

Electronic Supplementary Information

Direct palladium-catalyzed alkenylation, benzylation and alkylation of ethyl oxazole-4-carboxylate with alkenyl-, benzyl- and alkyl halides

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- General & experimental procedures with all spectral data

Experimental Section

General Informations

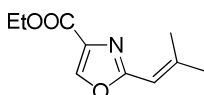
Dioxane was distilled from benzophenone/Na and toluene was distilled from calcium hydride. Melting points are uncorrected. Column chromatography was performed using silica gel (mesh size 60-80 mesh). ¹H NMR and ¹³C NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are given as ppm relative to the residual solvent peak. Microanalyses were carried out at the analytical laboratory of our Department (IRCOF). The ethyl oxazole-4-carboxylate **1** was prepared according literature.¹ Commercially available alkenyl-, benzyl-, allyl- and alkyl halides, 2-(dicyclohexylphosphino)biphenyl (JohnPhos Buchwald's ligand), Hermann-Beller's palladacycle and 1,3-bis-(mesitylimidazolyl)carbene (IMes) were used without further purification.

¹ C. Hoarau, A. Du Fou de Kerdaniel, N. Bracq, P. Grandclaoudon, A. Couture, F. Marsais, *Tetrahedron Lett.* 2005, **46**, 8573.

General procedure for direct vinylation, benzylation and alkylation of ethyl oxazole-4-carboxylate **1** with vinyl-, benzyl- and alkylhalides

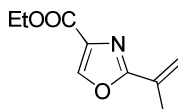
The direct (hetero)vinylation and alkylation reactions were carried out in a sealed tube at 110 °C for 18 h under Ar. A solution of ethyl oxazole-4-carboxylate (50 mg, 0.35 mmol) was allowed to react with vinyl or alkyl halide (2 equiv.) with palladium acetate (4 mg, 0.017 mmol), cesium carbonate (231 mg, 0.70 mmol) and 2-(dicyclohexylphosphino)biphenyl (12 mg, 10 mol %) in dioxane (1 ml). After filtration on Celite and concentration under vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of ethyl acetate (AcOEt) and petroleum ether (P) as the eluent to give the ethyl oxazole-4-carboxylate derivatives **3a-n**. The following detailed procedures are given using optimized experimental conditions (Table 1).

Ethyl 2-(2-methylprop-1-enyl)oxazole-4-carboxylate (**3a**)



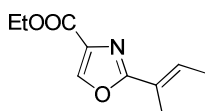
According the general procedure using **1** with 1-bromo-2-methylpropene (72 μ l, 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 1:9, Rf = 0.33) afforded **3a** (100%) as a colourless oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.36 (t, 3H, J = 7.1 Hz), 1.96 (s, 3H), 2.21 (s, 3H), 4.36 (q, 2H, J = 7.1 Hz), 6.13 (s, 1H), 8.11 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.3, 20.7, 27.4, 61.1, 111.1, 133.8, 142.3, 148.6, 161.6, 162.2; IR (KBr) ν 3157.5, 2981.0, 2936.5, 2913.8, 1742.6, 1719.4, 1659.4, 1575.8, 1564.1, 1448.1, 1370.7, 1333.0, 1316.2, 1278.3, 1224.1, 1177.3, 1112.9, 1025.3, 985.4, 944.3, 832.3, 766.2, 722.0, 473.9 cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ (195.2): C, 61.53; H, 6.71; N, 7.18. Found: C, 61.37; H, 6.62; N, 7.15.

Ethyl 2-(prop-1-en-2-yl)oxazole-4-carboxylate (**3b**)



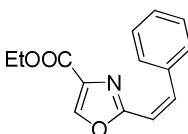
According the general procedure using **1** with 2-bromopropene (63 μ l, 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 1:9, Rf = 0.31) afforded **3b** (55%) as a colourless oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.37 (t, 3H, J = 7.2 Hz), 2.19 (s, 3H), 4.39 (q, 2H, J = 7.2 Hz), 5.46 (s, 1H), 6.02 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.4, 19.2, 61.4, 120.1, 131.3, 134.4, 143.7, 161.5, 163.4; IR (KBr) ν 3448.7, 3160.3, 2985.9, 1736.2, 1577.6, 1542.3, 1372.6, 1316.8, 1177.1, 1115.9, 1023.0, 766.5 cm^{-1} ; Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$ (181.2): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.51; H, 5.98; N, 7.64.

(E)-Ethyl 2-(but-2-en-2-yl)oxazole-4-carboxylate (3c)



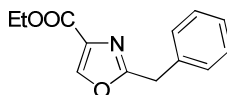
According to the general procedure using **1** with (*E*)-2-bromobut-2-ene (72 μ l, 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 1:9, R_f = 0.29) afforded **3c** (97%) as a colourless oil. (*Z*) ^1H NMR (CDCl_3 , 300 MHz) δ = 1.36 (t, 3H, J = 7.1 Hz), 1.84 (dd, 3H, J = 1.2 Hz, J = 7.2 Hz), 2.07 (dd, 3H, J = 1.2 Hz, J = 2.4 Hz), 4.37 (q, 2H, J = 7.1 Hz), 6.67-6.74 (m, 1H), 8.10 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 12.8, 14.2, 14.4, 61.3, 123.9, 131.3, 134.1, 143.2, 161.7, 164.5; IR (KBr) ν 3155.8, 2982.3, 2928.5, 1743.8, 1720.5, 1576.0, 1530.6, 1447.8, 1370.4, 1333.5, 1315.9, 1291.5, 1226.4, 1151.9, 1114.3, 1024.4, 983.1, 936.9, 830.1, 769.4, 733.8 cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ (195.5): C, 61.53; H, 6.71; N, 7.18. Found: C, 61.39; H, 6.64; N, 7.08.

(Z)-ethyl 2-styryloxazole-4-carboxylate (3d)



According to the general procedure using **1** with (*Z*)-(2-bromovinyl)benzene² (130 mg, 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 1:9, R_f = 0.34) afforded **3d** (60%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.39 (t, 3H, J = 6.9 Hz), 4.39 (q, 2H, J = 6.9 Hz), 6.47 (d, 1H, J = 12.8 Hz), 7.00 (d, 1H, J = 12.8 Hz), 7.35-7.38 (m, 3H), 7.49-7.53 (m, 2H), 8.06 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.4, 61.4, 114.3, 128.3, 128.9, 129.3, 134.4, 135.5, 138.7, 143.2, 161.0, 161.3; Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3$ (243.3): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.32; H, 5.28; N, 5.62.

Ethyl 2-benzyloxazole-4-carboxylate (3e)

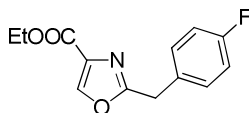


According to the general procedure using **1** with benzylchloride (82 μ l, 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 2:8, R_f = 0.41) afforded **3e** (86%) as a colourless oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.37 (t, 3H, J = 7.2 Hz), 4.16 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 7.26-7.30 (m, 5H), 8.13 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.5, 34.7, 61.3, 127.5, 128.9, 133.6, 134.7, 144.3, 161.4, 163.9; IR (KBr) ν 3162.9, 3088.5, 3064.2, 3031.1, 2982.2, 2931.3, 1736.5, 1582.6, 1496.1, 1455.5, 1371.5, 1316.4, 1176.7, 1109.2,

² H.C. Brown., S.K. Gupta, *J. Am. Chem. Soc.* 1972, **94**, 4370; H.C. Brown, T. Hamaoka, N. Ravindran, *J. Am. Chem. Soc.* 1973, **95**, 6456.

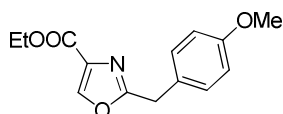
1024.0, 984.0, 767.6, 728.0, 697.4 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3$ (231.2): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.72; H, 5.55; N, 5.97.

Ethyl 2-(4-fluorobenzyl)oxazole-4-carboxylate (**3f**)



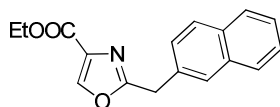
According to the general procedure using **1** with 4-fluorobenzylchloride (84 μl , 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 2:8, R_f = 0.29) afforded **3f** (75%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.29 (t, 3H, J = 7.1 Hz), 4.05 (s, 2H), 4.29 (q, 2H, J = 7.1 Hz), 6.89-6.95 (m, 2H), 7.16-7.21 (m, 2H), 8.06 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.3, 33.8, 61.3, 115.6, 115.9, 130.4, 133.6, 144.2, 144.3, 160.5, 161.2, 163.6, 163.7; IR (KBr) ν 3162.8, 2983.0, 2929.3, 1739.6, 1583.9, 1510.3, 1371.7, 1316.9, 1224.6, 1176.9, 1159.5, 1109.2, 1023.1, 834.0, 766.1 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{FNO}_3$ (249.2): C, 62.65; H, 4.85; F, 7.62; N, 5.62. Found: C, 62.59; H, 4.67; F, 7.58; N, 5.55.

Ethyl 2-(4-methoxybenzyl)oxazole-4-carboxylate (**3g**)



According to the general procedure using **1** with 4-methoxybenzylchloride (97 μl , 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 2:8, R_f = 0.28) afforded **3g** (91%) as a white powder (mp = 53-54 $^\circ\text{C}$). ^1H NMR (CDCl_3 , 300 MHz) δ = 1.35 (t, 3H, J = 7.2 Hz), 3.75 (s, 3H), 4.08 (s, 2H), 4.35 (q, 2H, J = 7.2 Hz), 6.83 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.7 Hz), 8.11 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 14.3, 33.7, 55.3, 61.2, 114.20, 126.6, 129.9, 133.5, 144.1, 144.2, 158.9, 161.3, 164.2; IR (KBr) ν 3138.6, 3097.2, 2963.8, 2937.7, 2837.7, 1725.4, 1612.4, 1587.0, 1513.9, 1299.3, 1252.0, 1175.8, 1138.8, 1106.8, 1033.7, 985.7, 831.3, 787.1, 773.2, 665.6, 555.5, 514.6 cm^{-1} ; Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$ (261.3): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.43; H, 5.77; N, 5.28.

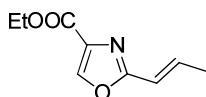
Ethyl 2-(naphthalen-2-ylmethyl)oxazole-4-carboxylate (**3h**)



According to the general procedure using **1** with 1-(chloromethyl)naphthalene (106 μl , 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 2:8, R_f = 0.33) afforded **3h** (80%) as a brown oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.37 (t, 3H, J = 7.2 Hz),

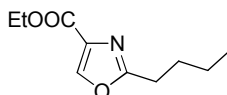
4.38 (q, 2H, $J = 7.2$ Hz), 4.60 (s, 2H), 7.43 (d, 2H, $J = 4.8$ Hz), 7.49-7.54 (m, 2H), 7.79-7.82 (t, 1H, $J = 4.8$ Hz), 7.85 (d 1H, $J = 7.6$ Hz), 8.06 (s, 1H), 8.11 (d, 1H, $J = 7.6$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 14.4, 32.5, 61.3, 123.7, 125.6, 126.0, 126.7, 127.7, 128.5, 128.8, 130.8, 131.8, 133.6, 133.9, 144.2, 161.4, 163.9$; IR (KBr) $\nu 3162.1, 3049.0, 2925.3, 2854.5, 1731.8, 1582.5, 1511.5, 1396.4, 1316.6, 1108.9, 1021.2, 785.7$ cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3$ (281.3): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.51; H, 5.22; N, 4.75.

(*E*)-Ethyl 2-(prop-1-enyl)oxazole-4-carboxylate (**3i**)



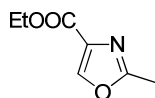
According to the general procedure using **1** with allylchloride (58 μl , 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 2:8, $R_f = 0.31$) afforded **3i** (97%) as a colourless oil. ^1H NMR (CDCl_3 , 300 MHz) $\delta = 1.37$ (t, 3H, $J = 7.1$ Hz), 1.94 (dd, 3H, $J = 1.8$ Hz, $J = 6.9$ Hz), 4.38 (q, 2H, $J = 7.1$ Hz), 6.33 (dd, 1H, $J = 1.8$ Hz, $J = 15.9$ Hz), 6.77-6.89 (m, 1H), 8.11 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 14.5, 18.7, 61.3, 117.3, 134.8, 137.8, 143.1, 161.6, 161.2$; IR (KBr) $\nu 2924.2, 2854.4, 1742.0, 1721.7, 1666.8, 1575.1, 1544.2, 1446.1, 1371.3, 1317.0, 1145.6, 1113.6, 1024.4, 964.4, 764.4, 703.2$ cm^{-1} ; Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$ (181.2): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.52; H, 5.98; N, 7.54.

Ethyl 2-butylloxazole-4-carboxylate (**3j**)

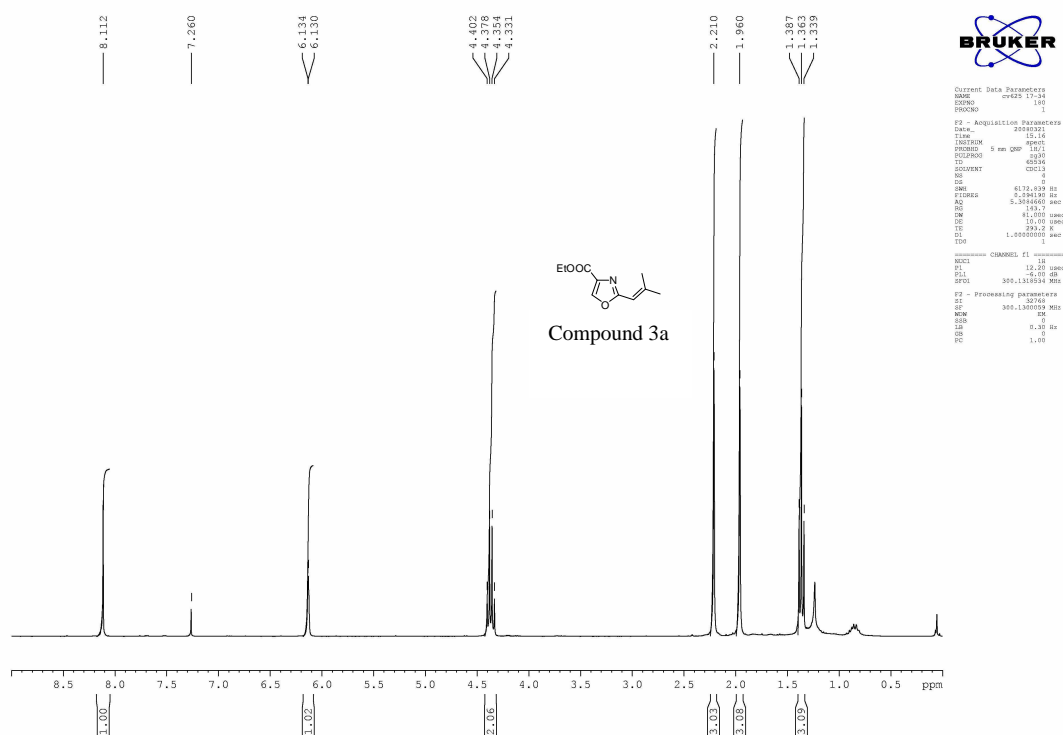


According to the general procedure using **1** with bromobutane (77 μl , 0.70 mmol). Standard workup followed by flash chromatography (AcOEt/PE 1:9, $R_f = 0.26$) afforded **3j** (60%) as a colourless oil. ^1H NMR (CDCl_3 , 300 MHz) $\delta = 0.90$ (t, 3H, $J = 7.5$ Hz), 1.32-1.37 (m, 6H), 1.73 (m, 2H), 2.78 (t, 2H, $J = 7.8$ Hz), 4.45 (q, 2H, $J = 7.2$ Hz), 8.11 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 13.8, 14.6, 22.4, 28.0, 29.2, 61.3, 133.6, 143.8, 161.7, 166.2$; IR (KBr) $\nu 3158.7, 2961.0, 2934.6, 2874.2, 1743.7, 1586.5, 1466.3, 1370.9, 1316.9, 1143.2, 1110.4, 1024.3, 979.9, 833.6, 771.8$ cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_3$ (197.2): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.72; H, 7.63; N, 6.96.

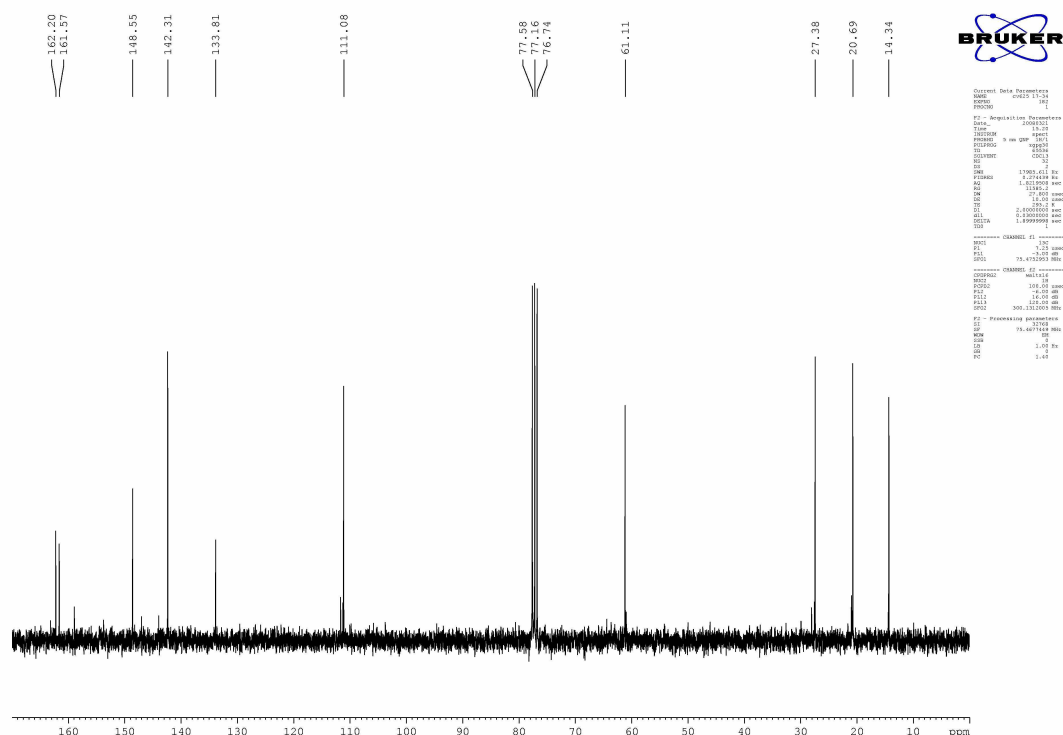
Ethyl 2-methyloxazole-4-carboxylate (**3l**)



According the general procedure using **1** with iodomethane (44 μ l, 0.70 mmol). Standard workup followed HPLC on silica gel (Li-chrosorb 10 μ m) (AcOEt/PE 4:6, R_f = 0.35) afforded **3l** (41%) as a white oil. ^1H NMR (CDCl_3 , 300 MHz) δ = 1.33 (t, 3H, J = 7.2 Hz), 2.46 (s, 3H), 4.32 (q, 2H, J = 7.2 Hz), 8.09 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ = 13.9, 14.3, 61.2, 133.5, 143.7, 161.4, 162.4; IR (KBr) ν 3126.0, 2984.3, 2936.3, 1740.6, 1592.7, 1445.8, 1371.4, 1337.5, 1317.3, 1295.8, 1219.1, 1146.4, 1110.2, 1029.6, 908.8, 832.0, 771.0, 674.2 cm^{-1} ; Anal. Calcd for $\text{C}_7\text{H}_9\text{NO}_3$ (155.1): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.08; H, 5.78; N, 8.95.



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