Supporting Information

Facile One-Pot Synthesis of 2,3,5-Substituted-1,2,4-Oxadiazolines from Nitriles in Aqueous Solution

B. Narasimhulu Naidu,* Margaret E. Sorenson

The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492

narasimhulu.naidu@bms.com

General Information: Unless otherwise noted all the reagents were used as purchased. The ^1H and ^{13}C NMR spectra were recorded either on a Bruker DPX-500 or on Bruker-DPX-300 MHz spectrometer. Chemical shifts are reported in ppm relative to internal reference. Mass spectra were determined on a Finnigan high-resolution Mass spectrometer. Analytical HPLC was performed on Shimadzu instrument using YMC 4.6 x 50 mm 5 μm Xterra column with 4 min linear gradient from 90:10 to 10:90 Water: CH₃OH containing 0.1% TFA at a flow rate of 4 mL/min with UV detection at 220 nm. Column chromatography was performed with EMD 240-400 mesh silica gel under low pressure of 3-5 psi.

Representative Procedure for the synthesis of 1,2,4-Oxadiazolines

(6a): A mixture of benzylnitrile (2.343 g, 20 mmol), N-methylhydroxylamine hydrochloride (0.835 g, 10 mmol) and Na₂CO₃ (0.64 g, 6 mmol) in 1:1 EtOH:H₂O (20 mL) was heated at 80 °C for 2 h. Then, the reaction mixture was cooled to ambient temperature and diethyl acetylenedicarboxylate (1.76 mL, 11 mmol) was added via syringe over 5 min. After 30 min, the reaction mixture was taken up into EtOAc (100 mL), washed with brine (2 X 20 mL), dried (Na₂SO₄), filtered, concentrated and the resulting yellow residue was purified by flash chromatography on silica gel column using 3:7 EtOAc/Hexanes mixture to afford the desired product **6a** as a yellow oil (2.61 g, 78%).

Table 1. Analytical data 1,2,4-Oxadiazolines

Product	Analytical data
6a	^1H NMR (500 MHz, CDCl ₃) δ : 7.32-7.23 (5H, m), 4.33-4.20 (2H, m), 4.13 (2H, q, $J = 7.0$ Hz), 3.67 (2H, s), 3.31 (1H, d, $J_{AB} = 16.2$ Hz), 3.00 (3H, s), 2.96 (1H, d, $J_{AB} = 16.2$ Hz), 1.29 (3H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl ₃) δ : 168.8, 168.4, 165.6, 134.0, 128.9, 128.7, 127.4, 103.7, 62.1, 60.8, 42.3, 40.1, 32.8, 14.2, 14.1. HRMS (M+H) calcd for C ₁₇ H ₂₃ N ₂ O ₅ : 335.1607; found: 335.1607. Anal. calcd for C ₁₇ H ₂₃ N ₂ O ₅ : C, 61.06; H, 6.63; N, 8.37; found: C, 60.80; H, 6.66; N, 8.30.
6b	^1H NMR (500 MHz, CDCl ₃) δ : 7.31-7.23 (5H, m), 4.35-4.20 (2H, m), 4.14 (2H, q, $J = 7.0$ Hz), 3.74-3.69 (1H, m), 3.65 (2H, q _{AB} , $J_{AB} = 15.1$ Hz), 3.26 (1H, d, $J_{AB} = 16.0$ Hz), 2.91 (1H, d, $J_{AB} = 16.0$ Hz), 1.30 (3H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz), 1.14 (3H, d, $J = 6.7$ Hz), 1.09 (3H, d, $J = 6.4$ Hz). ^{13}C NMR (125 MHz, CDCl ₃) δ : 168.9, 168.4, 163.6, 134.3, 128.8, 128.77, 127.3, 102.9, 62.0, 60.9, 53.0, 42.8, 33.3, 19.4, 19.3, 14.2, 14.17. HRMS (M+H) calcd for C ₁₉ H ₂₇ N ₂ O ₅ : 363.1920; found: 363.1926.
6c	^1H NMR (500 MHz, CDCl ₃) δ : 7.32-7.23 (5H, m), 4.33-4.19 (2H, m), 4.13 (2H, q, $J = 7.0$ Hz), 3.64 (2H, q _{AB} , $J_{AB} = 15.0$ Hz), 3.28-3.21 (1H, m), 3.24 (1H, d, $J_{AB} = 16.0$ Hz), 2.90 (1H, d, $J_{AB} = 16.0$ Hz), 1.76-1.45 (8H, m), 1.30 (3H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz), 1.12-1.05 (2H, m). ^{13}C NMR (125 MHz, CDCl ₃) δ : 168.9, 168.4, 163.4, 134.4, 128.8, 127.4, 103.0, 61.9, 60.9, 60.8, 42.8, 33.3, 29.9, 29.8, 25.84, 25.80, 25.2, 14.22, 14.17. HRMS (M+H) calcd for C ₂₂ H ₃₁ N ₂ O ₅ : 403.2233; found: 403.2243. Anal. calcd for C ₂₂ H ₃₁ N ₂ O ₅ : C, 65.65; H, 7.51; N, 6.96; found: C, 65.36; H, 7.72; N, 6.90.
6d	^1H NMR (500 MHz, CDCl ₃) δ : 7.35-7.29 (5H, m), 4.52 (2H, q _{AB} , $J_{AB} = 15.3$ Hz), 4.30-4.18 (2H, m), 4.16-4.07 (2H, m), 3.14 (1H, d, $J_{AB} = 16.3$ Hz), 2.55 (1H, d, $J_{AB} = 16.3$ Hz), 2.06 (3H, s), 1.29 (3H, t, $J = 7.0$ Hz), 1.22 (3H, t, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl ₃) δ : 168.8, 168.5, 162.9, 135.1, 128.8, 128.6, 128.2, 103.8, 62.1, 60.8, 56.5, 42.6, 14.2, 14.1, 13.2. HRMS (M+H) calcd for C ₁₇ H ₂₃ N ₂ O ₅ : 335.1607; found: 335.1591. Anal. calcd for C ₁₇ H ₂₃ N ₂ O ₅ : C, 61.06; H, 6.63; N, 8.37; found: C, 60.84; H, 6.67; N, 8.16.

¹H NMR (500 MHz, CDCl₃) δ: 4.32-4.17 (2H, m), 4.13 (2H, q, *J* = 7.3 Hz), 3.30 (1H, d, *J*_{AB} = 16.3 Hz), 3.10 (3H, s), 2.89 (1H, d, *J*_{AB} = 16.3 Hz), 2.47 (1H, m), 1.28 (3H, t, *J* = 7.3 Hz), 1.23 (3H, t, *J* = 7.3 Hz), 1.22 (3H, d, *J* = 7.0 Hz), 1.21 (3H, d, *J* = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃) δ: 172.3, 168.9, 168.7, 103.8, 62.0, 60.8, 42.4, 40.4, 26.2, 20.4, 20.3, 14.2, 14.1. HRMS (M+H) calcd for C₁₃H₂₃N₂O₅: 287.1607; found: 287.1618.

¹H NMR (500 MHz, CDCl₃) δ: 4.30-4.08 (4H, m), 3.27 (1H, d, *J*_{AB} = 16.3 Hz), 3.09 (3H, s), 2.87 (1H, d, *J*_{AB} = 16.3 Hz), 2.55 (1H, qt, *J* = 7.9 Hz), 1.94-1.69 (6H, m), 1.60-1.53 (2H, m), 1.26 (3H, t, *J* = 7.0 Hz), 1.21 (3H, t, *J* = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃) δ: 171.5, 168.9, 168.7, 103.9, 61.9, 60.7, 42.4, 40.4, 36.2, 31.2, 25.64, 25.60, 14.2, 14.1. HRMS (M+H) calcd for C₁₅H₂₅N₂O₅: 313.1763; found: 313.1754. Anal. calcd for C₁₅H₂₄N₂O₅: C, 57.67; H, 7.74; N, 8.96; found: C, 57.41; H, 7.62; N, 8.83.

¹H NMR (500 MHz, CDCl₃) δ: 7.72-7.70 (2H, m), 7.52-7.49 (1H, m), 7.44-7.41 (2H, m), 4.35-4.23 (2H, m), 4.19-4.12 (2H, m), 3.45 (1H, d, *J*_{AB} = 16.5 Hz), 3.17 (3H, s), 3.02 (1H, d, *J*_{AB} = 16.5 Hz), 1.31 (3H, t, *J* = 7.0 Hz), 1.21 (3H, t, *J* = 7.0 Hz). HRMS calcd for C₁₆H₂₁N₂O₅ (M + H): 321.1451; found: 321.1449.

¹H NMR (500 MHz, CDCl₃) δ: 7.56 (1H, dd, *J* = 7.6, 1.5 Hz), 7.44 (1H, td, *J* = 7.6, 1.6 Hz), 6.99 (1H, t, *J* = 7.5 Hz), 6.95 (1H, d, *J* = 8.2 Hz), 4.36-4.10 (4H, m), 3.85 (3H, s), 3.43 (1H, d, *J*_{AB} = 16.5 Hz), 3.05 (3H, s), 3.04 (1H, d, *J*_{AB} = 16.5 Hz), 1.32 (3H, t, *J* = 7.0 Hz), 1.25 (3H, t, *J* = 7.0 Hz). HRMS calcd for C₁₇H₂₃N₂O₆ (M + H): 351.1556; found: 351.1553.

¹H NMR (500 MHz, CDCl₃) δ: 7.32 (1H, t, *J* = 8.2 Hz), 6.55 (2H, d, *J* = 8.2 Hz), 4.38-4.24 (2H, m), 4.20-4.14 (2H, m), 3.80 (6H, s), 3.48 (1H, d, *J*_{AB} = 16.5 Hz), 3.03 (1H, d, *J*_{AB} = 16.5 Hz), 3.02 (3H, s), 1.33 (3H, t, *J* = 7.0 Hz), 1.26 (3H, t, *J* = 7.0 Hz). HRMS (ESI) calcd for C₁₈H₂₅N₂O₇S (M + H): 381.1662; found: 381.1656.

¹H NMR (500 MHz, CDCl₃) δ: 7.48-7.42 (1H, m), 6.99 (2H, t, *J* = 8.2 Hz), 4.37-4.24 (2H, m), 4.18 (2H, q, *J* = 7.0 Hz), 3.40 (1H, d, *J*_{AB} = 16.5 Hz), 3.11 (1H, d, *J*_{AB} = 16.5 Hz), 3.08 (3H, s), 1.32 (3H, t, *J* = 7.0 Hz), 1.26 (3H, t, *J* = 7.0 Hz). LCMS calcd for C₁₆H₁₉F₂N₂O₅ (M + H): 357.13; found: 357.38.

¹H NMR (300 MHz, CDCl₃) δ: 7.55 (1H, dd, *J* = 1.8, 0.7 Hz), 7.04 (1H, dd, *J* = 3.7, 0.7 Hz), 6.52 (1H, q, *J* = 1.8 Hz), 4.31-4.18 (2H, m), 4.17-4.09 (2H, m), 3.44 (1H, d, *J*_{AB} = 16.5 Hz), 3.33 (3H, s), 2.95 (1H, d, *J*_{AB} = 16.5 Hz), 1.28 (3H, t, *J* = 7.1 Hz), 1.21 (3H, t, *J* = 7.1 Hz). HRMS (M+H) calcd for C₁₄H₁₉N₂O₆: 311.12432; found: 311.1246.

¹H NMR (500 MHz, CDCl₃) δ: 8.65 (1H, d, *J* = 4.6 Hz), 8.04 (1H, d, *J* = 7.9 Hz), 7.77 (1H, td, *J* = 7.9, 1.5 Hz), 7.40-7.37 (1H, m), 4.31-4.23 (2H, m), 4.17-4.11 (2H, m), 3.46 (3H, s), 3.39 (1H, d, *J*_{AB} = 16.5 Hz), 3.03 (1H, d, *J*_{AB} = 16.5 Hz), 1.29 (3H, t, *J* = 7.2 Hz), 7.22 (3H, t, *J* = 7.2 Hz). ¹H NMR (125 MHz, CDCl₃) δ: 168.9, 168.4, 164.3, 149.4, 146.5, 136.9, 126.0, 125.1, 104.5, 62.3, 60.9, 42.7, 14.2, 14.1. HRMS (M+H) calcd for C₁₅H₂₀N₃O₅: 322.1403; found: 322.1389. Anal. calcd for C₁₅H₁₉N₃O₅: C, 56.06; H, 5.96; N, 13.07; found: C, 55.53; H, 6.09; N, 12.79.

¹H NMR (300 MHz, CDCl₃) δ: 8.91 (1H, d, *J* = 1.5 Hz), 8.73 (1H, dd, *J* = 4.9, 1.6 Hz), 8.02 (1H, dt, *J* = 7.7, 2.0 Hz), 7.39-7.35 (1H, m), 4.35-4.18 (2H, m), 4.14 (2H, qd, *J* = 6.1, 0.9 Hz), 3.40 (1H, d, *J*_{AB} = 16.8 Hz), 3.16 (3H, s), 3.02 (1H, d, *J*_{AB} = 16.8 Hz), 1.29 (3H, t, *J* = 7.1 Hz), 1.22 (3H, t, *J* = 7.1 Hz). HRMS (M+H) calcd for C₁₅H₂₀N₃O₅: 322.1403; found: 322.1399.

¹H NMR (300 MHz, CDCl₃) δ: 8.73 (2H, d, *J* = 5.9 Hz), 7.57 (2H, dd, *J* = 4.6, 1.6 Hz), 4.37-4.20 (2H, m), 4.15 (2H, q, *J* = 6.9 Hz), 3.40 (1H, d, *J*_{AB} = 16.8 Hz), 3.16 (3H, s), 3.04 (1H, d, *J*_{AB} = 16.5 Hz), 1.30 (3H, t, *J* = 7.1 Hz), 1.24 (3H, t, *J* = 7.1 Hz). HRMS (M+H) calcd for C₁₅H₂₀N₃O₅: 322.1403; found: 322.1401.

¹H NMR (500 MHz, CDCl₃) δ: 8.30 (1H, dd, *J* = 4.3, 1.2 Hz), 7.38 (1H, dd, *J* = 8.5, 4.3 Hz), 7.31 (1H, dd, *J* = 8.5, 1.2 Hz), 4.36-4.23 (2H, m), 4.20-4.13 (2H, m), 3.87 (3H, s), 3.49 (1H, d, *J*_{AB} = 16.5 Hz), 3.15 (3H, s), 3.06 (1H, d, *J*_{AB} = 16.5 Hz), 1.32 (3H, t, *J* = 7.0 Hz), 1.25 (3H, t, *J* = 7.0 Hz). HRMS calcd for C₁₆H₂₂N₃O₆ (M + H): 352.1509; found: 352.1508.

¹H NMR (300 MHz, CDCl₃) δ: 8.50 (1H, d, *J* = 1.8 Hz), 7.93 (1H, dd, *J* = 8.8, 2.2 Hz), 6.78 (1H, d, *J* = 8.4 Hz), 4.29-4.23 (2H, m), 4.19-4.09 (2H, m), 3.97 (3H, s), 3.43 (1H, d, *J*_{AB} = 16.5 Hz), 3.20 (3H, s), 3.02 (1H, d, *J*_{AB} = 16.5 Hz), 1.31 (3H, t, *J* = 7.1 Hz), 1.24 (3H, t, *J* = 7.1 Hz). HRMS (M+H) calcd for C₁₆H₂₂N₃O₆: 352.15087; found: 352.1513.

¹H NMR (300 MHz, CDCl₃) δ: 7.34-7.24 (5H, m), 6.07 (1H, dd, *J* = 3.59, 4.2 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 3.65 (2H, s), 2.94 (3H, s), 2.81 (1H, dd, *J*_{AB} = 15.9, 4.2 Hz), 2.67 (1H, dd, *J*_{AB} = 16.1, 6.9 Hz), 1.23 (3H, t, *J* = 7.1 Hz). HRMS (M+H) calcd for C₁₄H₁₉N₂O₃: 263.13958; found: 263.1396. Anal. calcd for C₁₄H₁₈N₂O₃ 0.45 H₂O: C, 62.18; H, 7.04; N, 10.36; found: C, 62.17; H, 6.80; N, 10.28.

^1H NMR (300 MHz, CDCl_3) δ : 7.33-7.21 (5H, m), 4.10 (2H, q, $J = 7.1$ Hz), 3.60 (2H, s), 2.91 (3H, s), 2.73 (2H, s), 1.59 (3H, s), 1.21 (3H, t, $J = 7.1$ Hz). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_3$: 277.15523; found: 277.1564. Anal. calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3$: C, 65.19; H, 7.29; N, 10.13; found: C, 65.34; H, 7.07; N, 9.82.

^1H NMR (300 MHz, CDCl_3) δ : 7.32-7.22 (5H, m), 3.59 (2H, d, $J = 5.5$ Hz), 2.88 (3H, s), 2.78 (2H, d, $J = 4.4$ Hz), 2.13 (3H, s), 1.88-1.68 (2H, m), 0.87 (3H, t, $J = 7.3$ Hz). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$: 261.16031; found: 261.1613. Anal. calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3 \cdot 0.1 \text{ H}_2\text{O}$: C, 68.73; H, 7.77; N, 10.69; found: C, 68.96; H, 7.57; N, 10.67.

Figure 1. ^1H NMR spectrum of **6b**

Figure 2. ^{13}C NMR spectrum of **6b**

Figure 3. ^1H NMR spectrum of **6e**

Figure 4. ^{13}C NMR spectrum of **6e**

Figure 5. ^1H NMR spectrum of **6g**

Figure 6. ^1H NMR spectrum of **6h**

Figure 7. ^1H NMR spectrum of **6i**

Figure 8. ^1H NMR spectrum of **6j**

Figure 9. ^1H NMR spectrum of **6k**

Figure 12. ^1H NMR spectrum of **6m**

Figure 13. ^1H NMR spectrum of **6n**

Figure 14. ^1H NMR spectrum of **6o**

Figure 15. ^1H NMR spectrum of **6p**