Supporting Information

for

Synthesis of 3,4,5-trisubstituted isoxazoles in water via a [3 + 2]-cycloaddition of nitrile oxides and 1,3-diketones, β-ketoesters, or β-ketoamides

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Synthetic schemes for phenyl hydroximoyl chlorides and 1,3-diketones, characterization data, and copies of $^1$H, $^{13}$C, and $^{19}$F NMR spectra
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Figure S1: Synthesis of phenyl hydroximoyl chlorides 1a–c.

Figure S2: Synthesis of 1,3-diketones 2b–e.

Characterization of compounds 3a–aa and 4:

(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(phenyl)methanone (3a)
Yield: 98%. Yellow sticky gel. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.69 – 7.62 (m, 2H), 7.49 – 7.39 (m, 3H), 7.32 (tt, $J = 7.5$, 1.4 Hz, 2H), 6.99 – 6.85 (m, 2H), 2.46 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 189.96, 173.09, 163.57 (d, $J = 250$ Hz), 161.05, 137.33, 133.62, 130.61 (d, $J = 7.5$ Hz), 129.49, 128.61, 124.38 (d, $J = 3.8$ Hz), 115.73, 115.57 (d, $J = 3.8$ Hz), 12.87. $^{19}$F NMR (471 MHz, CDCl$_3$) δ -110.63. HRMS m/z calcd. for C$_{17}$H$_{13}$FNO$_2$ [M+H]$^+$ 282.0930, found 282.0930.

3,4-Bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide (4)
General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture and no DIPEA. Yield: 95%. Clear sticky gel. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.60–7.56 (m, 4H), 7.42–7.37 (m, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.54 (d, $J = 57$ Hz), 162.06 (d, $J = 57$ Hz), 155.90, 131.65 (d, $J = 9.1$ Hz), 130.86 (d, $J = 9.1$ Hz), 129.49, 128.61, 124.38 (d, $J = 3.8$ Hz), 115.73, 115.57 (d, $J = 3.8$ Hz), 12.87.
Hz), 122.73 (d, J = 3.2 Hz), 119.04 (d, J = 3.2 Hz), 116.44 (d, J = 7.7 Hz), 116.22 (d, J = 7.7 Hz), 114.18. 19F NMR (377 MHz, DMSO- d6) δ -108.74 (ttd, J = 8.9, 5.4, 1.8 Hz, 1F), -108.82 (ttd, J = 8.9, 5.4, 1.4 Hz, 1F). HRMS m/z calcd. for C14H9N2O2F2 [M+H]+ 275.0632, found 275.0637.

(4-Bromophenyl)(5-methyl-3-phenylisoxazol-4-yl)methanone (3b)
Yield: 82%. White crystal. Mp 105–107 °C. 1H NMR (500 MHz, CDCl3) δ 7.55 (d, J = 8.4 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.35 (t, J = 7.3 Hz, 1H), 7.29 (t, J = 7.4 Hz, 2H), 2.55 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 189.01, 173.41, 161.83, 136.11, 131.86, 131.01, 128.74, 128.66, 128.60, 128.04, 115.40, 12.91. HRMS m/z calcd. for C17H13BrNO2 [M+H]+ 342.0130, found 342.0134.

(4-Bromophenyl)(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)methanone (3c)
Yield: 95%. White solid. Mp 84–86 °C. 1H NMR (500 MHz, CDCl3) δ 7.54 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.44 (t, J = 8.6 Hz, 2H), 6.98 (t, J = 8.6 Hz, 2H), 2.50 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 188.90, 173.39, 163.77 (d, J = 250 Hz), 160.95, 136.08, 132.04, 131.01, 130.66 (d, J = 8.8 Hz), 129.03, 124.23 (d, J = 3.8 Hz), 115.92(d, J = 21 Hz), 115.33, 13.00. 19F NMR (101 MHz, CDCl3) δ -110.18. HRMS m/z calcd. for C17H12BrFNO2 [M+H]+ 360.0035, found 360.0049.

(4-Bromophenyl)(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)methanone (3d)
Yield: 70%. White solid. Mp 91–93 °C. 1H NMR (400 MHz, CDCl3) δ 7.54 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 2.49 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 189.23, 173.12, 160.96, 136.18, 131.91, 131.07, 130.05, 128.77, 120.31, 115.11, 114.44, 114.15, 55.41, 12.89. HRMS m/z calcd. for C18H15BrNO3 [M+H]+ 372.0235, found 372.0245.

(4-Methoxyphenyl)(5-methyl-3-phenylisoxazol-4-yl)methanone (3e)
Yield: 78%. White solid. Mp 88–90 °C. 1H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 8.9 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.38 – 7.26 (m, 3H), 6.83 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H), 2.50 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 188.62, 171.89, 164.06, 161.78, 132.12, 130.26, 129.82, 128.60,
128.54, 128.36, 115.80, 113.88, 55.59, 12.69. HRMS m/z calcd. for C_{18}H_{16}NO_{3} [M+H]^+ 294.1130, found 294.1143.

(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(4-methoxyphenyl)methanone (3f)
Yield: 73%. White crystal. Mp 115–117 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.69 (d, \(J = 8.9\) Hz, 2H), 7.49 (dd, \(J = 8.8, 5.3\) Hz, 2H), 6.96 (t, \(J = 8.7\) Hz, 2H), 6.81 (d, \(J = 8.9\) Hz, 2H), 3.80 (s, 3H), 2.44 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 188.43, 171.97, 164.16, 163.60 (d, \(J = 250\) Hz), 160.84, 132.07, 130.50 (d, \(J = 9.1\) Hz), 130.14, 124.52 (d, \(J = 3.0\) Hz), 115.82, 115.64 (d, \(J = 5.0\) Hz), 113.94, 55.57, 12.69. \(^{19}\)F NMR (101 MHz, CDCl\(_3\)) δ -110.72. HRMS m/z calcd. for C\(_{18}\)H\(_{16}\)FNO\(_3\) [M+H]^+ 312.1036, found 312.1046.

(4-Methoxyphenyl)(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)methanone (3g)
Yield: 70%. White solid. Mp 84–86 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.75–7.69 (m, 2H), 7.47–7.41 (m, 2H), 6.85–6.77 (m, 4H), 3.82 (s, 3H), 3.76 (s, 3H), 2.44 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 188.89, 171.61, 164.10, 161.33, 160.82, 132.19, 130.33, 129.93, 120.70, 115.65, 114.10, 113.94, 55.63, 55.36, 12.70. HRMS m/z calcd. for C\(_{19}\)H\(_{18}\)NO\(_4\) [M+H]^+ 324.1236, found 324.1246.

(5-Methyl-3-phenylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3h)
Yield: 87%. White solid. Mp 78–80 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.73 (d, \(J = 7.8\) Hz, 2H), 7.60–7.47 (m, 2H), 7.37 (dt, \(J = 6.9, 1.5\) Hz, 2H), 7.34–7.19 (m, 3H), 2.58 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 189.08, 174.32, 161.96, 140.29, 134.52 (d, \(J = 33\) Hz), 130.03, 129.75, 128.71 (d, \(J = 12\) Hz), 127.99, 125.48 (q, \(J = 3.7\) Hz), 124.60, 122.14, 115.43, 13.06. \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) δ -63.29. HRMS m/z calcd. for C\(_{18}\)H\(_{13}\)F\(_3\)NO\(_2\) [M+H]^+ 332.0898, found 332.0888.

(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3i)
Yield: 85%. White solid. Mp 116–118 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.80–7.72 (m, 2H), 7.58 (d, \(J = 8.1\) Hz, 2H), 7.46–7.34 (m, 2H), 7.00–6.89 (m, 10H), 2.53 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 188.93, 174.22, 163.79 (d, \(J = 200\) Hz), 161.07, 140.24, 134.79 (q, \(J = 26\) Hz), 130.75 (d, \(J = 8.5\) Hz), 129.78, 125.67 (q, \(J = 3.7\) Hz), 124.12 (d, \(J = 3.4\) Hz), 122.37, 115.90 (d, \(J = 17\) Hz), 115.34, 13.14. \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) δ -63.25, -110.12. HRMS m/z calcd. for C\(_{18}\)H\(_{12}\)F\(_4\)NO\(_2\) [M+H]^+ 350.0804, found 350.0798.
(3-(4-Methoxyphenyl)-5-methylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3j)
Yield: 74%. Yellowish white solid. Mp 69–71 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 – 7.71 (m, 2H), 7.57 (d, \(J = 8.2\) Hz, 2H), 7.32 (d, \(J = 8.7\) Hz, 2H), 6.77 (d, \(J = 8.8\) Hz, 2H), 3.76 (s, 3H), 2.56 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 189.25, 174.06, 161.50, 161.00, 140.31, 134.47 (q, \(J = 33\) Hz), 129.98 (d, \(J = 35\) Hz), 125.50 (d, \(J = 4.0\) Hz), 124.74, 121.97, 120.15, 115.27, 114.11, 55.36, 13.05; \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta\) -63.21. HRMS \(m/z\) calcd. for C\(_{19}\)H\(_{15}\)F\(_3\)NO\(_3\) [M+H]\(^+\) 362.1004, found 362.1005.

(5-Methyl-3-phenylisoxazol-4-yl)(thiophen-2-yl)methanone (3k)
Yield: 86%. White solid. Mp 103–105 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.63 (dd, \(J = 4.9, 1.2\) Hz, 1H), 7.54 (dd, \(J = 7.9, 1.8\) Hz, 2H), 7.40 – 7.27 (m, 4H), 6.94 (dd, \(J = 4.9, 3.8\) Hz, 1H), 2.54 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 181.75, 172.00, 161.30, 144.02, 135.41, 135.21, 130.00, 128.75, 128.52, 128.26, 115.84, 12.67. HRMS \(m/z\) calcd. for C\(_{15}\)H\(_{12}\)NO\(_2\)S [M+H]\(^+\) 270.0589, found 270.0583.

(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(thiophen-2-yl)methanone (3l)
Yield: 92%. White solid. Mp 56–58 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66 (t, \(J = 3.5\) Hz, 1H), 7.59 – 7.50 (m, 2H), 7.32 (d, \(J = 3.8\) Hz, 1H), 7.07 – 6.94 (m, 3H), 2.52 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 181.59, 172.03, 163.74 (d, \(J = 250\) Hz), 160.39, 143.91, 135.66, 135.22, 130.51 (d, \(J = 8.8\) Hz), 128.35, 124.41 (d, \(J = 3.7\) Hz), 116.00, 115.78 (d, \(J = 12\) Hz), 12.72; \(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \(\delta\) -110.34. HRMS \(m/z\) calcd. for C\(_{15}\)H\(_{11}\)FNO\(_2\)S [M+H]\(^+\) 288.0495, found 288.0490.

(3-(4-Methoxyphenyl)-5-methylisoxazol-4-yl)(thiophen-2-yl)methanone (3m)
Yield: 80%. Sticky gel. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 (t, \(J = 3.5\) Hz, 1H), 7.54 – 7.46 (m, 2H), 7.32 (d, \(J = 3.5\) Hz, 1H), 6.96 (d, \(J = 4.0\) Hz, 1H), 6.88 – 6.80 (m, 2H), 3.78 (s, 3H), 2.52 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 182.04, 171.76, 160.96, 160.87, 144.12, 135.44, 135.29, 129.93, 128.35, 120.57, 115.70, 114.22, 55.39, 12.68. HRMS \(m/z\) calcd. for C\(_{16}\)H\(_{14}\)NO\(_3\)S [M+H]\(^+\) 300.0694, found 300.0696.
5-Methyl-N,3-diphenylisoxazole-4-carboxamide (3n)
Yield: 80%. White crystal. Mp 198–200 °C. 1H NMR and 13C NMR spectra matched with literature [1]. 1H NMR (400 MHz, CDCl3) δ 7.68 (m, 2H), 7.63 – 7.52 (m, 3H), 7.28 (m, 2H), 7.23 (m, 2H), 7.12 (brs, 1H), 7.10 (m, 1H), 2.80 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 175.31, 159.83, 159.34, 137.19, 130.85, 129.44, 129.26, 129.04, 128.01, 119.60, 111.24, 13.18. HRMS m/z calcd. for C17H15N2O2 [M+H]+ 279.1134, found 279.1139.

3-(4-Fluorophenyl)-5-methyl-N-phenylisoxazole-4-carboxamide (3o)
Yield: 82%. White crystal. Mp 172–174 °C. 1H NMR and 13C NMR spectra matched with literature [1]. 1H NMR (400 MHz, CDCl3) δ 7.72 – 7.57 (m, 4H), 7.32 – 7.20 (m, 3H), 7.18 – 7.05 (m, 2H), 2.82 (s, 3H), 13C NMR (101 MHz, CDCl3) δ 175.14, 164.29 (d, J = 250 Hz), 159.44, 159.12, 137.16, 131.40 (d, J = 8.8 Hz), 129.28, 125.01, 124.09 (d, J = 3.7 Hz), 119.80, 116.77 (d, J = 22 Hz), 111.48, 13.21. 19F NMR (471 MHz, CDCl3) δ -108.64. HRMS m/z calcd. for C17H14FN2O2 [M+H]+ 297.1039, found 297.1045.

3-(4-Methoxyphenyl)-5-methyl-N-phenylisoxazole-4-carboxamide (3p)
Yield: 78%. White crystal. Mp 144–146 °C. 1H NMR (400 MHz, CDCl3) δ 7.59 (d, J = 8.7 Hz, 2H), 7.36 – 7.19 (m, 4H), 7.15 – 7.04 (m, 3H), 3.89 (s, 3H), 2.77 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 175.26, 161.68, 159.69, 137.37, 130.81, 129.18, 124.76, 119.94, 119.83, 114.99, 111.25, 55.64, 13.30. HRMS m/z calcd. for C18H17N2O3 [M+H]+ 309.1239, found 309.1243.

Benzyl 5-methyl-3-phenylisoxazole-4-carboxylate (3q)
Yield: 85%. White solid. Mp 33–35 °C. 1H NMR (400 MHz, CDCl3) δ 7.67 – 7.57 (m, 2H), 7.52 – 7.46 (m, 1H), 7.46 – 7.38 (m, 2H), 7.34 (m, 3H), 7.28 – 7.19 (m, 2H), 5.25 (s, 2H), 2.75 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 176.21, 162.69, 161.89, 135.32, 129.79, 129.48, 128.65, 128.53, 128.44, 128.39, 128.16, 108.44, 66.61, 13.77. HRMS m/z calcd. for C18H16NO3 [M+H]+ 294.1130, found 294.1143.

Benzyl 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylate (3r)
Yield: 90%. White solid. Mp 49–51 °C. 1H NMR (400 MHz, CDCl3) δ 7.59 (t, J = 8.7, 2H), 7.36 (m, 3H), 7.25 (m, 2H), 7.07 (t, J = 8.7 Hz, 2H), 5.24 (s, 2H), 2.74 (s, 3H); 13C NMR (101 MHz,
CDCl$_3$ δ 176.41, 163.84 (d, $J = 250$ Hz), 161.86, 161.80, 135.21, 131.54 (d, $J = 8.0$ Hz), 128.72, 128.62, 128.53, 124.55 (d, $J = 4.0$ Hz), 115.28 (d, $J = 22$ Hz), 108.37, 66.76, 13.84. $^{19}$F NMR (101 MHz, CDCl$_3$) δ -111.14. HRMS m/z calcd. for C$_{18}$H$_{15}$FNO$_3$ [M+H]$^+$ 312.1036, found 312.1032.

Benzyl 3-(4-methoxyphenyl)-5-methylisoxazole-4-carboxylate (3s)
Yield: 75%. White solid. Mp 47–49 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 8.7$ Hz, 2H), 7.35 (m, 3H), 7.29 – 7.24 (m, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.26 (s, 2H), 3.86 (s, 3H), 2.73 (d, $J = 1.0$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.01, 162.23, 161.93, 160.81, 135.28, 130.79, 128.55, 128.38, 128.37, 120.58, 113.54, 108.19, 66.51, 55.30, 13.75. HRMS m/z calcd. for C$_{19}$H$_{18}$NO$_4$ [M+H]$^+$ 324.1236, found 324.1236.

Ethyl 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylate (3t)
Yield: 86%. White crystal. Mp 58–60 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.59 (m, 2H), 7.20 – 7.08 (m, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 2.73 (s, 3H); 13C NMR (101 MHz, CDCl$_3$) δ 175.96, 163.72 (d, $J = 250$ Hz), 161.85, 161.70, 131.43 (d, $J = 8.6$ Hz), 124.56 (d, $J = 3.6$ Hz), 115.07 (d, $J = 21$ Hz), 108.35, 60.78, 14.00, 13.61. $^{19}$F NMR (101 MHz, CDCl$_3$) δ -111.22. HRMS m/z calcd. for C$_{13}$H$_{13}$FNO$_3$ [M+H]$^+$ 250.0879, found 250.0878.

N-Benzyl-5-methyl-3-phenylisoxazole-4-carboxamide (3u)
Yield: 92%. White crystal. Mp 135–137 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.48 (m, 2H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.39 (dd, $J = 7.2$, 1.2 Hz, 2H), 7.32 – 7.24 (m, 3H), 7.09 (dd, $J = 7.3$, 2.3 Hz, 2H), 5.73 (s, 1H), 4.42 (d, $J = 5.7$ Hz, 2H), 2.73 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.27, 161.47, 160.19, 137.48, 130.48, 129.19, 129.08, 128.79, 128.15, 127.82, 127.71, 111.12, 43.67, 13.05. HRMS m/z calcd. for C$_{18}$H$_{17}$N$_2$O$_2$ [M+H]$^+$ 293.1290, found 293.1294.

N-Benzyl-3-(4-fluorophenyl)-5-methylisoxazole-4-carboxamide (3v)
Yield: 82%. White crystal. Mp 179–181 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.51 (dd, $J = 8.8$, 5.2 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.13 (dd, $J = 7.3$, 2.3 Hz, 2H), 7.05 (t, $J = 8.6$ Hz, 2H), 5.62 (s, 1H), 4.44 (d, $J = 5.7$ Hz, 2H), 2.71 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.04, 164.07 (d, $J = 250$ Hz), 161.38, 159.37, 137.47, 131.13 (d, $J = 8.0$ Hz), 128.92, 127.94 (d, $J = 2.0$ Hz), 124.18 (d, $J =
3.0 Hz), 116.48, 116.26, 111.28, 43.82, 12.99. $^{19}$F NMR (101 MHz, CDCl$_3$) δ -109.57. HRMS m/z calcd. for C$_{18}$H$_{16}$FN$_2$O$_2$ [M+H]$^+$ 311.1196, found 311.1194.

$N$-Benzy-3-(4-methoxyphenyl)-5-methylisoxazole-4-carboxamide (3w)

Yield: 74%. White crystal. Mp 143–145 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.46 – 7.39 (m, 2H), 7.27 (dt, $J = 6.3, 2.2$ Hz, 3H), 7.15 – 7.08 (m, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 5.78 (s, 1H), 4.42 (d, $J = 5.7$ Hz, 2H), 3.80 (s, 3H), 2.70 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.07, 161.62, 161.30, 159.90, 137.60, 130.48, 128.77, 127.91, 127.69, 120.05, 114.61, 111.04, 55.47, 43.63, 13.03. HRMS m/z calcd. for C$_{19}$H$_{19}$N$_2$O$_3$ [M+H]$^+$ 323.1396, found 323.1394.

(3-(4-Fluorophenyl)-5-(trifluoromethyl)isoxazol-4-yl)(phenyl)methanone (3x)

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Sticky gel. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 – 7.78 (m, 2H), 7.69 – 7.60 (m, 1H), 7.54 – 7.43 (m, 4H), 6.90 – 6.82 (m, 2H), 3.78 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 187.00, 164.34 (d, $J = 250$ Hz), 160.85, 156.77 (q, $J = 42$ Hz), 136.12, 135.26, 130.37 (d, $J = 8.8$ Hz), 129.79, 129.26, 122.67 (d, $J = 2.5$ Hz), 118.73, 118.72 (d, $J = 2.5$ Hz), 116.50 (d, $J = 21$ Hz); $^{19}$F NMR (471 MHz, CDCl$_3$) δ -62.55. HRMS m/z calcd. for C$_{17}$H$_{10}$F$_4$NO$_3$ [M+H]$^+$ 336.0648, found 336.0656.

(3-(4-Methoxyphenyl)-5-(trifluoromethyl)isoxazol-4-yl)(phenyl)methanone (3y)

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 35%. Sticky gel. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 – 7.79 (m, 2H), 7.67 – 7.58 (m, 1H), 7.54 – 7.43 (m, 4H), 6.90 – 6.82 (m, 2H), 3.78 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 187.40, 161.70, 161.28, 156.39 (q, $J = 42$ Hz), 136.24, 135.09, 129.81 (d, $J = 3.8$ Hz), 129.70, 129.20, 118.77 (d, $J = 5.0$ Hz), 118.65, 116.63, 114.66, 55.46; $^{19}$F NMR (471 MHz, CDCl$_3$) δ -62.55. HRMS m/z calcd. for C$_{18}$H$_{13}$F$_3$NO$_3$ [M+H]$^+$ 348.0848, found 348.0826.

(3-(4-Methoxyphenyl)-5-(trifluoromethyl)isoxazol-4-yl)(naphthalen-1-yl)methanone (3z)

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Yellow sticky gel. $^1$H NMR (400 MHz, CDCl$_3$)
δ 8.30 – 8.23 (m, 1H), 8.04 (dd, J = 8.7, 1.8 Hz, 1H), 8.01 – 7.85 (m, 3H), 7.72 – 7.51 (m, 4H), 6.90 – 6.80 (m, 2H), 3.76 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 187.24, 161.68, 161.38, 156.36 (q, J = 42 Hz), 136.49, 133.77, 133.21, 132.42, 130.04, 129.81, 129.65, 129.37, 128.04, 127.43, 123.83, 118.77, 118.75, 116.69, 114.68, 55.27. 19F NMR (471 MHz, CDCl3) δ -62.48. HRMS m/z calcd. for C22H15F3NO3 [M+H]+ 398.1004, found 398.1027.

(3-(4-Fluorophenyl)-5-(trifluoromethyl)isoxazol-4-yl)(naphthalen-1-yl)methanone (3aa)
General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Yellow sticky gel. 1H NMR (400 MHz, CDCl3) δ 8.30 – 8.15 (m, 1H), 8.15 – 7.82 (m, 4H), 7.73 – 7.48 (m, 4H), 7.10 – 6.98 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 186.83, 164.31 (d, J = 250 Hz), 160.94, 156.73 (q, J = 42 Hz), 136.54, 133.66, 133.21, 132.38, 130.32 (d, J = 8.0 Hz), 129.96 (d, J = 6.0 Hz), 129.47, 128.07, 127.53, 123.74, 122.72 (d, J = 3.0 Hz), 119.04, 118.83 (d, J = 2.0 Hz), 116.60, 116.38. 19F NMR (377 MHz, CDCl3) δ -62.41, -108.43. HRMS m/z calcd. for C21H12F4NO2 [M+H]+ 386.0804, found 386.0825.

Reference
1. Zhou, X.; Xu, X.; Shi, Z.; Liu, K.; Gao, H.; Li, W. Org. Biomol. Chem. 2016, 14, 5246–5250.
Figure S3: $^1$H and $^{13}$C NMR spectra of compound 3a.
Figure S4: $^{19}$F NMR spectrum of compound 3a.
Figure S5: $^1$H and $^{13}$C NMR spectra of compound 4.
Figure S6: $^{19}F$ NMR and HMBC spectra of compound 4. Compound 4 has a molecular formula of C$_{14}$H$_{3}$N$_{2}$O$_{2}$F$_{2}$, as evidenced from DART-HRMS analysis ($m/z$ calcd. for C$_{14}$H$_{3}$N$_{2}$O$_{2}$F$_{2}$ [M+H]$^+$ 275.0632, found 275.0637). The oxadiazole and fluorophenyl groups are revealed by $^{19}F$ and HMBC spectral data, which identified 4 as 3,4-bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide.
Figure S7: $^1$H and $^{13}$C NMR spectra of compound 3b.
Figure S8: $^1$H and $^{13}$C NMR spectra of compound 3c.
Figure S9: $^{19}$F NMR spectrum of compound 3c.
Figure S10: $^1$H and $^{13}$C NMR spectra of compound 3d.
Figure S11: $^1$H and $^{13}$C NMR spectra of compound 3e.
Figure S12: $^1$H and $^{13}$C NMR spectra of compound 3f.
Figure S13: $^{19}$F NMR spectrum of compound 3f.
Figure S14: $^1$H and $^{13}$C NMR spectra of compound 3g.
Figure S15: $^1$H and $^{13}$C NMR spectra of compound 3h.
Figure S16: $^{19}$F NMR spectrum of compound 3h.
Figure S17: $^1$H and $^{13}$C NMR spectra of compound 3i.
Figure S18: $^{19}$F NMR spectrum of compound 3i.
Figure S19: $^1$H and $^{13}$C NMR spectra of compound 3j.
Figure S20: $^{19}$F NMR spectrum of compound 3j.
Figure S21: $^1$H and $^{13}$C NMR spectra of compound 3k.
Figure S22: $^1$H and $^{13}$C NMR spectra of compound 3l.
Figure S23: $^{19}$F NMR spectrum of compound 3l.
Figure S24: $^1$H and $^{13}$C NMR spectra of compound 3m.
Figure S25: $^1$H and $^{13}$C NMR spectra of compound 3n.
Figure S26: $^1$H and $^{13}$C NMR spectra of compound 3o.
Figure S27: $^{19}$F NMR spectrum of compound 3o.
Figure S28: $^1$H and $^{13}$C NMR spectra of compound 3p.
Figure S29: $^1$H and $^{13}$C NMR spectra of compound 3q.
Figure S30: $^{1}$H and $^{13}$C NMR spectra of compound 3r.
Figure S31: $^{19}$F NMR spectrum of compound 3r.
Figure S32: $^1$H and $^{13}$C NMR spectra of compound 3s.
Figure S33: $^1$H and $^{13}$C NMR spectra of compound 3t.
Figure S34: $^{19}$F NMR spectrum of compound 3t.
**Figure S35:** $^1$H and $^{13}$C NMR spectra of compound 3u.
Figure S36: $^1$H and $^{13}$C NMR spectra of compound 3v.
**Figure S37:** $^{19}$F NMR spectrum of compound 3v.
Figure S38: $^1$H and $^{13}$C NMR spectra of compound 3w.
Figure S39: $^1$H and $^{13}$C NMR spectra of compound 3x.
Figure S40: $^{19}$F NMR spectrum of compound 3x.
Figure S41: $^1$H and $^{13}$C NMR spectra of compound 3y.
**Figure S42:** $^{19}$F NMR spectrum of compound 3y.
Figure S43: $^1$H and $^{13}$C NMR spectra of compound 3z.
Figure S44: $^{19}$F NMR spectrum of compound 3z.
Figure S45: $^1$H and $^{13}$C NMR spectra of compound 3aa.
Figure S46: $^{19}$F NMR spectrum of compound 3aa.