Linear Tetraheterocycles Composed of Both Bidentate Diisoxazole and Bidentate Isoxazole−Furyl/Thienyl/Pyridyl Motifs[1]

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Introduction

Isoxazoles[2] have long been targets of synthetic investigation because of their known biological[3] and ionophoric[4] properties. Generally, isoxazoles coordinate to metals through the nitrogen lone pair, although coordinations through the oxygen lone pair or aromatic π-electrons[5] are known—the latter being far less common. Oligoisoxazole derivatives have been studied in our laboratory previously but did not allow for head-to-head adjoinment of the 3−3′-diisoxazole moiety.[4c] Recently diisoxazoles,[6] diisoxazolines,[7] and diisoxazolidinones[8] have been synthesized, but not with this 3,3′-connectivity. Moreover, dioxazoles with direct bonding between heterocycles have been reported in marine natural products.[9] The goal of our synthetic effort was to prepare a small library of oligoisoxazoles (**16**−**22**) using 1,3-dipolar[10] nitrile oxide[11] cycloadditions. In the course of our study, we planned to develop a convergent route to a variety of tetraheterocyclic, triisoxazole-containing molecules.

Results and Discussion

The tetraheterocyclic synthesis commences with the preparation of benzyl propargyl ether (**1**) by the base-mediated (KH) coupling of benzyl alcohol and propargyl bromide. To avoid deprotonation of the terminal alkyne, benzyl alcohol was added first to the potassium hydride (1.0 equiv) suspended in THF. After alkoxide formation was complete (30 min at 0 °C), the electrophile was added. The benzyl propargyl ether was purified by vacuum distillation to give **1** (93%).

A modified Mukaiyama[12] method, employing catalytic triethylamine and 1,4-phenylene diisocyanate instead of phenyl isocyanate,[13] was used to dehydrate[14] methyl nitroacetate,[15] generating the corresponding nitrile oxide in situ. Concomitant 1,3-dipolar cycloaddition to the alkyne moiety of **1** delivered isoxazole **2** in 76% yield (Scheme 1). This modified dehydration method results in the formation of a diphenyl urea polymer that is easily separated from the isoxazole product by filtration. The ethyl ester analogue of isoxazole **2** (i.e., $-R = -CO_2Et$) was also prepared starting from the hydrochloride salt of glycine ethyl ester[16] using a modified Huisgen cycloaddition method[17] in 74% yield. In our hands, these two procedures for generating $RO_2C-C\equiv N^+-O^-$ were equally effective. Treating isoxazole **2** with DIBAL-H[18] (1.2 equiv in CH_2Cl_2 at −78 °C) delivered aldehyde **3** in 96% yield.

The oxime of aldehyde **3** was prepared using hydroxylamime hydrochloride and sodium acetate in a solution of ethanol−water.[19] Isolation of this *E*,*Z*-oxime mixture (**4**; 99%) followed by addition to a CH_2Cl_2/aqueous sodium hypochlorite[20] biphasic mixture containing propargyl bromide and catalytic triethylamine generated a nitrile oxide that underwent concomitant 1,3-dipolar cycloaddition. The oxime was dissolved in methylene chloride and added dropwise in an effort to reduce the formation of furoxan via nitrile oxide dimerization. The resulting "head-to-head" C3,C3′-diisoxazole product **5** (80%) possesses the electrophilic $-CH_2Br$ functional group necessary for the planned coupling.

Construction of the furyl/thienyl/pyridyl-isoxazole commenced with oxime formation ($NH_2OH\cdot HCl$, NaOAc) from three 2-heterocarboxaldehydes giving 2-pyridinealdoxime (**6**),[21] 2-thiophenealdoxime (**7**),[22] and 2-furanaldoxime (**8**)[23] in high yield (75−91%; Scheme 2). In situ nitrile oxide formation from **6** (aqueous NaOCl) in the presence of either propargyl alcohol, 3-butyn-1-ol, or 4-pentyn-1-ol delivered 3-(2-pyridyl)isoxazoles **9**−**11** in good yield (66−77%). Some dimerized furoxan was observed (≈10% by crude NMR). Isoxazole **9** has previously

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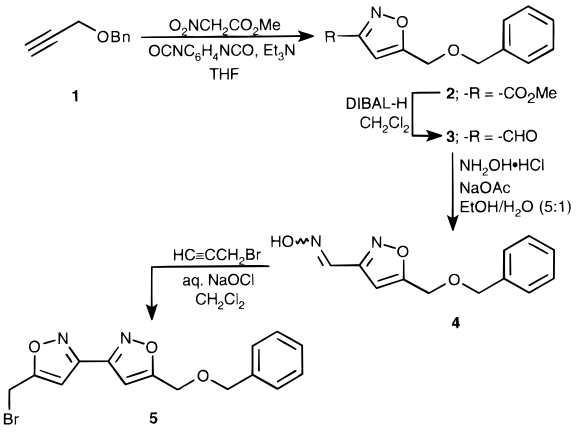
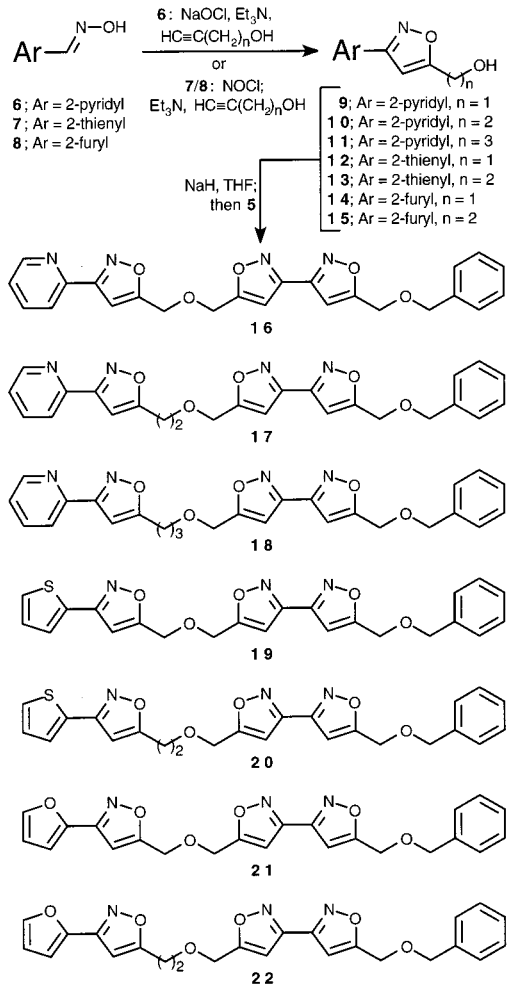
Scheme 1. Preparation of Diheterocyclic Intermediate 5



Scheme 2. Preparation of Diheterocyclic Intermediates 9−15 and Coupling with 5



been examined for inhibition of thrombocyte aggregation[24] and supercooperativity in platelet aggregation.[25]

The use of aqueous sodium hypochlorite for the oxidation/dehydrochlorination of 2-thiophenealdoxime and 2-furanaldoxime was ineffective owing to apparent anionic polymerization.[26] It proved necessary to prepare nitrile oxides from **7** and **8** by a two-step process—(1) halogenation followed by (2) dehydrohalogenation. The use of chlorine gas,[27] NCS,[28] and NBS[29] all gave partial halogenation at the C5 position of the thienyl and furyl heterocycles. Fortunately, nitrosyl chloride[30] (NOCl) selectively oxidized the oxime moiety without effecting ring halogenation. And, having thus effected R−CH=N−OH → R−C(Cl)=N−OH, the appropriate alkynol was then added to the crude hydroximoyl chloride followed by slow addition of Et_3N by syringe pump. The isolated yields of cycloadducts **12**−**15** were in the 40−55% range. On the basis of regenerated aldoxime (Et_3N neutralization of unwanted aldoxime hydrochloride formed as a side product in the NOCl oxidation step) and starting 2-heterocarboxaldehyde (aldoxime hydrolysis), the yields for **7**/**8** → **12**−**15** were quite good (≈70%).

With fragments **5** and **9**−**15** in hand, we turned to the preparation of the tetraheterocyclic, triisoxazole-containing targets. This was accomplished in straightforward fashion by Williamson ether synthesis. One equivalent of both fragments was added to THF followed by introduction of base. Sodium hydride proved to be most expedient, giving in situ alkoxide formation and concomitant O-alkylation. A single product was obtained in excellent yield (80−90%) in the reaction of **5** with **9**, **11**, **12**, or **14**. However, in the case of 5-(2-hydroxyethyl)-isoxazoles **10**, **13**, and **15**, some dehydration occurs giving a isoxazole-conjugated C5-vinyl. In these reactions, the yields of **17**, **20**, and **22** were 72%, 75%, and 72%, respectively.

Conclusion

An efficient route to tetraheterocyclic, triisoxazole-containing compounds with diversity potential has been developed. Incorporation of this structural motif into polymers with metal-specific binding is currently under investigation in collaboration with another laboratory. Metal-binding specificities for these compounds will be reported in due course.

Experimental Section

General Procedures. All reactions, unless otherwise described, were done under an inert atmosphere of dry nitrogen. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately prior to use. Methylene chloride was distilled from CaH_2. Triethylamine was distilled from CaH_2 and stored over KOH. Melting points were determined and are uncorrected. All infrared spectra were analyzed neat by FT-IR. ^1H and ^{13}C NMR were measured in $CDCl_3$ at 300 and 75 MHz, respectively. $CDCl_3$ was used as internal standard for ^{13}C NMR while tetramethylsilane was added as internal standard for ^1H NMR. Elemental analyses were determined at MidWest Microlab, Indianapolis, IN. Aldoximes **6**, **7**, and **8** were prepared from aldehydes using standard methods.[19]

Benzyl Propargyl Ether (1).[31] A mixture containing KH (2.41 g, 60.1 mmol), in THF (150 mL), was cooled to 0 °C and benzyl alcohol (6.50 g, 60.1 mmol) added. After 30 min, an 80%

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solution of propargyl bromide (63.1 mmol) in toluene was added slowly. The reaction was warmed to room temperature and stirred for 1 h or until starting benzyl alcohol was no longer present by TLC. Sodium sulfate decahydrate was added to quench any base that had not reacted, and the mixture was filtered through Celite and concentrated under reduced pressure to afford a light yellow oil. The crude product was purified by vacuum distillation to give **1** (8.20 g, 93%) as a colorless oil. Bp 94−97 °C/6.5 mmHg; IR 3296, 3032, 2116, 1088 cm^{-1}; ^1H NMR δ 7.38−7.29 (m, 5H), 4.60 (s, 2H), 4.17 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H); ^{13}C NMR δ 137.4, 128.2, 127.8, 127.6, 79.7, 74.4, 71.3, 56.9.

Methyl 5-[(benzyloxy)methyl]isoxazole-3-carboxylate (2). Alkyne **1** (3.32 g, 22.7 mmol) and methyl nitroacetate (2.71 g, 22.7 mmol) were combined in THF (100 mL), and 1,4-phenylene diisocyanate (9.10 g, 56.8 mmol) was added in one portion. The reaction was then initiated with the addition of a catalytic amount of triethylamine. When the reaction had gone to completion (3 d as judged by TLC), 2−3 drops of water were added to quench any excess isocyanate. The polymerized urea by-product was removed by filtration through a plug of Celite, and the filtrate was concentrated to obtain cycloaddition product **2** (4.26 g, 76%) as a light yellow solid. Mp 44−45 °C; IR 3129, 2860, 1724, 1202 cm^{-1}; ^1H NMR δ 7.38−7.32 (m, 5H), 6.70 (s, 1H), 4.66 (s, 2H), 4.61 (s, 2H), 3.98 (s, 3H); ^{13}C NMR δ 171.4, 160.2, 156.2, 136.9, 128.6, 128.1, 127.9, 103.5, 73.2, 62.5, 52.7. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.20; H, 5.33; N, 5.47.

5-[(Benzyloxy)methyl]isoxazole-3-carbaldehyde (3). Ester **2** (1.63 g, 6.60 mmol) in methylene chloride (20 mL) was cooled to −78 °C in a dry ice−acetone bath. DIBAL-H (5.28 mL, 7.92 mmol) in toluene was then slowly added by syringe over 2 min, and the reaction was kept at −78 °C with stirring for 1 d. The reaction was quenched at −78 °C with ice (10 g), and Rochelle salt (20 mL of saturated aqueous solution) was added after the biphasic mixture was allowed to warm to room temperature. The layers were separated, the aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine and dried with sodium sulfate. The concentrated product was then purified by flash chromatography (18% ethyl acetate in hexanes) to give **3** (1.38 g, 96%) as a colorless oil. IR 3137, 2861, 2794, 1710, 1126 cm^{-1}; ^1H NMR δ 10.14 (s 1H), 7.38−7.30 (m, 5H), 6.65 (s, 1H), 4.67 (s, 2H), 4.62 (s, 2H); ^{13}C NMR δ 184.1, 171.5, 161.9, 136.9, 128.4, 128.0, 127.7, 100.0, 73.0, 62.3. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.97; H, 5.22; N, 6.11.

5-[(Benzyloxy)methyl]isoxazole-3-carbaldoxime (4). Aldehyde **3** (1.16 g, 5.34 mmol) was added to hydroxylamine hydrochloride (0.75 g, 10.7 mmol) in a solution of water and ethanol (20 mL; 1:5). To this solution was added sodium acetate (2.18 g, 16 mmol), and the mixture was allowed to stir for 1 h at room temperature. The ethanol was then removed by rotoevaporation, and methylene chloride and water were added. The layers separated, and the aqueous layer was extracted twice more with methylene chloride. The combined organic layers were dried with sodium sulfate, filtered, and concentrated to give product **4** (1.24 g, 99%) as a mixture of *E*- and *Z*-isomers, which were both carried on to the next step. Mp 82−83 °C; IR 3262, 3123, 2880, 1498, 1434, 1350 cm^{-1}; ^1H NMR δ 9.10−8.30 (b, var., 1H), 8.25 (s, 1H), 7.40−7.30 (m, 5H), 6.62 (s, 1H), 4.63 (s, 2H), 4.62 (s, 2H); ^{13}C NMR δ 169.9, 158.0, 141.4, 137.1, 128.5, 128.1, 127.9, 100.3, 73.2, 62.7. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.07. Found: C, 62.03; H, 5.13; N, 11.85.

5-Bromomethyl-5′-[(benzyloxy)methyl]-3,3′-diisoxazole (5). To an excess of propargyl bromide (6.5 mmol) in methylene chloride (20 mL) was added aqueous NaOCl (8.6 mmol; industrial bleach containing 12.5 wt % of NaOCl). As the bleach was added, triethylamine (3 drops) was also added. After the biphasic solution was cooled to 0 °C, oxime **4** (1.24 g, 5.34 mmol) in methylene chloride (15 mL) was added dropwise over 40 min, and the reaction was allowed to stir overnight (0 °C → room temperature). After completion, the layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to give **5** (1.49 g, 80%). Mp 80−81 °C; IR 3123, 1597, 1351, 1065 cm^{-1}; ^1H NMR δ 7.38−7.31 (m, 5H), 6.81 (s, 1H), 6.78 (s, 1H), 4.66 (s, 2H), 4.61 (s, 2H), 4.48 (s, 2H); ^{13}C NMR δ 170.7, 168.8, 154.6, 153.9, 137.1, 128.4, 128.0, 127.8, 102.1, 101.2, 73.0, 62.6, 17.9. Anal. Calcd for $C_{15}H_{13}BrN_2O_3$: C, 51.59; H, 3.75; N, 8.02. Found: C, 51.77; H, 3.75; N, 7.95.

(3-(2-Pyridyl)isoxazol-5-yl)methanol (9).[24,25] 2-Pyridinealdoxime **6** (1.32 g, 11 mmol) and propargyl alcohol (3.03 g, 54 mmol) were dissolved in methylene chloride (30 mL), and the solution was cooled to 0 °C. Aqueous NaOCl (1.43 g, 20 mmol) was added dropwise over 30 min, and the reaction was stirred vigorously for 8 h (0 °C → room temperature). The layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried with sodium sulfate and concentrated. The crude sample was purified by column chromatography (50−75% ethyl acetate in hexanes) to give **9** (1.41 g, 74%). Mp 100−100.5 °C; IR 3156, 2864, 1600, 1082, 1062 cm^{-1}; ^1H NMR δ 8.65 (dd, J = 5 and 1 Hz, 1H), 8.04 (dd, J = 7 and 1 Hz, 1H), 7.82 (td, J = 8 and 2 Hz, 1H), 7.37 (ddd, J = 7.5, 5, and 1 Hz, 1H), 6.91 (s, 1H), 4.82 (s, 2H), 4.77 (b, var., 1H); ^{13}C NMR δ 173.0, 162.7, 149.4, 148.2, 137.00, 124.4, 121.7, 100.6, 55.8.

2-(3-(2-Pyridyl)isoxazol-5-yl)ethanol (10).[32] The procedure described for **9** was employed to scale with the following differences: 2-pyridinealdoxime (1.81 g, 15 mmol), 3-butyn-1-ol (2.29 g, 33 mmol), and NaOCl (1.96 g, 27 mmol) were used to give **10** (1.86 g, 66%). Mp 60−62 °C; IR 3272, 3139, 2932,1065, 1042 cm^{-1}; ^1H NMR δ 8.62 (dd, J = 5 and 1 Hz, 1H), 8.00 (dd, J = 7 and 1 Hz, 1H), 7.78 (td, J = 8 and 2 Hz, 1H), 7.33 (ddd, J = 7.5, 5, and 1 Hz, 1H), 6.76 (s, 1H), 4.00 (t, J = 6 Hz, 2H), 4.0 (b, var., 1H), 3.07 (t, J = 6 Hz, 2H); ^{13}C NMR δ 171.6, 162.4, 149.0, 147.9, 136.7, 124.1, 121.3, 100.4, 54.2, 30.0.

3-(3-(2-Pyridyl)isoxazol-5-yl)propanol (11). The procedure described for **9** was employed to scale with the following differences: 2-pyridinealdoxime (520 mg, 4.3 mmol), 4-pentyn-1-ol (895 mg, 11 mmol), and NaOCl (570 mg, 7.7 mmol) were used to give **11** (670 mg, 77%). Mp 53−54 °C; IR 3338, 3137, 2959, 1597, 1048 cm^{-1}; ^1H NMR δ 8.64 (dd, J = 5 and 1 Hz, 1H), 8.03 (dd, J = 7 and 1 Hz, 1H), 7.79 (td, J = 8 and 2 Hz, 1H), 7.33 (ddd, J = 7.5, 5 and 1 Hz, 1H), 6.67 (s, 1H), 3.73 (t, J = 6 Hz, 2H), 3.7 (b, var., 1H), 2.94 (t, J = 7.5 Hz, 2H), 2.01 (tt, J = 7.5 and 6 Hz, 2H); ^{13}C NMR δ 173.9, 162.8, 149.3, 148.3, 136.9, 124.3, 121.5, 99.6, 60.9, 30.1, 23.0. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.74; H, 6.01; N, 13.72.

(3-(2-Thienyl)isoxazol-5-yl)methanol (12). NOCl (8.7 mmol) was generated at room temperature in a separate flask from $NaNO_2$ (606 mg, 8.8 mmol) and concentrated HCl (1.48 mL, 18 mmol)[33] and, with nitrogen gas, swept into an etheral (20 mL) solution of 2-thiophenealdoxime (372 mg, 2.9 mmol) at −20 °C over a period of 30 min. The reaction was allowed to stir for 24 h and then stand for 24 h while keeping the solution between −20 and −10 °C. Finally, the solution was allowed to warm to room temperature, and propargyl alcohol (410 mg, 7.3 mmol) was added. Using a syringe pump, triethylamine (355 mg, 3.5 mmol) diluted in ether (10 mL) was slowly added, and the reaction was stirred overnight, at which time water (45 mL) was added. The layers were separated, the aqueous layer was extracted with ether, and the combined extracts were washed with water, saturated $NaHCO_3$, and brine, dried with sodium sulfate, and concentrated by rotatory evaporation. The product was purified by column chromatography on silica gel (35% ethyl acetate in hexanes) to give **12** (239 mg, 45%). Mp 55−57 °C; IR 3359, 3128, 1229, 1155, 1035 cm^{-1}; ^1H NMR δ 7.43 (dd, J = 3.5 and 1 Hz, 1H), 7.41 (dd, J = 5 and 1 Hz, 1H), 7.10 (dd, J = 5 and 3.5 Hz, 1H), 6.49 (s, 1H), 4.79 (s, 2H), 2.9 (b, var., 1H); ^{13}C NMR δ 172.2, 157.5, 130.1, 127.7, 127.6, 127.5, 100.0, 56.0.

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2-(3-(2-Thienyl)isoxazol-5-yl)ethanol (13). The procedure described for **12** was employed to scale with the following differences: 2-thiophenealdoxime (358 mg, 2.8 mmol), HCl (1.43 mL, 17 mmol), sodium nitrite (583 mg, 8.4 mmol), 3-butyn-1-ol (493 mg, 7.0 mmol), and triethylamine (342 mg, 3.4 mmol) to were used give **13** (286 mg, 52%). Mp 51−52 °C; IR 3369, 2936, 1598, 1050 cm^{-1}; ^1H NMR δ 7.39 (dd, J = 3.5 and 1 Hz, 1H), 7.38 (dd, J = 5 and 1 Hz, 1H), 7.08 (dd, J = 5 and 3.5 Hz, 1H), 6.36 (s, 1H), 3.92 (t, J = 6 Hz, 2H), 3.4 (b, var., 1H), 2.48 (t, J = 6 Hz, 2H); ^{13}C NMR δ 171.2, 157.4, 130.6, 127.4, 127.3, 126.6, 100.1, 59.6, 30.1.

(3-(2-Furyl)isoxazol-5-yl)methanol (14).[34] The procedure described for **12** was employed to scale with the following differences: 2-furanaldoxime (945 mg, 8.5 mmol), HCl (4.29 mL, 52 mmol), sodium nitrite (1.76 g, 26 mmol), propargyl alcohol (1.43 g, 26 mmol), and triethylamine (1.03 g, 10 mmol) were used to give **14** (646 mg, 46%). Mp 83−84 °C; IR 3337, 3128, 2934, 1064, 1013 cm^{-1}; ^1H NMR δ 7.53 (d, J = 1 Hz, 1H), 6.88 (d, J = 3.5 Hz, 1H), 6.51 (dd, J = 3.5 and 1 Hz, 1H), 6.50 (s, 1H), 4.78 (s, 2H), 3.5 (b, var., 1H); ^{13}C NMR δ 171.9, 157.0, 154.0, 144.0, 111.7, 110.5, 99.5, 56.2.

2-(3-(2-Furyl)isoxazol-5-yl)ethanol (15). The procedure described for **12** was employed to scale with the following differences: 2-furanaldoxime (1.40 g, 13 mmol), HCl (6.35 mL, 77 mmol), sodium nitrite (2.61 g, 38 mmol), 3-butyn-1-ol (2.65 g, 38 mmol), and triethylamine (1.53 g, 15 mmol) were used to give **15** (903 mg, 40%). Mp 99−100 °C; IR 3358, 3127, 2954, 1052, 1014 cm^{-1}; ^1H NMR δ 7.52 (d, J = 1 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 6.50 (dd, J = 3.5 and 1 Hz, 1H), 6.36 (s, 1H), 3.97 (t, J = 6 Hz, 2H), 3.03 (t, J = 6 Hz, 2H), 2.8 (b, var., 1H); ^{13}C NMR δ 170.9, 154.7, 144.2, 143.7, 111.6, 110.1, 99.6, 59.8, 30.2. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.05; N, 7.87.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-pyridyl)isoxazol-5-yl)-methoxy]-methyl}-3,3′-diisoxazole (16). Alcohol **9** (205 mg, 1.2 mmol) and bromide **5** (407 mg, 1.2 mmol) were dissolved in THF (2 mL) and added to a slurry of NaH (30.8 mg, 1.3 mmol) in THF (8 mL) at 0 °C via cannulation. The solution was allowed to stir for 30 min, at which time it was warmed to room temperature with stirring for 3 h. The reaction was quenched with water and extracted with ethyl acetate, and the combined organic layers were dried with sodium sulfate and the filtrate was concentrated to give a crude solid. Purification by column chromatography (50−75% ethyl acetate in hexanes) gave **16** as a white powder (437 mg, 84%). Mp 99−100.5 °C; IR 3125, 2889, 1099, 1065 cm^{-1}; ^1H NMR δ 8.68 (d, J = 5 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.80 (td, J = 8 and 2 Hz, 1H), 7.35 (m, 6H), 6.98 (s, 1H), 6.85 (s, 1H), 6.80 (s, 1H), 4.79 (s, 2H), 4.79 (s, 2H), 4.69 (s, 2H), 4.64 (s, 2H); ^{13}C NMR δ 170.4, 169.2, 168.4, 163.2, 154.2, 154.0, 149.8, 149.7, 148.1, 136.8, 128.5, 128.0, 127.8, 124.5, 121.6, 102.6, 101.8, 101.3, 72.9, 63.2, 63.0, 62.4. Anal. Calcd for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.61. Found: C, 64.85; H, 4.61; N, 12.48.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-pyridyl)isoxazol-5-yl)-ethoxy]-methyl}-3,3′-diisoxazole (17). The procedure described for **16** was employed to scale with the following differences: alcohol **10** (156 mg, 818 μmol), bromide **5** (286 mg, 818 μmol), and NaH (21.6 mg, 899 μmol) were used to give **17** (274 mg, 73%). Mp 116−117 °C; IR 3125, 2889, 1106, 1064 cm^{-1}; ^1H NMR δ 8.56 (dd, J = 3 and 1 Hz, 1H), 7.94 (dd, J = 8 and 1 Hz, 1H), 7.67 (td, J = 8 and 2 Hz, 1H), 7.26 (m, 6H), 6.69 (s, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 4.60 (s, 2H), 4.58 (s, 2H), 4.53 (s, 2H), 3.82 (t, J = 6.5 Hz, 2H), 3.05 (t, J = 6.5 Hz, 2H); ^{13}C NMR δ 170.6, 170.4, 170.0, 163.4, 154.2, 154.1, 149.6, 148.5, 136.9, 136.7, 128.5, 128.1, 127.8, 124.3, 121.5, 101.5, 101.4, 100.8, 72.9, 68.1, 63.6, 62.4, 27.6. Anal. Calcd for $C_{25}H_{22}N_4O_5$: C, 65.49; H, 4.84; N, 12.22. Found: C, 65.43; H, 4.86; N, 12.20.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-pyridyl)isoxazol-5-yl)-propoxy]-methyl}-3,3′-diisoxazole (18). The procedure described for **16** was employed to scale with the following differences: alcohol **11** (148 mg, 723 μmol), bromide **5** (252 mg, 723 μmol), and NaH (19.1 mg, 795 μmol) to give **18** (304 mg, 89%). Mp 107−108 °C; IR 3111, 3032, 2887, 1117, 1068 cm^{-1}; ^1H NMR δ 8.66 (dd, J = 6.5 and 1 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.77 (td, J = 8 and 2 Hz, 1H), 7.36 (m, 6H), 6.79 (s, 1H), 6.78 (s, 1H), 6.65 (s, 1H), 4.68 (s, 2H), 4.67 (s, 2H), 4.64 (s, 2H), 3.64 (t, J = 6 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.08 (tt, J = 7.5 and 6 Hz, 2H); ^{13}C NMR δ 173.5, 170.4, 170.4, 163.2, 154.2, 154.2, 149.6, 148.7, 136.9, 136.8, 128.5, 128.1, 127.9, 124.3, 121.5, 101.4, 101.3, 100.0, 73.0, 69.8, 63.6, 62.5, 27.5, 23.4. Anal. Calcd for $C_{26}H_{24}N_4O_5$: C, 66.09; H, 5.12; N, 11.86. Found: C, 66.24; H, 5.21; N, 11.84.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-thienyl)isoxazol-5-yl)-methoxy]-methyl}-3,3′-diisoxazole (19). The procedure described for **16** was employed to scale with the following differences: alcohol **12** (127 mg, 701 μmol), bromide **5** (245 mg, 701 μmol), NaH (18.5 mg, 771 μmol), and chromatography (35−50% ethyl acetate in hexanes) were used to give **19** (255 mg, 81%). Mp 72−73 °C; IR 3122, 2927, 2867, 1096, 1069 cm^{-1}; ^1H NMR δ 7.46 (dd, J = 3.5 and 1 Hz, 1H), 7.43 (dd, J = 5 and 1 Hz, 1H), 7.37 (m, 5H), 7.11 (dd, J = 5 and 3.5 Hz, 1H), 6.85 (s, 1H), 6.80 (s, 1H), 6.57 (s, 1H), 4.78 (s, 2H), 4.75 (s, 2H), 4.69 (s, 2H), 4.64 (s, 2H); ^{13}C NMR δ 170.6, 169.2, 168.5, 157.7, 154.3, 154.0, 136.9, 130.4, 128.5, 128.1, 127.9, 127.7, 127.6, 127.6, 102.0, 101.6, 101.4, 73.0, 63.4, 63.2, 62.5. Anal. Calcd for $C_{23}H_{19}N_3O_5S$: C, 61.46; H, 4.26; N, 9.35. Found: C, 61.14; H, 4.32; N, 9.30.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-thienyl)isoxazol-5-yl)-ethoxy]-methyl}-3,3′-diisoxazole (20). The procedure described for **16** was employed to scale with the following differences: alcohol **13** (105 mg, 539 μmol), bromide **5** (188 mg, 539 μmol), NaH (14.2 mg, 593 μmol), and chromatography (35−50% ethyl acetate in hexanes) were used to give **20** (187 mg, 75%). Mp 132−133 °C; IR 3136, 3060, 2911, 1092 cm^{-1}; ^1H NMR δ 7.42 (dd, J = 3.5 and 1 Hz, 1H), 7.34 (m, 6H), 7.07 (dd, J = 5 and 3.5 Hz, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 6.33 (s, 1H), 4.67 (s, 2H), 4.66 (s, 2H), 4.61 (s, 2H), 3.87 (t, J = 6.5 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H); ^{13}C NMR δ 170.5, 170.4, 169.9, 157.6, 154.2, 154.0, 136.8, 130.8, 128.5, 128.0, 127.8, 127.5, 127.3, 127.3, 101.5, 101.3, 100.1, 72.9, 68.0, 63.5, 62.4, 27.5. Anal. Calcd for $C_{24}H_{21}N_3O_5S$: C, 62.19; H, 4.57; N, 9.07. Found: C, 62.04; H, 4.55; N, 8.96.

5-[(Benzyloxy)-methyl]-5′-{[(3-(2-furyl)isoxazol-5-yl)-methoxy]-methyl}-3,3′-diisoxazole (21). The procedure described for **16** was employed to scale with the following differences: alcohol **14** (54.1 mg, 327 μmol), bromide **5** (114 mg, 327 μmol), NaH (8.6 mg, 360 μmol), and chromatography (40−60% ethyl acetate in hexanes) were used to give **21** (112 mg, 79%). Mp 110−111 °C; IR 3124, 2913, 1106, 1067 cm^{-1}; ^1H NMR δ 7.56 (d, J = 1.5 Hz, 1H), 7.37 (m, 5H), 6.92 (d, J = 3.5 Hz, 1H), 6.85 (s, 1H), 6.80 (s, 1H), 6.59 (s, 1H), 6.53 (dd, J = 3.5 and 1.5 Hz, 1H) 4.78 (s, 2H), 4.76 (s, 2H), 4.69 (s, 2H), 4.64 (s, 2H); ^{13}C NMR δ 170.6, 169.2, 168.2, 154.9, 154.4, 154.1, 144.0, 143.9, 136.9, 128.6, 128.1, 127., 111.8, 110.5, 102.0, 101.4, 101.2, 73.0, 63.3, 63.2, 62.5. Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.70. Found: C, 63.55; H, 4.37; N, 9.48.

5-[(Benzyloxy)methyl]-5′-{[(3-(2-furyl)isoxazol-5-yl)-ethoxy]methyl}-3,3′-diisoxazole (22). The procedure described for **16** was employed to scale with the following differences: diheterocyclic alcohol **15** (227 mg, 1.27 mmol), bromide **5** (442 mg, 1.27 mmol), NaH (33.5 mg, 1.4 mmol), and chromatography (40% to 60% ethyl acetate in hexanes) were used to give **22** (409 mg, 72%). Mp 81−82 °C; IR 3124, 3065, 2909, 1108 cm^{-1}; ^1H NMR δ 7.52 (d, J = 2 Hz, 1H), 7.36 (m, 5H), 6.86 (d, J = 3.5 Hz, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 6.49 (dd, J = 3.5 and 2 Hz, 1H) 6.35 (s, 1H), 4.69 (s, 2H), 4.68 (s, 2H), 4.63 (s, 2H), 3.89 (t, J = 6.5 Hz, 2H), 3.10 (t, J = 6.5 Hz, 2H); ^{13}C NMR δ 170.5, 170.1, 170.0, 154.9, 154.2, 154.1, 144.3, 143.7, 136.5, 128.5, 128.1, 127.8, 111.6, 110.0, 101.5, 101.4, 99.6, 73.0, 68.0, 63.6, 62.5, 27.5. Anal. Calcd for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.64; H, 4.82; N, 9.33.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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