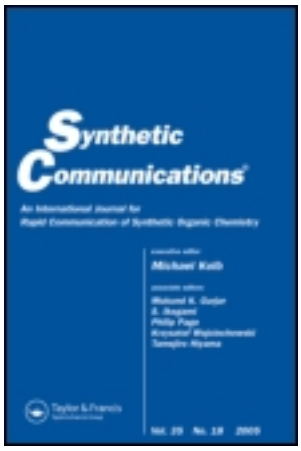

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Preparation and Reactivity of Ethyl 2-Vinyloxazole-4-carboxylate

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ABSTRACT

The one-step synthesis of ethyl 2-vinyloxazole-4-carboxylate is described. The reactivity of this synthetically useful oxazole fragment towards addition and Heck coupling was examined.

An increasing number of biologically active compounds contain the 2,4-disubstituted oxazole ring including the streptogramin A antibiotics,[1] the potent antitumor phorboxazoles,[2] the highly cytotoxic disorazoles,[3] the secondary metabolite ajudazols,[4] and the bengazoles.[5] One possible biosynthetic origin for the oxazole ring is the cyclization–dehydrogenation of a serine residue. Walsh and coworkers have isolated

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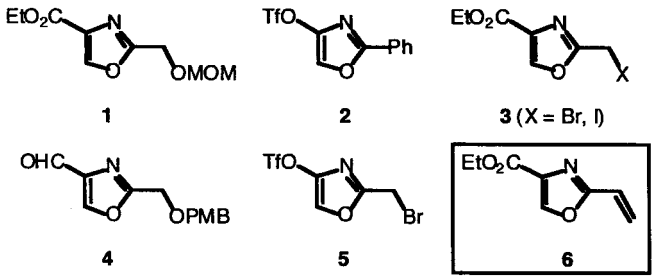
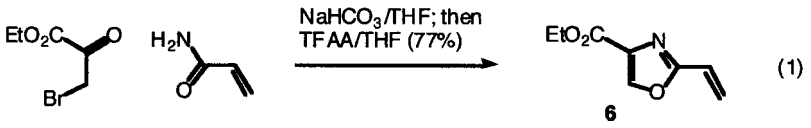
an enzyme complex, microcin B17 synthase, from *E. coli* which catalyses the formation of oxazole rings.[6]

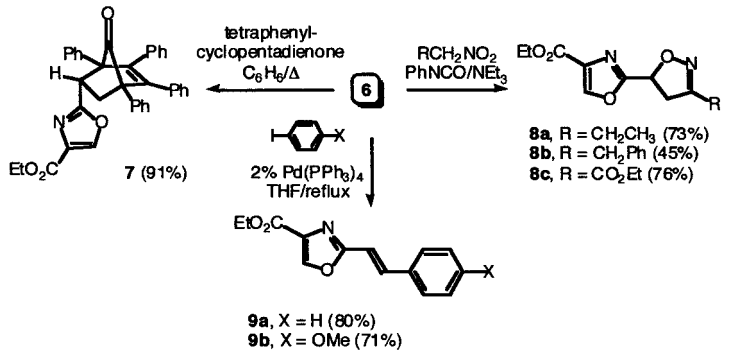
In order to address the synthetic challenge presented by the oxazole ring, a number of methodologies have been reported for the cyclization–oxidation (or oxidation–cyclization) of β-hydroxyamides.[7] Alternatively, a number of oxazole ring containing segments (e.g. **1**–**5**)[8] have been developed which have been used in natural product synthesis.[9] We herein report on the preparation and reactivity of a new oxazole synthon, ethyl 2-vinyloxazole-4-carboxylate (**6**).



Hantzch-Panek condensation[8c] of ethyl bromopyruvate with acrylamide followed by treatment with trifluoroacetic anhydride gave the title compound **6** in good yield (Eq. 1). The structure of **6** was assigned on the basis of its NMR and MS spectral data. In particular, signals at δ 162, 144, and 135 ppm in the ^{13}C NMR spectrum correspond to the oxazole ring, while the signals at δ 125 and 123 ppm correspond to the vinyl group. Compound **6** has a tendency to polymerize if stored for long periods of time.



The reactivity of **6** towards cycloaddition was examined. To this end, reaction with tetraphenylcyclopentadienone to afford 5-(oxazolyl)-bicyclo[2.2.1]hept-2-en-7-one as a mixture of *endo*- and *exo*-cycloadducts (>10:1). Recrystallization of the reaction mixture gave the pure *endo*-adduct **7** (Sch. 1). The *endo*-relative stereochemistry was assigned on the basis of the relative chemical shifts of the H5 signal for the *endo*- and *exo*-isomers (δ 4.78 and 3.73 ppm respectively). These relative



Scheme 1.

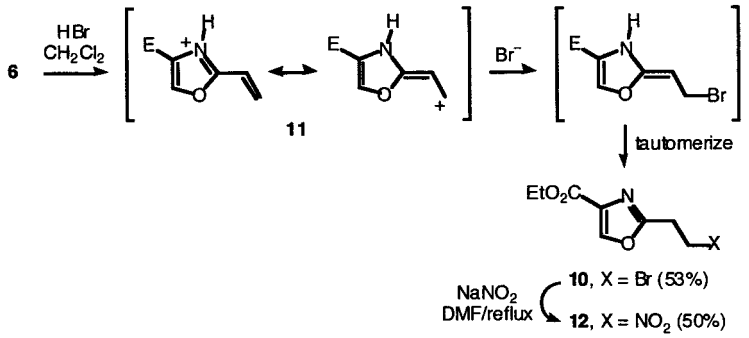
chemical shifts may be compared with the *endo*- and *exo*-isomers of 1,2,3,4,5-pentaphenylbicyclo[2.2.1]hept-2-ene-7-one (δ 4.27 and 3.80 ppm respectively).[10]

Reaction of **6** with nitropropane, nitroethylbenzene or ethyl nitroacetate in the presence of phenyl isocyanate/triethylamine[11] gave the linked oxazole-isoxazolines **8a**–**c** respectively (Sch. 1). The structural assignments of **8a**–**c** are based on their NMR spectral data. In particular, the isoxazoline methine proton appears as a doublet of doublets ca. δ 5.5–5.8 ppm, while the diastereotopic isoxazoline methylene protons appear as multiplets in the range ca. δ 3.9–3.2 ppm.

Heck-type coupling[12] of vinyloxazole **6** with iodobenzene or *p*-iodoanisole gave the cinnamyloxazoles **9a** and **9b** respectively (Sch. 1). The product **9a** was identified by comparison a sample prepared by the literature method.[8c] The structure of **9b** was assigned by comparison of its NMR spectral data with that of **9a**. Oxazoles of general structure **9** have previously been examined as antidiabetic agents.[13]

Addition of HBr to **6** gave the 2-(2-bromoethyl)oxazole **10** in good yield (Sch. 2). The structural assignment of **10** as a 1° haloalkane was based in its ^{1}H NMR spectral data. Notably, signals corresponding to the (2-bromoethyl) substituent appear at δ 3.73 (t, 2H) and 3.42 (t, 2H). The regioselectivity of this addition may be rationalized in the following manner: initial protonation of the oxazole nitrogen renders the vinyl terminus an electrophilic center (c.f. **11**, Sch. 2). Subsequent nucleophilic attack by bromide ion, followed by tautomerization affords the oxazole product **10**.

Bromide substitution with the ambident nucleophile sodium nitrite occurs at nitrogen to give the 2-(2′-nitroethyl)oxazole **12** (Sch. 2).



Scheme 2.

The structural assignment of **12** as a 2-(2′-nitroethyl)oxazole is based on comparison of the ^{1}H signal for the nitro-α-methylene of both **12** and (2′-nitroethyl)benzene[14] (δ 4.86 and 4.58 ppm respectively). The preparation of only one other 2-(2′-nitroethyl)oxazole has been reported.[15]

In summary, ethyl 2-vinyloxazole-4-carboxylate is prepared in one-step from readily available starting materials. The reactivity of this oxazole containing fragment toward addition should make it an appealing starting point for the introduction of this functionality into natural products.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded on a Mattson 4020 FT-IR instrument. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. Mass spectra were measured on a Hewlett Packard 5890 GCMS-instrument with a 5970 mass selective detector. Elemental analyses were obtained from the Midwest Microlab, Indianapolis, IN and high resolution mass spectra were obtained from the Washington University Resource for Biomedical and Bioorganic mass spectrometry.

Ethyl 2-vinyloxazole-4-carboxylate (6). To stirred suspension of acrylamide (2.41 g, 33.9 mmol) and powdered $NaHCO_3$ (11.4 g, 136 mmol) in THF (130 mL) under nitrogen was added ethyl bromopyruvate (5.2 mL, 37 mmol). The reaction mixture was heated at 55–60°C for 15 h, at which time additional ethyl bromopyruvate (5.2 mL, 37 mmol) was added with

heating for an additional 8 h. The reaction mixture was cooled to room temperature and the solid impurities were removed by filtration through celite. The filtrate was concentrated under reduced pressure. The crude residue was immediately dissolved in THF (15 mL) cooled to 0°C and treated with trifluoroacetic anhydride (15 mL). This stirred solution was warmed to room temperature and stirred overnight. The reaction mixture was slowly quenching with saturated aqueous $NaHCO_3$ (30 mL), the layers separated and the aqueous layer was extracted with ethyl acetate (3×75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexanes–ethyl acetate = 3:1) provided **6** as a yellow oil (4.34 g, 77%): ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 6.64 (dd, $J = 11.2$, 17.8 Hz, 1H), 6.30 (d, $J = 17.7$ Hz, 1H), 5.74 (d, $J = 11.2$ Hz, 1H), 4.40 (q, $J = 6.9$ Hz, 2H), 1.40 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 161.9, 144.1, 135.1, 124.9, 123.5, 62.0, 15.0; MS m/z (%) = 167 (M^+, 15), 139 ($M^+ - C_2H_4$, 52), 122 ($M^+ - OCH_2CH_3$, 22), 55 (100). EI-HRMS calcd. for $C_8H_9NO_3$ (M^+): m/z 167.0582. Found: m/z 167.0582.

5-(4′-Ethoxycarbonyl-2′-oxazoyl)-1,2,3,4-tetraphenylbicyclo[2.2.1]hept-2-en-7-one (7). In an oven dried round bottom flask was added tetraphenylcyclopentadienone (1.0 g, 2.6 mmol), benzene (50 mL) and **6** (0.56 g, 3.4 mmol, 1.3 equiv.). The solution was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was concentrated and the residue purified by column chromatography (SiO_2, hexanes–ethyl acetate = 3:1) to afford **7** as a colorless solid (1.3 g, 91%): M.p. 182–185°C; ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1H), 7.44 (d, $J = 7.9$ Hz, 3H), 7.34–6.85 (m, 13H), 6.76 (t, $J = 7.3$ Hz, 2H), 6.17 (d, $J = 7.3$ Hz, 2H), 4.78 (dd, $J = 5.6$, 9.4 Hz, 1H), 4.46–4.35 (m, 2H), 3.08–2.96 (m, 2H), 1.40 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.5, 164.7, 160.8, 154.3, 145.1, 144.2, 139.3, 134.7, 134.3, 134.0, 133.1, 133.0, 130.7, 130.2, 130.1, 129.6, 129.5, 129.3, 128.5, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 126.7, 68.2, 61.9, 61.8, 37.6, 36.3, 15.4. Anal. calcd. for $C_{37}H_{29}NO_3$: C, 80.56; H, 5.30; N, 2.54. Found: C, 80.36; H, 5.26; N, 2.21.

5-(4′-Ethoxycarbonyl-2′-oxazoyl)-3-ethylisoxazoline (8a). To a solution of **6** (0.20 g, 1.2 mmol), nitropropane (0.32 g, 3.6 mmol) and phenyl isocyanate (0.40 g, 3.6 mmol) in benzene (10 mL) was added, via a syringe pump apparatus, a solution of triethylamine (0.40 g, 3.6 mmol) in benzene (15 mL) over a period of 48 h. The solution was filtered to separate the white solid and the solid washed with hexanes. The combined organic solutions were washed twice with brine and dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 10:1) to give **8a** as a yellow oil (0.21 g, 73%): ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 5.54 (dd, $J = 6.9$, 11.1 Hz, 1H), 4.31

(q, $J = 7.1$ Hz, 2H), 3.53 (dd, $J = 6.9$, 17.2 Hz, 1H), 3.29 (dd, $J = 11.1$, 17.2 Hz, 1H), 2.37 (q, $J = 7.5$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.14 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.4, 161.0, 160.0, 145.2, 133.6, 73.4, 61.7, 41.5, 21.3, 14.6, 11.1. EI-HRMS calcd. for $C_{11}H_{14}N_2O_4$ (M^+): m/z 238.0954. Found: m/z 238.0947.

3-Benzyl-5-(4′-ethoxycarbonyl-2′-oxazoyl)isoxazoline (8b). The reaction of **6** (0.50 g, 3.0 mmol) with (2-nitroethyl)benzene, in a fashion similar to the preparation of **8a**, gave **8b** as a yellow oil (0.39 g, 43%): ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H), 7.36–7.16 (m, 5H), 5.56 (dd, $J = 7.1$, 11.2 Hz, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 3.77 (d, $J = 14.9$ Hz, 1H), 3.68 (d, $J = 14.9$ Hz, 1H), 3.44 (dd, $J = 7.1$, 17.3 Hz, 1H), 3.18 (dd, $J = 11.2$, 17.3 Hz, 1H), 1.34 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.2, 161.0, 158.0, 145.2, 133.7, 129.1, 129.0, 128.9, 127.5, 73.9, 61.8, 41.0, 34.0, 14.7. EI-HRMS calcd. for $C_{16}H_{16}N_2O_4$ (M^+): m/z 300.1110. Found: m/z 300.1107.

5-Ethoxycarbonyl-(4′-ethoxycarbonyl-2′-oxazoyl)isoxazoline (8c). Reaction of **6** (1.0 g, 6.0 mmol) with ethyl nitroacetate, in a fashion similar to the preparation of **8a**, gave **8c** as a yellow oil (1.28 g, 76%): ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 5.81 (dd, $J = 7.1$, 11.6 Hz, 1H), 4.32 (2 × q, $J = 7.1$ Hz, 4H), 3.84 (dd, $J = 7.6$, 18.1 Hz, 1H), 3.58 (dd, $J = 11.8$, 18.1 Hz, 1H), 1.33 (2 × t, $J = 7.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 160.7, 160.6, 159.6, 151.4, 145.3, 133.8, 76.3, 62.6, 61.7, 38.0, 14.4, 14.2. EI-HRMS calcd. for $C_{12}H_{14}N_2O_6$ (M^+): m/z 282.0852. Found: m/z 282.0840.

Ethyl 2-cinnamyl-1,3-oxazole-4-carboxylate (9a). To $Pd(PPh_3)_4$ (0.10 g, 0.086 mmol) in THF (10 mL), under N_2, was added **6** (0.50 g, 3.0 mmol) and iodobenzene (0.82 g, 4.0 mmol). The reaction mixture was heated at reflux for 16 h. After cooling, the mixture was filtered through a 2'' bed of silica gel and the silica bed was washed with ethyl acetate. The combined organic layers were washed with 1 N HCl, followed by saturated aqueous $NaHCO_3$, and then brine, dried and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexanes–ethyl acetate = 3:1) gave **9a** as a light yellow solid (0.59 g, 80%). The NMR spectral data for this product was identical with the literature values.[8c]

Ethyl 2-(4′-methoxycinnamyl)-1,3-oxazole-4-carboxylate (9b). To $Pd(PPh_3)_4$ (0.025 g, 0.022 mmol) in THF (10 mL), under N_2, was added **6** (0.20 g, 1.2 mmol) and 4-iodoanisole (0.28 g, 1.2 mmol). The reaction mixture was heated at reflux for 16 h. After cooling, the mixture was filtered through a 2'' bed of silica gel and the silica bed was washed with ethyl acetate. The combined organic layers were washed with 1 N HCl, followed by saturated aqueous $NaHCO_3$, and then brine,

dried and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexanes–ethyl acetate = 3:1) gave **9b** as a nearly colorless solid (0.22 g, 71%): M.p. 88–90°C; ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.57 (d, $J = 16.4$ Hz, 1H), 7.43 and 6.88 (AA'XX', $J_{AX} = 8.8$ Hz, 4H), 6.78 (d, $J = 16.4$ Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.81 (s, 3H), 1.39 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.2, 161.1, 160.6, 142.9, 137.7, 134.5, 128.9, 127.7, 114.5, 110.7, 61.9, 56.1, 15.4. Anal. calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.11; H, 5.43; N, 5.10.

Ethyl 2-(2′-bromoethyl)oxazole-4-carboxylate (10). To a stirred mixture of **6** (1.78 g, 10.6 mmol) in methylene chloride (30 mL) was added HBr (48%, 2.6 g, 16 mmol) and the reaction mixture was stirred vigorously at room temperature overnight. Saturated aqueous sodium bicarbonate (20 mL) was added, the layers were separated and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined organic layers were dried ($MgSO_4$ and the solvent was evaporated under reduced pressure. The residue purified by column chromatography (SiO_2, hexanes–ethyl acetate = 3:1) to yield **10** as white crystals (1.39 g, 53%): m.p. 63–66°C; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 3.73 (t, $J = 7.2$ Hz, 2H), 3.42 (t, $J = 7.2$ Hz, 2H), 1.39 (t, $J = 7.2$, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 161.7, 144.7, 134.2, 61.9, 32.3, 27.6, 14.9; MS m/z (%) = 249, 247 (M^+, 15), 221 and 219 (M^+–C_2H_4, 84), 204 and 202 (M^+–OCH_2CH_3, 41), 168 (M^+–Br, 25), 140 (45), 137 and 135 (100), 122 (69), 109 and 107 (60). EI-HRMS calcd. for $C_8H_{10}NO_3{}^{79}Br$ (M^+): m/z 246.9844. Found: m/z 246.9849. Calcd. for $C_8H_{10}NO_3{}^{81}Br$ (M^+): m/z 248.9824. Found: m/z 248.9831.

Ethyl 2-(2′-nitroethyl)oxazole-4-carboxylate (12). To a stirred mixture of $NaNO_2$ (1.50 g, 21.7 mmol) in DMF (25 mL) at room temperature was added **10** (2.00 g, 8.06 mmol). The reaction mixture was immersed in a water bath and stirred overnight. The reaction mixture was then poured into a mixture of ice cold water (50 mL) and ether (50 mL). The layers were separated and the aqueous phase was extracted with ether (4×5 mL). The combined ethereal layers were washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 2:1) to yield **12** as a yellow liquid (0.90 g, 50%): ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 4.86 (t, $J = 6.7$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.49 (t, $J = 6.7$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 161.2, 144.9, 134.4, 71.4, 62.0, 26.2, 14.8. FAB-HRMS calcd. for $C_8H_{10}N_2O_5Li$ (M^+Li^+): m/z 221.0749. Found: m/z 221.0745.

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