A Facile Synthesis of 1,2,4-Oxadiazolidin-3-ones via Tandem *O, N*-Addition of Hydroxyureas to Methyl Propiolate

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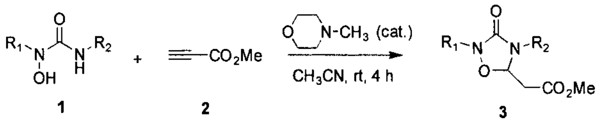
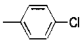
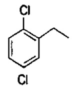
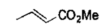
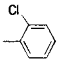
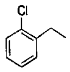
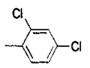
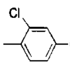
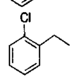
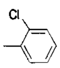
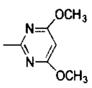
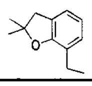
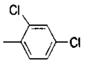
Abstracts: 1,2,4-Oxadiazolidin-3-ones were synthesized from tandem *O, N*-addition of hydroxyureas to methyl propiolate in good to excellent yields.

The synthesis of 1,2,4-oxadiazolidin-3-one was first reported by Lopresti and coworker in 1958 for development of related heterocycles with barbituric acid and hydantoin derivatives because of their widespread uses in medicine.[1] Since then, only a few groups have reported the synthesis of 1,2,4-oxadiazolidin-3-ones for use in fungicides or herbicides.[2,3] The routes towards 1,2,4-oxadiazolidin-3-ones employed in their procedures involve the reaction of carbamonyl chlorides and hyroxylamines,[1] the condensation of hydroxyureas and ketones,[2] and the reaction of hydroxyureas and bromochloromethane or diiodomethane in basic conditions.[3] In the previous paper,[4] we reported that hydroxamic acids readily reacted with a methyl propiolate to provide the corresponding *N*-acyloxaziridines in excellent yields. In connection with these results, we envisioned that *N*-hydroxyureas might undergo a tandem *O,N*-addition to a methyl propiolate to afford the corresponding 1,2,4-oxadiazolidin-3-ones under the condition employed previously. Here we wish to report a facile synthesis of 1,2,4-oxadiazolidin-3-ones via tandem *O,N*-addition of hydroxyureas to methyl propiolate.

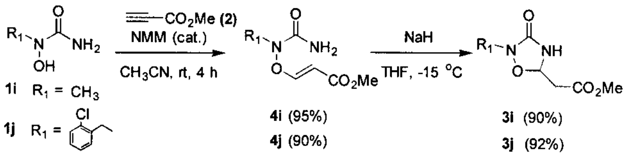


Scheme 1

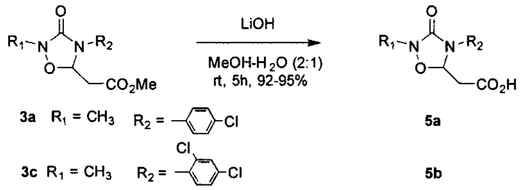
Table. Synthesis of 1,2,4-Oxadiazolidin-3-ones **3a-3h**

Compounds	Hydroxyurea (**1**) R_1	Hydroxyurea (**1**) R_2	Products (**3**) Yields (%)	Compounds	Hydroxyurea (**1**) R_1	Hydroxyurea (**1**) R_2	Products (**3**) Yields (%)
a	CH_3		96	e			92
b	CH_3		86	f			90
c	CH_3		95	g			80
d	CH_3		87	h			86

A variety of hydroxyureas **1a-1h** were synthesized by treatment of hydroxyamines with the corresponding isocyanates in excellent yields (90-95%). The cyclization via *O, N*-addition of hydroxyureas to methyl propiolate was performed in the presence of 4-methylmorpholine to afford the corresponding oxadiazolidin-3-ones **3a-3h** in good to excellent yields. The cyclization reactions employed here were completed within 4 hours and no significant by-products were observed. The results were summerized in **Table** and all isolated products **3a-3h** gave satisfatory spectroscopic data on ^1H NMR, IR, MS, and HRMS.



Scheme 2



Scheme 3

In addition, the hydroxyurea derivatives **1i, 1j** were synthesized by treatment of the corresponding hydroxylamines with potassium cyanate according to the known procedure.[5] However, when these compounds were subjected to the reaction as illustrated in **Scheme 2**, only *O*-added products **4, 5** were obtained in good yields with no observation of cyclized products. These intermediates **4, 5** were isolated and treated with sodium hydride in THF at 15 °C to afford the cyclized products **3i, 3j** in excellent yields. For further manipulation of those products, **3a** and **3c** were hydrolyzed with lithium hydroxide to provide the corresponding acids **5a** and **5b** in good yields.

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References and Notes

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(6) General procedure for the preparation of **3a-3h**; To a solution of hyroxyurea (1.0 equiv.) and methyl propiolate (1.05 equiv.) in acetonitrile was added 4-methyl morpholine (0.2 equiv.) at room temperature. The reaction mixture was stirred for 4 h and

concentrated under reduced pressure. The crude product was recrystallized in ether/hexane or purified by column chromatography on silica gel (hexane/ethyl acetate = 2 : 1) to afford the products of **3a-3h** as crystals or oil. Spectroscopic data for selected compounds; (**3a**): crystals, mp 83-85 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.37 (s, 4H), 6.13 (dd, *J* = 2.9, 7.6 Hz, 1H), 3.67 (s, 3H), 2.95 (dd, *J* = 7.5, 16.3 Hz, 1H), 2.77 (dd, *J* = 3.0, 16.3 Hz, 1H); FT-IR 3073.4, 2960.2, 1744.4, 1712.6, 1500.8, 1432.4, 1407.9, 1387.7, 1171.8, 813.8; MS (20eV) m/z (rel intensity) 285 [(M+1)$^+$, 19.4], 284 (M$^+$, 67.6), 238 (2.6), 227 (6.5), 211 (100), 194 (1.1), 183 (10.3), 153 (12.6), 138 (28.0), 127 (78.3); HRMS calcd for $C_{12}H_{13}N_2O_4Cl$ 284.05638, found 284.05661; (**3b**): a light yellow oil; ^{1}H NMR (CDCl$_3$) δ7.52-7.46 (m, 1H), 7.36-7.27 (m, 3H), 6.06 (dd, *J* = 4.1, 7.1 Hz, 1H), 3.59 (s, 3H), 3.15 (s, 3H), 2.90 (dd, *J* = 6.9, 16.1 Hz, 1H), 2.68 (dd, *J* = 4.1, 16.1 Hz, 1H); FT-IR 2988.7, 2954.2, 1739.9, 1486.5, 1439.5, 1414.2, 1387.3, 1199.0, 1168.0, 758.3; MS (20eV) m/z (rel intensity) 240 [(M+1)$^+$, 3.0], 239 (M$^+$, 5.9), 166 (12.3), 124 (1.6), 123 (20.9), 122 (12.1), 121 (100), 111 (1.3), 110 (13.6), 109 (13.8); HRMS calcd for $C_{12}H_{13}N_2O_4Cl$ 284.05638, found 284.05521; **(3c):** a white solid; mp 90-93 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.51 (s, 1H), 7.31 (s, 2H), 6.03 (dd, *J* = 4.1, 6.7 Hz, 1H), 3.62 (s, 3H), 3.14 (s, 3H), 2.88 (dd, *J* = 6.7, 16.1 Hz, 1H), 2.67 (dd, *J* = 4.1, 16.1 Hz, 1H); FT-IR 3092.6, 2954.4, 1743.0, 1486.5, 1415.5, 1386.6, 1167.9, 870.9, 751.8; MS (20eV) m/z (rel intensity) 319 [(M+1)$^+$, 5.7], 318 (M$^+$, 16.0), 245 (49.8), 226 (30.3), 187 (7.3), 172 (20.1), 161 (57.1), 85 (100); HRMS calcd for $C_{12}H_{12}N_2O_4Cl_2$ 318.01741, found 318.01758; **(3e):** a colorless oil; ^{1}H NMR (DMSO-d_6) δ7.84 (d, *J* = 14.5 Hz, 1H), 7.44-7.26 (m, 4H), 5.96 (dd, *J* = 3.2, 6.9 Hz, 1H), 5.20 (d, *J* = 14.5 Hz, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.62 (d, *J* = 16.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.92 (dd, *J* = 6.9, 16.2 Hz, 1H), 2.84 (dd, *J* = 4.1, 16.2Hz, 1H); FT-IR 3071.4, 2954.7, 1742.4, 1711.6, 1640.9, 1440.9, 1415.1, 1329.3, 1266.6, 1225.8, 1175.2, 835.3, 754.9; MS (20eV) m/z (rel intensity) 369 [(M+1)$^+$, 5.1], 368 (M$^+$, 1.1), 337 (20.7), 295 (6.4), 277 (20.8), 233 (5.5), 142 (61.8), 125 (100), 101 (54.5); HRMS calcd for $C_{16}H_{17}N_2O_6Cl$ 368.07751, found 368.07709; **(3f):** a white solid; mp 99-103 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.57-7.52 (m, 2H), 7.41-7.25 (m, 5H), 6.08 (dd, *J* = 4.2, 7.2 Hz, 1H), 4.86 (d, *J* = 17.0 Hz, 1H), 4.71 (d, *J* = 17.0 Hz, 1H), 3.56 (s, 3H), 2.88 (dd, *J* = 6.1, 16.1 Hz, 1H), 2.73 (dd, *J* = 2.5, 16.1 Hz, 1H); FT-IR 3081.9, 2947.9, 1729.9, 1491.6, 1439.0, 1413.9, 1188.2, 1047.4, 750.8; MS (20eV) m/z (rel intensity) 429 [(M+1)$^+$, 10.9], 428 (M$^+$, 17.6), 395 (11.7), 355 (7.6), 226 (28.4), 161 (25.1), 140 (70.6), 125 (100); HRMS calcd for $C_{18}H_{15}N_2O_4Cl_3$ 428.00974, found 428.00973; **(3g):** a pale yellow oil; ^{1}H NMR (CDCl$_3$) δ7.52-7.19 (m, 8H), 6.04 (dd, *J* = 4.5, 6.1 Hz, 1H), 4.80 (d, *J* = 16.7 Hz, 1H), 4.66 (d, *J* = 16.7 Hz, 1H), 3.46 (s, 3H), 2.81 (dd, *J* = 6.3, 16.0 Hz, 1H), 2.63 (dd, *J* = 4.2, 16.0 Hz, 1H); FT-IR 3068.3, 2958.2, 1738.8, 1486.5, 1440.7, 1408.1, 1261.1, 1161.0, 1059.1, 1038.4, 754.0; MS (20eV) m/z (rel intensity) 395 [(M+1)$^+$, 7.8], 394 (M$^+$, 18.3), 359 (17.1), 321 (11.6), 259 (4.7), 192 (55.4), 140 (99.2), 127 (58.1), 125 (100); HRMS calcd for $C_{18}H_{16}N_2O_4Cl_2$ 394.04871, found 394.04864; **(3h):** a pale yellow gel; ^{1}H NMR (CDCl$_3$) δ7.51-6.77 (m, 6H), 6.04 (dd, *J* = 4.3, 5.6 Hz, 1H), 4.63 (dd, *J* = 16.0, 19.2 Hz, 2H), 3.53 (s, 3H), 3.01 (s, 2H), 2.82 (dd, *J* = 6.0, 16.4 Hz, 1H), 2.65 (dd, *J* = 4.9, 16.4 Hz, 1H), 1.46 (s, 6H); FT-IR 3073.2, 2974.5, 1741.6, 1485.4, 1456.9, 1404.1, 1261.0, 1161.1, 1140.0, 878.1; MS (20eV) m/z (rel intensity) 464 (M$^+$, 3.6), 391 (0.5), 321 (1.4), 202 (0.9), 162 (11.8), 161 (100); HRMS calcd for $C_{22}H_{22}N_2O_5Cl_2$ 464.09057 found 464.09062; **(3i):** a colorless oil; ^{1}H NMR (CDCl$_3$) δ 6.50 (s, 1H), 5.53 (dd, *J* =3.5, 7.4 Hz, 1H), 3.79 (s, 3H), 3.18 (s, 3H), 2.87 (dd, *J* = 3.5, 17.4 Hz, 1H), 2.76 (dd, *J* = 7.2, 17.4 Hz, 1H); FT-IR 3425.3, 3301.6, 2967.6, 1715.8, 1668.2, 1611.5; HRMS calcd for $C_6H_{10}N_2O_4$ 174.0641, found 174.0654; **(3j):** a clear oil; ^{1}H NMR (CDCl$_3$) δ7.52-7.18 (m, 4H), 6.58 (s, 1H), 5.57 (dd, *J* =3.7, 7.5 Hz, 1H), 4.76 (d, *J* = 17.4 Hz, 1H), 4.52 (d, *J* = 17.4 Hz, 1H), 3.70 (s, 3H), 2.88 (dd, *J* = 3.7, 18.5 Hz, 1H), 2.76 (dd, *J* = 7.9, 18.5 Hz, 1H); FT-IR 3294.7, 3075.8, 2955.1, 1730.9, 1631.9; HRMS calcd for $C_{12}H_{13}N_2O_4Cl$ 284.0563, found 284.0550; **(4i):** a colorless solid; mp 95-96 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.59 (d, *J* = 12.1 Hz, 1H), 5.71 (d, *J* = 12.4 Hz, 1H), 5.34 (s, 2H), 3.78 (s, 3H), 3.19 (s, 3H); FT-IR 3435.4, 3301.6, 3235.9, 2958.6, 1713.6, 1661.6, 1610.5; HRMS calcd for $C_6H_{10}N_2O_4$ 174.0641, found 174.0654; **(4j):** a colorless solid; mp 136-138 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.43 (d, *J* = 12.4 Hz, 1H), 7.45-7.20 (m, 4H), 5.62 (d, *J* = 12.4 Hz, 1H), 5.37 (s, 2H), 4.92 (s, 2H), 3.69 (s, 3H); FT-IR 3409.4, 3301.6, 3228.6, 3099.0, 2948.6, 1692.0, 1634.8, 1602.4; HRMS calcd for $C_{12}H_{13}N_2O_4Cl$ 284.0563, found 284.0550; **(5a):** a white solid; mp 172-173 ^{o}C; ^{1}H NMR (DMSO-d_6) δ7.48 (s, 4H), 6.22 (t, *J* = 4.6 Hz, 1H), 3.00 (s, 3H), 2.75 (d, *J* = 4.6 Hz, 2H); FT-IR 3107.9, 1714.52, 1500.5, 1429.8, 1180.7, 815.5; MS (20eV) m/z (rel intensity) 271 [(M+1)$^+$, 6.3], 270 (M$^+$, 41.3), 213 (26.2), 211 (77.6), 183 (9.5), 153 (27.2), 138 (56.9), 127 (88.5), 111 (44.7), 90 (38.2), 71 (100); HRMS calcd for $C_{11}H_{11}N_2O_4Cl$ 270.04073, found 270.04062; **(5b):** a white solid; mp 100-103 ^{o}C; ^{1}H NMR (CDCl$_3$) δ7.50 (s, 1H), 7.31 (s, 2H), 6.02 (dd, *J* = 3.5, 6.8 Hz, 1H), 3.23 (s, 3H), 2.92 (dd, *J* = 7.0, 16.6 Hz, 1H), 2.69 (dd, *J* = 3.7, 16.6 Hz, 1H); FT-IR 3093.6, 1738.69, 1487.2, 1422.3, 1179.2, 873.4; MS (20eV) m/z (rel intensity) 305 [(M+1)$^+$, 8.9], 304 (M$^+$, 22.6), 245 (64.7), 214 (9.5), 187 (12.3), 172 (28.3), 161 (79.4), 124 (28.3), 71 (100); HRMS calcd for $C_{11}H_{10}N_2O_4Cl$ 304.00176, found 304.00161.