Supporting Information
for DOI: 10.1055/s-0031-1289865
© Georg Thieme Verlag KG Stuttgart · New York 2011
Supporting Information

Facile Synthesis of 5-Carboxamide-oxazolines via a Passerini 3CC/Staudinger/aza-Wittig Sequence

Jing Wu, Jian-Chao Liu, Long Wang, Ming-Wu Ding*

Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, People’s Republic of China
Fax +86(27)67862041; E-mail: mwding@mail.ccnu.edu.cn

Table of Contents

General Methods……………………………………………………………………..S2
Preparations and Characterization data of Compounds 1…………S2-S4
Preparations and Characterization data of Compounds 4. ……..S4-S6
1H NMR and 13C NMR Spectrums for Compounds 1 and 4……..S7-S21
**General Methods:**
Reactions were generally carried out in an appropriate round bottom flask with magnetic stirring. Thin layer chromatography (TLC) was performed on a silica gel. All melting points were taken on a Digital Melting Point without correction. $^1$H, and $^{13}$C spectra were recorded on a 400 MHz or 600 MHz Varian Mercury Plus spectrometer. Chemical shifts for $^1$H NMR spectra are reported in ppm downfield from TMS, chemical shifts for $^{13}$C NMR spectra are reported in ppm relative to internal chloroform ($\delta$ 77.0 ppm for $^{13}$C), and chemical shifts. The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartlet; br refers to a broad signal. MS were measured on a Finnigan Trace MS spectrometer. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

**General Procedure for the Synthesis of Chlorides 1 via Passerini Reaction**
To a solution of chloroacetaldehyde (solution 40% in water) (0.50 mL, 3 mmol) in methanol (15 mL) was added sequentially acid (3 mmol) and isocyanide (3 mmol) at room temperature. After the reaction was completed at ambient temperature (monitoring by TLC), the solvent was removed off under reduced pressure and the residue was recrystallized from ether/petroleum ether to give the chloride 1. The prepared new compounds are as follows:

**1-(tert-Butylcarbamoyl)-2-chloroethyl benzoate (1a):**
White crystals, mp: 141-142 °C; IR (KBr, cm$^{-1}$): 3310, 3087, 2983, 1732, 1670, 1561, 1263, 1123, 711; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ (ppm): 8.10 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.67-7.51 (m, 3H, Ar-H), 6.11 (s, 1H, NH), 5.58 (t, $J = 3.6$ Hz, 1H, COCH), 4.15-3.95 (m, 2H, ClCH$_2$), 1.39 (s, 9H, 3CH$_3$); MS (m/z, %): 283 (M$^+$, 1), 211 (5), 122 (9), 105 (100), 77 (21); Anal.Calcd for C$_{14}$H$_{18}$ClNO$_3$: C, 59.26; H, 6.39; N, 4.94. Found: C, 59.34; H, 6.58; N, 4.82.

**1-(Butylcarbamoyl)-2-chloroethyl 4-chlorobenzoate (1b):**
White crystals, mp: 110-111 °C; IR (KBr, cm$^{-1}$): 3287, 3096, 2955, 2870, 1733, 1665, 1593, 1263, 1092, 758; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$ (ppm): 8.05-7.44 (m, 4H, Ar-H), 6.21 (s, 1H, NH), 5.67 (t, $J = 3.6$ Hz, 1H, COCH), 4.14-3.97 (m, 2H, ClCH$_2$), 3.39-3.28 (m, 2H, NCH$_2$), 1.55-1.32 (m, 4H, 2CH$_2$), 0.92 (t, $J = 7.2$ Hz, 3H, CH$_3$); MS (m/z, %): 317 (M$^+$, 1), 245 (3), 156 (17), 139 (100), 111 (17); Anal.Calcd for C$_{14}$H$_{17}$Cl$_2$NO$_3$: C, 52.84; H, 5.39; N, 4.40. Found: C, 52.71; H, 5.62; N, 4.73.

**1-(Butylcarbamoyl)-2-chloroethyl 3-nitrobenzoate (1c):**
White crystals, mp: 146-147 °C; IR (KBr, cm$^{-1}$): 3312, 3089, 2967, 2886, 1730, 1662, 1602, 1301, 1123, 1090, 756; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$ (ppm): 8.91 (s, 1H, Ar-H), 8.51-7.74 (m, 3H, Ar-H), 6.25 (s, 1H, NH), 5.69 (t, $J = 5.4$ Hz, 1H, COCH), 4.15-4.01(m, 2H, ClCH$_2$), 3.94-3.30 (m, 2H, NCH$_2$), 1.56-1.52 (m, 2H, CH$_2$), 1.38-1.35 (m, 2H, CH$_2$), 0.93 (t, $J = 7.2$ Hz, 3H, CH$_3$); MS (m/z, %): 328 (M$^+$, 1), 256 (7), 167 (19), 150 (100), 122 (24); Anal.Calcd for C$_{14}$H$_{17}$Cl$_2$NO$_5$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.30; H, 5.37; N, 8.69.
1-(Cyclohexylcarbamoyl)-2-chloroethyl 3-nitrobenzoate (1d):

White crystals, mp: 165-166 °C; IR (KBr, cm\(^{-1}\)): 3320, 3018, 2936, 2901, 2897, 1721, 1638, 1598, 1332, 1292, 1097, 778; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 8.91 (s, 1H, Ar-H), 8.51-7.73 (m, 3H, Ar-H), 6.07 (s, 1H, NH), 5.64 (m, \(J = 4.2\) Hz, 1H, COCH), 4.14-3.83 (m, 2H, ClCH\(_2\)), 3.88-3.83 (m, 1H, NCH), 1.99-1.16 (m, 10H, 5CH\(_2\)); MS (m/z, %): 354 (M\(^+\), 1), 256 (11), 167 (23), 150 (100), 122 (29); Anal.Calcd for C\(_{16}\)H\(_{19}\)ClN\(_2\)O\(_5\): C, 54.17; H, 5.40; N, 7.90. Found: C, 54.39; H, 5.73; N, 7.65.

1-(tert-Butylcarbamoyl)-2-chloroethyl 4-chlorobenzoate (1e):

White crystals, mp: 119-120 °C; IR (KBr, cm\(^{-1}\)): 3306, 3086, 2973, 1733, 1669, 1560, 1252, 1094, 756; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 8.02 (d, \(J = 8.4\) Hz, 2H, Ar-H), 7.49 (d, \(J = 8.4\) Hz, 2H, Ar-H), 6.02 (s, 1H, NH), 5.55 (t, \(J = 3.6\) Hz, 1H, COCH), 4.13-3.93 (m, 2H, ClCH\(_2\)), 1.38 (s, 9H, 3CH\(_3\)); MS (m/z, %): 317(M\(^+\), 1), 245 (7), 156 (15), 139 (100), 111 (22); Anal.Calcd for C\(_{14}\)H\(_{17}\)Cl\(_2\)NO\(_3\): C, 52.84; H, 5.39; N, 4.40. Found: C, 52.56; H, 5.02; N, 4.25.

1-(tert-Butylcarbamoyl)-2-chloroethyl 4-methylbenzoate (1f):

White crystals, mp: 107-108 °C; IR (KBr, cm\(^{-1}\)): 3316, 3065, 2963, 2901, 1722, 1643, 1618, 1323, 1219, 1041, 798; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 7.98 (d, \(J = 7.8\) Hz, 2H, Ar-H), 7.31 (d, \(J = 7.8\) Hz, 2H, Ar-H), 6.10 (s, 1H, NH), 5.57 (s, 1H, COCH), 4.14-3.94 (m, 2H, ClCH\(_2\)), 2.45 (s, 3H, CH\(_3\)), 1.38 (s, 9H, 3CH\(_3\)); MS (m/z, %): 297 (M\(^+\), 1), 225 (5), 136 (7), 119 (100), 91 (26); Anal.Calcd for C\(_{15}\)H\(_{20}\)ClNO\(_3\): C, 60.50; H, 6.77; N, 4.70. Found: C, 60.23; H, 6.92; N, 4.45.

1-(Cyclohexylcarbamoyl)-2-chloroethyl benzoate (1g):

White crystals, mp: 145-147 °C; IR (KBr, cm\(^{-1}\)): 3288, 3094, 2930, 2853, 1727, 1660, 1592, 1321, 1264, 1118, 705; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 8.19-7.53 (m, 5H, Ar-H), 6.13 (s, 1H, NH), 5.67 (s, 1H, COCH), 4.15-3.98 (m, 2H, ClCH\(_2\)), 3.90-3.75 (m, 1H, NCH), 1.98-1.17 (m, 10H, 5CH\(_2\)); MS (m/z, %): 309 (M\(^+\), 2), 211 (5), 122 (12), 105 (100), 77 (15); Anal.Calcd for C\(_{16}\)H\(_{20}\)ClNO\(_3\): C, 62.03; H, 6.51; N, 4.52. Found: C, 62.31; H, 6.72; N, 4.37.

1-(Cyclohexylcarbamoyl)-2-chloroethyl 4-methylbenzoate (1h):

White crystals, mp: 176-177 °C; IR (KBr, cm\(^{-1}\)): 3286, 2933, 2855, 1725, 1663, 1562, 1265, 1115, 1068; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 7.99-7.27 (m, 4H, Ar-H), 6.15 (s, 1H, NH), 5.65 (s, 1H, COCH), 4.14-3.96 (m, 2H, ClCH\(_2\)), 3.90-3.78 (m, 1H, NCH), 2.45 (s, 3H, CH\(_3\)), 1.98-1.15 (m, 10H, 5CH\(_2\)); MS (m/z, %): 323 (M\(^+\), 2), 207 (8), 136 (12), 119 (100), 91 (15); Anal.Calcd for C\(_{17}\)H\(_{22}\)ClNO\(_3\): C, 63.06; H, 6.85; N, 4.33. Found: C, 63.18; H, 6.98; N, 4.10.

1-(tert-Butylcarbamoyl)-2-chloroethyl 2-methylbenzoate (1i):

White crystals, mp: 106-107 °C; IR (KBr, cm\(^{-1}\)): 3303, 3083, 2970, 1716, 1664, 1559, 1252, 1102, 741; \(^1\)H NMR (CDCl\(_3\), 600MHz) \(\delta\) (ppm): 8.00-7.31 (m, 4H, Ar-H), 6.12 (s, 1H, NH), 5.55 (t, \(J = 3.6\) Hz, 1H, COCH), 4.15-3.96 (m, 2H, ClCH\(_2\)), 2.65 (s, 3H, CH\(_3\)), 1.39 (s, 9H, 3CH\(_3\)); MS (m/z, %): 297 (M\(^+\), 1), 225 (5), 136 (8),
1-(Cyclohexylcarbamoyl)-2-chloroethyl 2-methylbenzoate (1j):
White crystals, mp: 110-111 °C; IR (KBr, cm-1): 3313, 3030, 2968, 2910, 1719, 1665, 1615, 1334, 1278, 1092, 799; 1H NMR (CDCl3, 600MHz) δ (ppm): 7.99 (d, J = 7.8 Hz, 1H, Ar-H), 7.50-7.31 (m, 3H, Ar-H), 6.15 (s, 1H, NH), 5.63 (t, J = 3.6 Hz, 1H, COCH), 4.15-3.99 (m, 2H, ClCH2), 3.87-3.84 (m, 1H, NCH), 2.67 (s, 3H, CH3), 1.97-1.15 (m, 10H, 5CH 2); MS (m/z, %): 323 (M +, 1), 225 (9), 136 (10), 119 (100), 91 (29); Anal.Calcd for C17H22ClNO3: C, 63.06; H, 6.85; N, 4.33. Found: C, 63.35; H, 7.02; N, 4.25.

General Procedure for the Synthesis of 5-Carboxamide-oxazolines 4

A mixture of chloride 1 (1 mmol) and sodium azide (0.13 g, 2 mmol) was stirred for 2 hours at 100 °C in anhydrous DMF (10 mL). After the completion of the reaction (monitoring by TLC), the reaction mixture was filtered, the residue was concentrated in vacuo and toluene (10 mL) was added. Then triphenylphosphine (0.26 g, 1 mmol) in toluene (5 mL) was added dropwise at room temperature. The reaction mixture was stirred for 2 hours at room temperature and then for additional hours (Table 2) at refluxing temperature. The solvent was removed off under reduced pressure and the residue was purified by silica gel chromatography (hexanes:EtOAc, 3:1) to afford 5-carboxamide-oxazolines 4 in moderate to good yields. The prepared new compounds are as follows:

N-tert-Butyl-4,5-dihydro-2-phenyloxazole-5-carboxamide (4a):
White crystals, mp: 106-107 °C; IR (KBr, cm-1): 3290, 3091, 2968, 1725, 1672, 1649, 1543 , 1263, 1217, 1141, 1101, 1059, 1027, 717, 694; 1H NMR (CDCl3, 600MHz) δ (ppm): 7.97 (d, J = 7.8 Hz, 2H, Ar-H), 7.56-7.45 (m, 3H, Ar-H), 6.17 (s, 1H, NH), 4.95-4.91 (m, 1H, COCH), 4.42-4.14 (m, 2H, NCH 2), 1.34 (s, 9H, 3CH 3); 13C NMR (CDCl 3, 150MHz) δ (ppm): 169.6, 162.4, 131.6, 128.5, 128.00, 127.9, 126.9, 59.5, 51.1, 28.5; MS (m/z, %): 246 (M +, 2), 146 (23), 105 (100), 77 (34); Anal.Calcd for C 14H18N2O2: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.92; H, 7.54; N, 11.65.

N-Butyl-2-(4-chlorophenyl)-4,5-dihydrooxazole-5-carboxamide (4b):
White crystals, mp: 142-143 °C; IR (KBr, cm-1): 3276, 3091, 2965, 1648, 1561, 1466, 1091, 1074, 835; 1H NMR (CDCl3, 600MHz) δ (ppm): 7.91 (d, J = 8.4 Hz, 2H, Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 6.31 (s, 1H, NH), 5.05-5.02 (m, 1H, COCH), 4.43-4.17 (m, 2H, NCH 2), 3.36-3.23 (m, 2H, NCH2), 1.53-1.48 (m, 2H, CH 2), 1.38-1.36 (m, 2H, CH 2), 0.92 (t, J = 7.2 Hz, 3H, CH3); 13C NMR (CDCl3, 150MHz) δ (ppm): 170.3, 161.7, 138.1, 129.5, 129.3, 128.9, 125.3, 59.7, 38.9, 31.5, 20.00, 13.7; MS (m/z, %): 280 (M +, 5), 208 (29), 180 (86), 152 (36), 139 (100), 125 (92); Anal.Calcd for C14H17ClN2O2: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.52; H, 6.43; N, 10.21.

N-Butyl-4,5-dihydro-2-(3-nitrophenyl)oxazole-5-carboxamide (4c):
White crystals , mp: 151-152 °C; IR (KBr, cm-1): 3278, 3112, 2956, 1736,1657, 1530, 1352, 1254, 1133, 719; 1H NMR (CDCl3, 600MHz) δ (ppm): 8.91 (s, 1H, Ar-H), 8.51-8.43 (m, 2H, Ar-H), 7.76 (t, J = 7.2 Hz, 1H, Ar-H), 6.20 (s, 1H, NH), 5.68 (t, J = 4.2 Hz, 1H, COCH), 4.13-4.03 (m, 2H, NCH2), 3.46-3.20 (m, 2H, NCH2), 1.60-1.53 (m, 2H, CH2), 1.38-1.36 (m, 2H, CH2), 0.93 (t, J = 7.2 Hz, 3H, CH3); 13C NMR (CDCl3, 150MHz) δ (ppm): 165.8, 163.1, 148.3, 135.5, 130.4, 130.1, 128.3, 124.8, 74.1, 43.5,
39.4, 31.4, 19.9, 13.7; MS (m/z, %): 291 (M⁺, 3), 219 (30), 191 (100), 163 (36), 150 (30), 117 (32). Anal. Calcd for C₁₄H₁₇N₃O₄: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.95; H, 6.07; N, 14.28.

N-Cyclohexyl-4,5-dihydro-2-(3-nitrophenyl)oxazole-5-carboxamide (4d):

White crystals, mp: 214-215 °C; IR (KBr, cm⁻¹): 3231, 2932, 2851, 1643, 1533, 1241, 1033, 765; ¹H NMR (CDCl₃, 600MHz) δ (ppm): 8.78 (s, 1H, Ar-H), 8.39-8.32 (m, 2H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 6.16 (s, 1H, NH), 5.10-5.07 (m, 1H, COCH), 4.48-4.22 (m, 2H, NCH₂), 3.83-3.81 (m, 1H, NCH), 2.00-1.13 (m, 10H, 5CH₂); ¹³C NMR (CDCl₃, 150MHz) δ (ppm): 169.3, 161.6, 139.8, 131.2, 130.3, 129.3, 125.6, 125.0, 76.0, 59.5, 47.6, 32.5, 24.6, 21.6; MS (m/z, %): 317 (M⁺, 7), 236 (27), 219 (22), 191 (100), 163 (37), 150 (33), 117 (40); Anal. Calcd for C₁₆H₁₉N₃O₄: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.25; H, 6.41; N, 13.53.

N-Cyclohexyl-4,5-dihydro-2-phenyloxazole-5-carboxamide (4g):

White crystals, mp: 171-173 °C; IR (KBr, cm⁻¹): 3276, 2932, 1558, 1449, 1251, 1066, 691; ¹H NMR (CDCl₃, 600MHz) δ (ppm): 7.86-7.26 (m, 4H, Ar-H), 6.16 (s, 1H, NH), 4.92-4.89 (m, 1H, COCH), 4.39-4.13 (m, 2H, NCH₂), 3.85-3.75 (m, 1H, NCH), 1.95-1.09 (m, 10H, 5CH₂); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 169.7, 162.5, 142.2, 129.2, 129.1, 127.9, 124.0, 76.8, 59.4, 51.1, 28.5, 21.4; MS (m/z, %): 260 (M⁺, 30), 160 (100), 132 (32), 119 (51), 105 (55); Anal. Calcd for C₁₆H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.04; H, 8.02; N, 10.98.

N-Cyclohexyl-4,5-dihydro-2-(4-methylphenyl)oxazole-5-carboxamide (4h):

White crystals, mp: 192-193 °C; IR (KBr, cm⁻¹): 3282, 2935, 1650, 1555, 1071; ¹H NMR (CDCl₃, 600MHz) δ (ppm): 7.86-7.26 (m, 4H, Ar-H), 6.20 (s, 1H, NH), 5.01-4.98 (m, 1H, COCH), 4.41-4.14 (m, 2H, NCH₂), 3.82-3.79 (m, 1H, NCH), 2.42 (s, 3H, CH₃), 1.97-1.08 (m, 10H, 5CH₂); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 169.7, 162.7, 142.3, 129.3, 129.2, 128.0, 124.1, 76.8, 59.7, 47.8, 33.0, 24.6, 21.6; MS (m/z, %): 286 (M⁺, 8), 188 (9), 160 (81), 119 (100), 105 (34); 86 (34).
N-tert-Butyl-4,5-dihydro-2-(2-methylphenyl)oxazole-5-carboxamide (4i):

White crystals, mp: 130 °C; IR (KBr, cm⁻¹): 3279, 3083, 2972, 2931, 1664, 1645, 1559, 1364, 1245, 1042; ^1H NMR (CDCl₃, 600MHz) δ (ppm): 7.80 (d, J = 7.2 Hz, 1H, Ar-H), 7.40-7.27 (m, 3H, Ar-H), 6.19 (s, 1H, NH), 4.89-4.86 (m, 1H, COCH), 4.44-4.19 (m, 2H, NCH₂), 2.62 (s, 3H, CH₃), 1.37 (s, 9H, 3CH₃); ^13C NMR (CDCl₃, 150MHz) δ (ppm): 169.7, 162.5, 138.9, 131.3, 130.8, 129.4, 129.3, 126.1, 125.6, 76.3, 59.9, 51.1, 28.5, 21.9; MS (m/z, %): 260 (M⁺, 26), 160 (100), 132 (36), 119 (48), 105 (51); Anal.Calcd for C₁₇H₂₂N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.11; H, 7.98; N, 9.88.

N-Cyclohexyl-4,5-dihydro-2-(2-methylphenyl)oxazole-5-carboxamide (4j):

White crystals, mp: 136-137 °C; IR (KBr, cm⁻¹): 3324, 2933, 2853, 1654, 1559, 1247, 1043, 726; ^1H NMR (CDCl₃, 600MHz) δ (ppm): 7.81 (d, J = 7.8 Hz, 1H, Ar-H), 7.40-7.27 (m, 3H, Ar-H), 6.24 (s, 1H, NH), 4.98-4.95 (m, 1H, COCH), 4.46-4.20 (m, 2H, NCH₂), 3.83-3.78 (m, 1H, NCH), 2.64 (s, 3H, CH₃), 1.97-0.89 (m, 10H, 5CH₂); ^13C NMR (CDCl₃, 150MHz) δ (ppm): 169.4, 162.4, 138.7, 131.1, 130.6, 129.2, 125.9, 125.4, 75.9, 59.7, 47.6, 32.5, 25.0, 24.4, 21.7; MS (m/z, %): 286 (M⁺, 31), 160 (100), 132 (42), 119 (98), 105 (62), 98 (35), 91 (23); Anal.Calcd for C₁₇H₂₅N₂O₂: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.01; H, 7.98; N, 9.96.