 mL) was cooled to –44 ^{o}C followed by the addition of anhydrous hydrazine (625 mg, 613 μL, 19.4 mmol). The reaction was allowed to slowly warm to room temperature and stirred for 20 h. At 20 h, additional hydrazine (156 mg, 153 μL, 4.85 mmol) was added, followed by stirring for an additional 20 h at room temperature. Over the course of the reaction, a solid white precipitate formed. Upon complete consumption of starting material as indicated by TLC, the precipitate was collected by vacuum filtration and dried under high vacuum to provide **11** (2.5 g) as the major regioisomer (5:1 by ^{1}H NMR) in 63% yield. Both regioisomers are carried through the synthesis. TLC (ethyl acetate) R_f 0.5; ^{1}H NMR (DMSO-d_6) δ 10.08 (s, 1H), 4.71 (br, 2H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 157.2, 156.6, 153.0, 146.8, 144.3, 63.2, 53.5, 52.8; EI-MS m/e 215.054 (M^+ calcd. for 215.054 $C_7H_9N_3O_5$).

(N_3-**Hi**(OMe)-OMe: **12**) A mixture of **11** (1 g, 4.65 mmol) in 1N HCl (13.2 mL) was cooled to 0 ^{o}C. To this mixture was added a solution of sodium nitrite (370 mg, 5.34 mmol) in water (3 mL), dropwise with vigorous stirring. Upon addition of sodium nitrite, a solid white precipitate began to form. After completion of addition, the slurry was stirred for an additional 10 min. The precipitate was extracted with DCM (3 x 50 mL)

and dried over sodium sulfate. Removal of the organics in vacuo provided **12** (630 mg) as a flaky white solid in 60% yield. TLC (5:2 hexanes/ethyl acetate) R_f 0.65; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3H), 3.90 (s 3H). The material was taken on directly to the next step in the synthesis.

(Boc-**Hi**(OMe)-OMe: **13**) A mixture of **12** (600 mg, 2.65 mmol), benzene (10 mL), and freshly distilled t-butanol (294 mg, 3.98 mmol) was refluxed for 45 min. The organics were removed in vacuo and the solid subjected to column chromatography (1:1 hexanes/ethyl acetate) to provide **13** (548 mg) as the major regioisomer in 76% yield. TLC (1:1 hexanes/ethyl acetate) R_f 0.35; ^{1}H NMR (DMSO-d_6) δ 9.76 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 157.3, 154.0, 151.0, 146.8, 139.6, 80.3, 61.9, 53.2, 27.8; EI-MS m/e 272.101 (M^+ calcd. for 272.101 $C_{11}H_{16}N_2O_6$).

(Boc-**Hi**(OMe)-OH: **14**) A mixture of **13** (500 mg, 1.83 mmol), MeOH (5 mL), and 1N NaOH (5 mL) was stirred at room temperature for 1 h, at which time the saponification was determined complete by TLC. The MeOH was removed in vacuo and the aqueous layer taken to pH = 2 using 1N HCl. The milky white precipitate was extracted using ethyl acetate (3 x 25 mL) and the organics dried over sodium sulfate. The ethyl acetate was removed in vacuo and the resulting thin film redissolved in benzene (25 mL). Removal of the benzene by rotoevaporation provided **14** (415 mg) as a fine white powder in 88% yield. ^{1}H NMR showed the presence of the alternate regioisomer (15%). Regioisomers were determined to be inseparable by TLC but easily separated by reverse-phase preparatory HPLC (0.1% TFA/ACN). TLC (ethyl acetate, 10% acetic acid) R_f 0.6; ^{1}H NMR (DMSO-d_6) δ 9.67 (s, 1H), 3.88 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (DMSO-d_6)

δ 157.2, 153.6, 151.8, 146.8, 139.8, 80.3, 61.9, 27.8; EI-MS m/e 258.085 (M^+ calcd. for 258.085 $C_{10}H_{14}N_2O_6$).

References:

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