SUPPORTING INFORMATION

(45 PAGES)

Manuscript entitled “ A New Easy Approach to the Synthesis of 2,5-Disubstituted and 2,4,5-Trisubstituted 1,3-Oxazoles. The reaction of 1-(Methylthio)acetone with nitriles”.

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Manuscript number:

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General. Dichloromethane was purified by distillation over P₂O₅. Triflic anhydride was prepared from TfOH and distilled twice over P₂O₅ before use. ¹H NMR and ¹³C NMR were recorded in CDCl₃ at 300 and 500 MHz and 75 and 125 MHz and referenced to 7.26 and 77.00 ppm respectively. Homonuclear *J* couplings were confirmed by single-frequency experiments. Multiplicity assignments of ¹³C NMR signals were made from DEPT spectra. HMBC and HMBQ spectra were recorded using the standard pulse sequences from Bruker.

Characterization data of compounds

2,5-Dimethyl-4-(methylthio)-1,3-oxazole (8a): colorless oil; yield 88%; bp 75 °C/0.4 torr (kugelrohr); IR (film) ν 2926, 1585, 1161, 1088, 733 cm⁻¹; ¹H NMR δ 2.24 (s, 3H, CH₃), 2.29 (s, 3H, CH₃), 2.34 (s, 3H, CH₃S); ¹³C NMR δ 9.8 (CH₃-C5), 13.4 (CH₃-C2), 17.3 (CH₃S), 128.2 (C5), 148.2 (C4), 159.3 (C2); MS (EI) *m/z* (%B) 143 (M⁺, 7), 110 (M-SH, 4), 43 (CH₃CO⁺, 100); Anal. Calcd for C₆H₉NOS: C, 50.32; H, 6.33; N, 9.78; S, 22.39. Found: C, 50.11; H, 6.19; N, 9.66; S, 22.10.

2-Ethyl-5-methyl-4-(methylthio)-1,3-oxazole (8b): pale yellow oil; yield 80%; bp 100 °C/0.4 torr (kugelrohr); IR (film) ν 2963, 1578, 1261, 1072, 799 cm⁻¹; ¹H NMR δ 1.27 (t, *J* = 7.7 Hz, 3H, CH₃CH₂), 2.27 (s, 3H, CH₃), 2.31 (s, 3H, CH₃S), 2.69 (q, *J* = 7.7 Hz, 2H, CH₂); ¹³C NMR δ 9.7 (CH₃-C5), 10.5 (CH₃CH₂), 17.2 (CH₃S), 21.2 (CH₂), 128.0 (C5), 148.0 (C4), 163.5 (C2); MS (EI) *m/z* (%B) 157 (M⁺, 11), 124 (M-SH, 4), 57 (C₂H₅CO⁺, 100); Anal. Calcd for C₇H₁₁NOS: C, 53.47; H, 7.05; N, 8.91; S, 20.39. Found: C, 53.22; H, 6.87; N, 8.69; S, 20.19.

5-Methyl-2,4-bis(methylthio)-1,3-oxazole (8c): colorless oil; yield 70%, bp 75 °C/0.4 torr (kugelrohr); IR (film) ν 2924, 1676, 1499, 1175, 733 cm⁻¹; ¹H NMR δ 2.31 (s, 3H, CH₃), 2.34 (s, 3H, CH₃S), 2.61 (s, 3H, CH₃S); ¹³C NMR δ 10.3 (CH₃-C5), 14.5 (CH₃S), 17.8 (CH₃S), 130.1 (C5), 150.4 (C4), 159.0 (C2); MS (EI) *m/z* (%B) 175 (M⁺, 100), 160 (M-CH₃, 45), 118(42). Due to the difficulty found to purify completely this compound, **8c** was used without purification as starting material to prepare **13c**.

5-Methyl-2-(4-methylphenyl)-4-(methylthio)-1,3-oxazole (8e): yellow oil; yield 89%, bp 125 °C/0.4 torr; IR (film) ν 2922, 1591, 1501, 1107, 826, 733 cm^{-1} ; ^1H NMR δ 2.29 (s, 3H, CH_3Ph), 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3S), 7.14 (d, $J = 8.0$ Hz, 2H; Ar-H), 7.82 (d, $J = 8.0$ Hz, 2H, Ar-H); ^{13}C NMR δ 10.2 ($\text{CH}_3\text{-C5}$), 17.6 (CH_3S), 21.1 (CH_3Ph), 124.3, 125.7, 129.1, 130.1 (arom.), 140.0 (C5), 148.6 (C4), 159.9 (C2); MS (EI) m/z (%B) 219 ($\text{M}^{+\bullet}$, 27), 186 (M-SH, 18), 119 ($\text{CH}_3\text{C}_6\text{H}_5\text{CO}^+$, 100), 91 (C_7H_7^+ , 42); Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NOS}$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.65; H, 5.70; N, 6.42; S, 14.39.

2-(4-Chlorophenyl)-5-methyl-4-(methylthio)-1,3-oxazole (8f): pale yellow needles (from EtOH); yield 90%, mp 63-64 °C; IR (KBr) ν 1593, 1483, 1404, 1261, 1088 cm^{-1} ; ^1H NMR δ 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3S), 7.44 (d, $J = 8.7$ Hz, 2H; Ar-H), 8.00 (d, $J = 8.7$ Hz, 2H, Ar-H); ^{13}C NMR δ 10.6 ($\text{CH}_3\text{-C5}$), 18.0 (CH_3S), 125.3, 127.5, 129.1 (arom.), 130.5 (C5), 136.6 (arom), 149.7 (C4), 159.2 (C2); MS (EI) m/z (%B) 239 ($\text{M}^{+\bullet}$, 27), 206 (M-SH, 58), 139 ($\text{ClC}_6\text{H}_5\text{CO}^+$, 100); Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{ClNOS}$: C, 55.11; H, 4.20; N, 5.84; S, 13.38. Found: C, 54.87; H, 4.10; N, 5.90; S, 13.14.

5-Methyl-4-(methylthio)-2-(4-methoxyphenyl)-1,3-oxazole (8g): white crystals (from MeOH); yield 86%, mp 57-58 °C; IR (KBr) ν 1611, 1499, 1252, 1022, 839 cm^{-1} ; ^1H NMR δ 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3S), 3.77 (s, 3H, CH_3O), 6.88 (d, $J = 8.8$ Hz, 2H; Ar-H), 7.88 (d, $J = 8.8$ Hz, 2H, Ar-H); ^{13}C NMR δ 10.3 ($\text{CH}_3\text{-C5}$), 17.8 (CH_3S), 55.1 (CH_3O), 113.9, 119.9, 127.5 (arom), 130.0 (C5), 148.4 (C4), 159.8 (arom.), 161.0 (C2); MS (EI) m/z (%B) 235 ($\text{M}^{+\bullet}$, 100), 202 (M-SH, 71), 135 ($\text{CH}_3\text{OC}_6\text{H}_5\text{CO}^+$, 37); Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 60.98; H, 5.44; N, 5.84; S, 13.50.

5-Methyl-2-(4-methylbenzyl)-4-(methylthio)-1,3-oxazole (8h): yellow oil; yield 76%, bp 175 °C/0.4 torr; IR (film) ν 2924, 1572, 1514, 1151, 1088, 779 cm^{-1} ; ^1H NMR δ 2.27 (s, 3H, CH_3Ph), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3S), 4.00 (s, 2H, CH_2), 7.15 (m, 4H, Ar-H); ^{13}C NMR δ 10.0 ($\text{CH}_3\text{-C5}$), 17.4 (CH_3S), 20.7 (CH_3Ph), 34.0 (CH_2), 128.3, 129.0, 128.8,

132.1 (arom), 136.2 (C5), 148.9 (C4), 161.2 (C2); MS (EI) m/z (%B) 233 ($M^{+•}$, 39), 200 (M-SH, 27), 105 ($C_8H_9^+$, 100); Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found C, 66.80; H, 6.33; N, 5.89; S, 13.61.

2-(4-Chlorobenzyl)-5-methyl-4-(methylthio)-1,3-oxazole (8i): yellow oil; yield 75%, bp 150 °C/0.4 torr (kugelrohr); IR (film) ν 1572, 1493, 1090, 1016, 783 cm^{-1} ; 1H NMR δ 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3S), 4.00 (s, 2H, CH_2), 7.25 (m, 4H, Ar-H); ^{13}C NMR δ 10.0 (CH_3 -C5), 17.7 (CH_3S), 33.7 (CH_2), 128.4, 128.7, 129.8, 132.6 (arom), 133.6 (C5), 149.0 (C4), 160.4 (C2); MS (EI) m/z (%B) 253 ($M^{+•}$, 100), 220 (M-SH, 40), 125 ($ClC_7H_6^+$, 27); Anal. Calcd. for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.77; Cl, 13.97; N, 5.52; S, 12.64. Found: C, 56.59; H, 4.60; Cl, 13.59; N, 5.55; S, 12.48.

5-Methyl-4-(methylthio)-2-(4-nitrobenzyl)-1,3-oxazole (8j): yellow crystals (from MeOH); yield 72%, mp 93-94 °C; IR (KBr) ν 1578, 1518, 1344, 739 cm^{-1} ; 1H NMR δ 2.28 (s, 3H, CH_3), 2.33 (s, 3H, CH_3S), 4.14 (s, 2H, CH_2), 7.46 (d, $J = 8.7$ Hz, 2H, Ar-H), 8.15 (d, $J = 8.7$ Hz, 2H, Ar-H) ^{13}C NMR δ 10.3 (CH_3 -C5), 17.7 (CH_3S), 34.3 (CH_2), 123.8, 129.2, 129.7 (arom), 142.5 (C5), 147.1 (arom), 149.7 (C4), 159.5 (C2); MS (EI) m/z (%B) 264 ($M^{+•}$, 100), 231 (M-SH, 54), 87 (44); Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.40; H, 4.38; N, 10.52; S, 11.96.

2-[5-Methyl-4-(methylthio)-1,3-oxazol-2-yl]benzonitrile (8k): yellow oil; yield 52%, bp 150 °C/0.4 torr; IR (film) ν 2227, 1587, 1437, 773 cm^{-1} ; 1H NMR δ 2.44 (s, 3H, CH_3), 2.46 (s, 3H, CH_3S), 7.49 (td, $J = 7.7, 1.2$ Hz, 1H, Ar-H), 7.65 (td, $J = 7.7, 1.2$ Hz, 1H, Ar-H), 7.76 (dd, $J = 7.7, 1.2$ Hz, 1H, Ar-H), 8.14 (dd, $J = 7.7, 1.2$ Hz, 1H, Ar-H); ^{13}C NMR δ 10.4 (CH_3 -C5), 17.2 (CH_3S), 109.1 (arom.) 117.4 (CN), 128.0, 128.9, 129.7, 131.6, 132.5, (arom), 134.5 (C5), 149.4 (C4), 156.5 (C2); MS (EI) m/z (%B) 230 ($M^{+•}$, 30), 215 (M- CH_3 , 8), 195 (M-SH, 43), 130 ($NCC_6H_4CO^+$, 100); Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.33; H, 4.30; N, 12.12; S, 13.79.

4-[5-Methyl-4-(methylthio)-1,3-oxazol-2-yl]benzonitrile (8l): white crystals (from EtOH); yield 46%, mp 107-108 °C; IR (KBr) ν 2231, 1215 cm^{-1} ; ^1H NMR δ 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3S), 7.74 (m, 2H, Ar-H), 8.13 (m, 2H, Ar-H); ^{13}C NMR δ 10.7 ($\text{CH}_3\text{-C5}$), 17.8 (CH_3S), 113.3 (arom.) 118.4 (CN), 126.4, 130.9, 131.8 (arom), 132.6 (C5), 145.4 (C4), 158.1 (C2); MS (EI) m/z (%B) 230 ($\text{M}^{+\bullet}$, 100), 215 (M- CH_3 , 8), 195 (M-SH, 31), 130 ($\text{NCC}_6\text{H}_4\text{CO}^+$, 88) 102 (NCC_6H_4^+ , 35); Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OS}$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.44; H, 4.28; N, 12.09; S, 13.81.

5-Methyl-2-{2-[5-methyl-4-(methylthio)-1,3-oxazol-2-yl]phenyl}-4-(methylthio)-1,3-oxazole (10): undestillable yellow oil; yield 75%; IR (film) ν 1541, 1377, 1215, 929 cm^{-1} ; ^1H NMR δ 2.33 (s, 6H, 2 CH_3), 2.41 (s, 6H, 2 CH_3S), 7.54, 7.90 (AA'XX' system, 4H, Ar-H); ^{13}C NMR δ 10.3 ($\text{CH}_3\text{-C5}$), 17.5 (CH_3S), 126.6, 129.7, 130.0 (arom), 130.3 (C5), 148.7 (C3), 159.0 (C2); MS (EI) m/z (%B) 332 ($\text{M}^{+\bullet}$, 70), 317 (M- CH_3 , 37), 299 (M-SH, 31), 232 ($[\text{C}_5\text{H}_6\text{NOS}]\text{C}_6\text{H}_5\text{CO}^+$, 34); Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$: C, 57.81; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.66; H, 4.77; N, 8.29; S, 19.10.

2-Phenyl-5-methyl-1,3-oxazole (12d): colorless oil; yield 86%, bp 100 °C/0.4 torr (kugelrohr); IR (film) ν 1684, 1217, 758 cm^{-1} ; ^1H NMR δ 2.42 (d, $J = 1.1$ Hz, 3H, CH_3), 6.88 (q, $J = 1.1$ Hz, 1H, H4), 7.46 (m, 3H, Ar-H), 8.03 (m, 2H, Ar-H); ^{13}C NMR δ 10.9 ($\text{CH}_3\text{-C5}$), 124.0, 125.9, 127.6, 128.6 (arom), 129.8 (C5), 148.8 (C4), 160.6 (C2); MS (EI) m/z (%B) 159 ($\text{M}^{+\bullet}$, 77), 145 (M- CH_3 , 16), 116 (M- CH_3CO , 49), 105 ($\text{C}_6\text{H}_5\text{CO}^+$, 100), 77 (C_6H_5^+ , 51); Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.33; H, 5.59; N, 8.71.

5-Methyl-2,4-bis(methylsulfonyl)-1,3-oxazole (13c): yellow oil; yield 91%, bp 175 °C/0.4 torr (kugelrohr); IR (film) ν 1518, 1329, 1163 cm^{-1} ; ^1H NMR δ 1.96 (s, 3H, CH_3), 2.77 (s, 3H, CH_3SO_2), 3.00 (s, 3H, CH_3SO_2); ^{13}C NMR δ 15.9 ($\text{CH}_3\text{-C5}$), 18.6 (CH_3SO_2), 35.9 (CH_3SO_2), 100.3 (C5), 161.0 (C4), 196.9 (C2); MS (EI) m/z (%B) 239 ($\text{M}^{+\bullet}$, not observed), 144 (M- CH_3SO_3 , 100), 102 (60); MS (ESI, MeOH) m/z 246 [$\text{M}+\text{Na}-\text{O}$] $^+$; Anal.

Calcd. for $C_6H_9NO_5S_2$: C, 30.12; H, 3.79; N, 5.85; S, 26.80. Found: C, 29.90; H, 3.60; N, 5.77; S, 26.69.

2-(4-Chlorophenyl)-5-methyl-4-(methylsulfonyl)-1,3-oxazole (13f): white crystals (from MeOH); yield 97%, mp 139-140 °C; IR (KBr) ν 1485, 1315, 1153 cm^{-1} ; 1H NMR δ 2.71 (s, 3H, CH_3), 3.22 (s, 3H, CH_3SO_2), 7.46 (d, J = 8.6 Hz, 2H, Ar-H), 7.97 (d, J = 8.6 Hz, 2H, Ar-H); ^{13}C NMR δ 11.5 (CH_3 -C5), 42.7 (CH_3SO_2), 124.4, 127.9, 129.3, 135.9 (arom.), 137.6 (C5), 153.4 (C4), 159.4 (C2); MS (EI) m/z (%B) 271 (M^{+} , 22), 139 ($ClC_6H_5CO^{+}$, 100); Anal. Calcd. for $C_{11}H_{10}ClNO_3S$: C, 48.62; H, 3.71; Cl, 13.05; N, 5.15; S, 11.80. Found: C, 48.50; H, 3.59; Cl, 12.89; N, 5.10; S, 11.70.

5-Methyl-4-(methylsulfonyl)-2-(4-nitrobenzyl)-1,3-oxazole (13j): white crystals (from MeOH); yield 97%, mp 141-142 °C; IR (KBr) ν 1522, 1348, 1317, 1149, 1107 cm^{-1} ; 1H NMR δ 2.59 (s, 3H, CH_3), 3.15 (s, 3H, CH_3SO_2), 4.20 (s, 2H, CH_2), 7.49 (d, J = 8.6 Hz, 2H, Ar-H), 8.21 (d, J = 8.6 Hz, 2H, Ar-H); ^{13}C NMR δ 11.2 (CH_3 -C5), 33.9 (CH_2), 42.7 (CH_3SO_2), 124.0, 129.8, 134.6 (arom.), 141.3 (C5), 147.2 (arom.), 154.0 (C4), 160.1 (C2); MS (EI) m/z (%B) 296 (M^{+} , 22), 266 (M-NO, 5), 164 ($NO_2C_6H_5CH_2CO^{+}$, 100); Anal. Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.45; S, 10.82. Found: C, 48.53; H, 3.97; N, 9.49; S, 10.70.

Reaction of methylthioketone **7** with two different nitriles.

The reaction was carried out using 1.0 mmol of **7**, 1.1 mmol of Tf_2O and 0.55 mmol of 4-chlorobenzonitrile and 0.55 mmol of 4-chlorophenylacetonitrile following the general procedure reported in the manuscript. After basic hydrolysis, extraction and drying, the solvent was removed in vacuo and the residue analyzed by 1H NMR. Compounds **8f** and **8i** were obtained in 69% overall yield and ratio 55/45.

13j

12g

Figure S1. Fluorescence spectra of bis-oxazolyl derivative **11**

Figure S2. ^1H NMR (500 MHz) at 5 °C of the reaction mixture of methylthioacetone **7** and Tf_2O after 1h.

Figure S3. Expansions of the CH, CH_2 and CH_3 zones of Figure S2.

Figure S4. ^{13}C NMR (125 MHz) at 5 °C of the reaction mixture of methylthioacetone **7** and Tf_2O after 1h.

Figure S5. Expansions of the CO, CH, CH_2 and CH_3 zones of Figure S.

Figure S6. HMQC and HMBC spectra of the reaction mixture of methylthioacetone **7** and Tf₂O after 1h

Figure S7. ^1H NMR spectra (500 MHz) of the reaction of methylthioacetone **7** with Tf_2O after 15h

Scheme S1. Detected intermediates in the reaction mixture of **7** with Tf_2O with their ^1H NMR chemical shifts (^{13}C NMR chemical shifts are enclosed in brackets) in ppm

Figure S8. HMQC spectra of the reaction mixture 15h after the addition of benzonitrile