

Supporting Information

Re: JO026202q

Conventional Benchtop Experimental Procedures:

1,3-Dimethoxy-4-nitrobenzene (10a): Reacted 1.04 g (7.50 mmol) **9** with 1.05 equivalents of **3** in 40 mL DCM for 15 h to obtain an isolated yield of 1.13 g (82% with 5% **10b** isomer). FW = 183.1; ^1H NMR (DMSO- d_6) δ 7.97 (d, J = 9Hz, 1H), 6.80 (d, J = 2Hz, 1H), 6.67 (dd, J_1 = 9Hz, J_2 = 3Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H); GC/MS (CI, m/z) 183 (M^+ and base peak).

1,3-Dimethoxy-2-nitrobenzene (10b): FW = 183.1; ^1H NMR (DMSO- d_6) δ 7.48 (t, 1H), 6.89 (d, 2H), 3.86 (s, 6H); GC/MS, (CI, m/z) 183 (M^+ and base peak).

2-Bromo-1-(4-hydroxy-3-nitrophenyl)ethanone (12): Small Scale: Reacted 1.70 g (7.91 mmol) **11** with 1.15 equivalents of **3** in 30 mL DCM for 27 h to obtain an isolated yield of 1.93 g (93%). Large Scale: Reacted 19.98 g (92.93 mmol) **11** with 1.10 equivalents of **3** in 325 mL DCM for 23 h to obtain an isolated yield of 21.90 g (91%). Recrystallized from hot hexane to give a faint yellow solid. FW = 260.0; ^1H NMR (DMSO- d_6) δ 12.18 (brd. s, 1H), 8.49 (s, 1H), 8.13 (d, 1H), 7.24 (d, 1H), 4.89 (s, 2H); ES/MS (CI, m/z) 260 (M^+), 258 (base peak); FTIR (KBr) 3279, 3086, 2997, 2940, 1695, 1568, 1329 cm^{-1} ; mp uncorrected = 87.8 to 89.4 $^{\circ}\text{C}$, (lit. mp [twice recrystallized] = 91.5 to 92.0 $^{\circ}\text{C}$).²⁷ Anal. Calcd for $\text{C}_8\text{H}_6\text{BrNO}_4$: C, 36.95%; H, 2.33%; N, 5.39%; Br, 30.73%. Found C, 37.28 %; H, 2.34%; N, 5.44%; Br, 30.90%.

2,4,6-Trimethoxy-3-nitrobenzonitrile (14): Small Scale: Reacted 1.48 g (7.51 mmol) **13** (98%) with 1.50 equivalents of **3** in 40 mL DCM for 53 h to obtain an isolated yield of 1.54 g (86%). Large Scale: Reacted 17.80 g (90.29 mmol) **13** (98%) with 1.66 equivalents of **3** in 300 mL DCM for 1 h in a dry ice/acetone bath, then for 3 h in a dry ice/acetonitrile bath, followed by 48 h at RT (52 h total)¹¹ to obtain an isolated yield of 17.59 g (82%). Recrystallized from methanol. FW = 238.2; ^1H NMR (DMSO- d_6) δ 6.79 (s, 1H), 4.02 (s, 6H), 4.01 (s, 1H); FI/MS (APCI, m/z) 209 (M^+ -30 and base peak); FTIR (ATR film) 3114, 2994, 2957, 2924, 2984, 2228, 1529, 1349 cm^{-1} ; mp uncorrected = 195.2 to 195.6 $^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_5$: C, 50.42%; H, 4.23%; N, 11.76%. Found C, 50.60 %; H, 4.18%; N, 11.80%.

4-tert-Butyl-2-nitrophenol (16): Scaled according to the *General Procedure* with a smaller proportion of DCM solvent. Reacted 12.2 g (82.3 mmol) **15** with 1.04 equivalents of **3** in 325 mL DCM for 24 h to obtain an isolated yield of 15.0 g (94%). FW = 193.3; ^1H NMR (CDCl_3) δ 7.84 (s, 1H), 7.40 (d, 1H), 7.12 (d, 1H), 2.42 (s 3H), 1.21 (s, 9H); GC/MS (CI, m/z) 194 (M^+ +1), 178 (base peak).

2,4-Dimethoxy-5-nitrobenzonitrile (18): Small Scale: Reacted 1.23 g (7.54 mmol) **17** (98%) with 1.25 equivalents of **3** for 3.5 h in a dry ice/acetone bath, then at rt for 45 h to obtain an isolated yield of 1.40 g (89%) shown by ^1H NMR to be 89% pure). Large Scale: Reacted 16.65 g (100.0 mmol) **17** (98%) with 1.50 equivalents of **3** in 465 mL DCM for 30 min in a dry ice/acetone bath, then 3.5 h in a dry ice/acetonitrile bath, followed by 48 h at rt¹¹ to obtain an isolated yield of 18.99 g (91%). Recrystallized from methanol. FW = 208.2; ^1H NMR (DMSO- d_6) δ 8.46 (d, J = 3Hz, 1H), 6.99 (s, J = 3Hz, 1H), 4.06 (s, 6H); GC/MS (CI, m/z) 208 (M^+), 161 (base peak); FTIR (ATR film): 3126, 3073, 3000, 2958, 2924, 2852, 2232, 1524, 1354 cm^{-1} ; mp uncorrected = 195.8 to 196.4 °C. Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_4$: C, 51.93%; H, 3.87%; N, 13.46%. Found C, 51.93 %; H, 3.85%; N, 11.45%.

N-(3,5-dimethoxy-2-nitrophenyl)methanesulfonamide (22a): Reacted 1.75 g (7.51 mmol) **21** with 1.05 equivalents of **3** in 20 mL DCM for 1.5 h to obtain an HPLC purified yield of 0.25 g (11%). FW = 276.3; ^1H NMR (CDCl_3) δ 8.31 (s, 1H), 6.88 (d, J = 3Hz, 1H), 6.32 (d, J = 3Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.03 (s 3H); ^{13}C NMR (CDCl_3 , 300 MHz) 164.01 (1C), 156.35 (1C), 134.75 (1C), 97.65 (1C), 96.45 (1C), 57.18 (1C), 56.47 (1C), 40.57 (1C); FI/MS (ANCI, m/z) 275 (M^- -1).

N-(3,5-dimethoxy-4-nitrophenyl)methanesulfonamide (22b): Reacted 0.544 g (2.35 mmol) **21** with fuming nitric acid in acetic anhydride in an ice bath for 30 minutes, removed ice bath, stirred for 4 h at rt, and worked up reaction to obtain an HPLC purified yield of 0.070 g (10%). FW = 276.3; ^1H NMR (CDCl_3) δ 6.48m (s, 2H), 6.87 (s, 6H), 3.07 (s, 3H); ^{13}C NMR (CDCl_3 , 300 MHz) 153.49 (2C), 140.26 (1C), 126.28 (1C), 95.85 (2C), 57.07 (2C), 40.12 (1C); FI/MS (APCI, m/z) 277 (M^+ +1).

2-Chloro-4,6-dimethoxy-5-nitropyrimidine (31): Method I (Small Scale): Based upon the General Procedure, reacted 1.53 g (10.8 mmol) 96% **1** with 3.38 g (12.0 mmol) **2** as a stirred suspension in 40 mL DCM at rt for 2.25 h. Next, 1.31 g (7.50 mmol) **30** in 10 mL DCM were added at -72 to -70 °C; then, the dry ice/acetone cooling bath was removed, and the reaction suspension was stirred at rt for 48 h. Work-up provided a crude, isolated yield of 1.61 g (98%). FW = 219.6; ^1H NMR (DMSO- d_6) δ 4.06 (s, 6H); GC/MS (CI, m/z) 220 (M^+ +1 and base peak); FTIR (KBr): 3126, 3073, 3000, 2958, 2924, 2852, 1524, 1354 cm^{-1} ; HPLC purity analysis = 99.9%; mp uncorrected = 131.8 to 132.0 °C. Anal. Calcd for $\text{C}_6\text{H}_6\text{ClN}_3\text{O}_4$: C, 32.82%; H, 2.75%; Cl, 16.15%; N, 19.14%. Found C, 33.12 %; H, 2.81%; Cl, 16.43%; N, 18.95%.

Method I (Large Scale): This scale-up for the synthesis of **31** was based upon the *General Procedure* with variations convenient for the 383 scaling factor. Into a 12 L three-necked flask equipped with an overhead stirrer, thermometer, N_2 gas inlet, and addition funnel were placed 587g (431 mmol) **1** and 400 mL DCM. The suspension was

stirred at rt under N₂ for 1 h. Added dropwise to the stirred suspension were 1216 g or 725 mL (431 mmol) **2** over 45 min at a rate to keep the reaction temperature below 25 °C. The addition funnel was rinsed with 100 mL DCM which were added to the stirred reaction suspension. The suspension was stirred at rt under an N₂ gas atmosphere for 2 h. The stirred suspension was cooled to –78 °C in a dry ice/acetone bath. A solution containing 500 g (2864 mmol) **30** dissolved in 300 mL DCM was added dropwise over 1.5 h. The cooling bath was removed and the suspension was stirred at rt under an N₂ gas atmosphere for 38 h. The reaction was quenched by pouring into *ca.* 2000 g of ice and bringing the aqueous phase of the mixture to pH of 8 using aqueous NaHCO₃. The lower DCM layer was separated, and the upper H₂O layer was washed with 3 x 100 mL of DCM. The combined DCM portions were washed with 2 x 1000 mL H₂O. The DCM solution was dried over anhydrous MgSO₄ and filtered. The DCM was removed by rotary evaporation and dried at rt in a vacuum oven to give 615 g of **31** (98%) as a white solid shown to be 95% pure by NMR analysis.

Method II: A 3 L round bottom flask equipped with an overhead stirrer, thermocouple, and nitrogen gas inlet was charged with 100 g (573 mmol) **30**, 116.98 g (859 mmol) **1** and 1L of DCM. The mixture was cooled to 5 °C, and 144 mL (859 mmol) **2** were added at a rate to keep the resultant reaction suspension at 20 °C or less. The mixture was stirred under a nitrogen gas atmosphere at 20 °C for 18 h when HPLC analysis indicated less than 3% of reactant **30** remained. The reaction suspension was cooled to 2 °C and quenched by adding 500 mL H₂O causing a temperature rise to 20 °C. The aqueous mixture was treated with 50% (w/w) 138 g (1719 mmol) NaOH to give pH 9. The separated DCM phase was diluted with 500 mL of heptane, the resulting solution was heated to reflux, and the DCM was removed by distillation until pot and distillation head temperatures both reached 98 °C.¹³ The resulting mixture was cooled to rt, filtered, and the cake was washed with 500 mL heptane. The solid was dried under a 25 mmHg vacuum at 50 °C for 15.5 h to give 104.29 g light yellow solid **31** (83%). Analysis showed a 98.5% purity based on the HPLC area percent.

2,4,6-Trimethoxy-5-nitropyrimidine (33): The scale-up of this reaction also was based closely upon the *General Procedure*. A 5-L round bottom flask assembled with an overhead stirrer, thermometer, N₂ inlet, and addition funnel was charged with 920 g (675 mmol) **1** and 1000 mL DCM. The suspension was stirred at rt under N₂ for 15 min. Added dropwise over 35 min were 190 g or 118 mL (674 mmol) **2** at a rate that kept the reaction temperature from rising more than 5 °C. A solution containing 76.9 g (452 mmol) **32** dissolved in a minimum amount of DCM was added over 85 min so that the reaction temperature remained at 5 °C or less. The stirred suspension was reacted at rt under an N₂ gas atmosphere overnight. The reaction was quenched by adding 5000 g of

ice to stirred reaction suspension and bringing the reaction mixture to pH 8 using 10% aqueous NaHCO₃. The lower DCM layer was separated and washed with 3 x 1500 mL of H₂O. The combined DCM portions were dried over anhydrous Na₂SO₄ and filtered. The DCM solvent was removed by rotary evaporation, and dried to give *ca.* 70 g of a green solid. Recrystallization from MeOH/H₂O afforded 50.5 g (52%) of analytically pure product. FW = 215.2; ¹H NMR (CDCl₃) δ 4.06 (s, 6H), 4.02 (s, 3H); FI/MS (APCI, *m/z*) 216 (M⁺+1 and base peak); FTIR (ATR film): 3047, 3009, 2957, 2877, 2847, 1578, 1338 cm⁻¹. Anal. Calcd for C₇H₉N₃O₅: C, 39.07%; H, 4.22%; N, 19.53%. Found C, 39.14 %; H, 4.19%; N, 19.61%.

Methyl 5-nitro-2-furoate (35a): This reaction was conducted with slight modification of the *General Procedure* using 1.5 equivalents of **3** in 60 mL DCM solvent. In 100 mL three-necked flask, 2.40 g (16.9 mmol) 96% **1** with 5.00 g (17.7 mmol) **2** in 36 mL DCM were stirred at rt for a minimum of 1.5 hours. At -73 °C, 1.45 g (11.3 mmol) **34** in 24 mL DCM was added dropwise. The dry ice/acetone bath was removed and replaced with a dry ice/ethylene glycol cooling bath, and the reaction was stirred at 0.6 to 1.4 °C for 3 h. before removing bath and stirring at rt for 23.5 h prior to work-up. Skipping the 3 h dry ice/ethylene glycol bath portion and simply removing the dry ice/acetone cooling bath had little effect on the product yield or isomeric product percentages. The reaction was quenched by adding 40 mL of 5% NaHCO₃ to bring the aqueous layer to pH 8. The reaction mixture was transferred using a 35 mL DCM rinse of the reaction flask followed by a 75 mL H₂O rinse. The DCM layer was separated and washed with 5 x 40 mL H₂O, and the combined H₂O washes were back extracted with 25 mL DCM. The combined DCM portions were dried over anhydrous MgSO₄. Solvent removal by rotary evaporation and drying to a constant weight at rt in a vacuum oven gave 1.62 g (84% as a **35a** & **35b** isomeric mixture). The 1.62 g of isolated product mixture consisted of 91% **35a** and 9% **35b**. Recrystallization from 14 mL of a 5:2 v/v MeOH/H₂O solution afforded 1.27 g (66%) of **35a** as a white fluffy solid. FW = 171.1; ¹H NMR (DMSO-*d*₆) δ 7.78 (d, 1H), 7.59 (d, 1H); GC/MS (CI, *m/z*) 172 (M⁺+1); FTIR (ATR film): 3163, 3131, 3060, 3018, 2961, 2879, 2852, 1727, 1530, 1353 cm⁻¹; HPLC purity analysis = 100%. Anal. Calcd for C₆H₅NO₅: C, 42.12%; H, 2.95%; N, 8.19%. Found, C, 42.24 %; H, 2.97%; N, 8.10%.

Methyl 5-nitrothiophene-2-carboxylate/methyl and 4-nitrothiophene-2-carboxylate mixture (37a/37b): This reaction was conducted the same as with reactant **36** as a slight modification of the *General Procedure* using 1.5 equivalents of **3** in a total of 60 mL DCM solvent. The nitration was begun by reacting 2.40 g (16.9 mmol) 96% **1** with 5.08 g (18.0 mmol) **2** in 36 mL DCM and stirring at the suspension at rt for a minimum of 1.5 h. Next, 1.65 g (11.3 mmol) **36** in 24 mL DCM were added at -72 °C.

The ice bath was then removed and the reaction was stirred at rt for 42 h. Reaction quenching and work-up was conducted exactly as outlined for product **35a** to obtain an isolated yield of 1.91 g (90% as a **37a** & **37b** isomeric mixture). The 1.91 g of isolated product mixture consisted of 62 % **37a** and 38% **37b**. FW = 187.2; Isomer **37a**: ^1H NMR (CDCl_3) δ 7.86 (d, 1H), 7.68 (d, 1H), 3.94 (s, 3H); ^1H NMR (DMSO-d_6) δ 8.14 (d, 1H), 7.82 (d, 1H), 3.89 (s, 3H); GC/MS (CI, m/z) 188 ($\text{M}^+ + 1$ and base peak). Isomer **37b**: FW = 187.2; ^1H NMR (CDCl_3) δ 8.44 (s, 1H), 8.25 (s, 1H), 3.94 (s, 3H); ^1H NMR (DMSO-d_6) δ 9.05 (s, 1H), 8.19 (s, 1H), 3.87 (s, 3H); GC/MS (CI, m/z) 188 ($\text{M}^+ + 1$).

Methyl 5-formyl-2-furoate (39): This reaction was conducted with a slight modification of the *General Procedure* using 1.10 equivalents of **3** over a 76 h reaction time at rt. Initially, 1.17 g (8.24 mmol) 96% **1** were reacted with 2.40 g (8.51 mmol) **2** in 28 mL DCM by stirring at RT for a minimum of 1.5 h. Next, 1.31 g (7.51 mmol) **38** in 12 mL DCM were added at -71.2 to 72.0 $^\circ\text{C}$; then, the dry/ice acetone cooling bath was removed, and the reaction suspension was stirred at rt for 76 h. After a scaled aqueous work-up following the *General Procedure*, an isolated yield of 0.88 g was obtained that NMR analysis showed to be 71% **39** and 29% reactant **38**. FW = 154.1; ^1H NMR (DMSO-d_6) δ 9.75 (s, 1H), 7.63 (d, 1H), 7.50 (d, 1H); GC/MS (CI, m/z) 155 ($\text{M}^+ + 1$) with base peak = 123.

3,5-Dimethyl-4-nitroisoxazole (43): A 100 mL three-necked round bottom flask, charged with 3.58 g (25.2 mmol) 96% **1** and 10 mL DCM, was stirred at rt under N_2 while 7.17 g (25.4 mmol) of neat **2** were weighed out under an N_2 atmosphere. Neat **2** was added dropwise with a disposable capillary pipette directly to the stirred suspension followed by 2 mL DCM. The reaction suspension was stirred at rt for 1.5 h to obtain **3** *in-situ*. Using a disposable capillary pipette, 1.66 g (16.9 mmol) liquid **42** were added dropwise to the stirred reaction suspension followed by 3 mL DCM. The reaction suspension was refluxed 3.5 h and was then cooled to rt for work-up. The reaction was quenched by adding 50 mL of 5% NaHCO_3 to stirred solution to bring upper aqueous layer to pH 8. The reaction solution was transferred to an Erlenmeyer flask using a 100 mL DCM wash of the reaction flask followed by a 150 mL H_2O rinse. The lower DCM layer was separated and washed with 5 x 60 mL H_2O . The combined H_2O portions were back-extracted with 60 mL DCM. The two DCM portions were combined and dried over MgSO_4 and then filtered. Solvent removal by rotary evaporation and drying at rt in a vacuum oven gave 2.22 g of **43** as a cream-colored solid (92%) shown by NMR to contain 5% reactant **42**. The 2.22 g isolated sample was placed into a vacuum oven at 45 $^\circ\text{C}$ for 7 h to obtain 2.03 g (84%) product showing a 100% purity. FW = 142.1; ^1H NMR (DMSO-d_6) δ 2.76 (s, 3H), 2.46 (s, 3H); FTIR (ATR film): 3003, 2963, 2935, 2874, 1515, 1361 cm^{-1} ; HPLC purity analysis = 100%; GC/MS (CI, m/z) 143 ($\text{M}^+ + 1$). Anal.

Calcd for $C_5H_6N_2O_3$: C, 42.26%; H, 4.26%; N, 19.71%. Found C, 42.28 %; H, 4.28; N, 19.70%.

Methyl 5-methyl-4-nitroisoxazole-3-carboxylate (45): A 100 mL three-necked round bottom flask was charged with 3.66 g (25.8 mmol) 96% **1** and 10 mL DCM. The suspension was stirred under N_2 while 7.48 g (26.5 mmol) of neat **2** were weighed out under an N_2 gas atmosphere. With addition funnel, the neat **2** was added dropwise to the stirred suspension under an N_2 atmosphere. The addition funnel was then rinsed with 2 mL DCM, and this rinse was added to the stirred reaction suspension. The suspension was stirred at rt for 1 h and 50 min to obtain **3** *in-situ*. Added directly to the stirred reaction suspension were 2.50 g (17.2 mmol) solid **44** followed by 3 mL DCM. The stirred reaction suspension was refluxed 24 h under an N_2 gas atmosphere and was cooled to rt for work-up. Reaction solution was transferred to an Erlenmeyer flask using a 50 mL DCM wash of the reaction flask. Stirred contents of the Erlenmeyer flask were brought to pH 8 with 65 mL 5% aqueous $NaHCO_3$ solution and 125 mL H_2O were added. The lower DCM layer was separated and washed with 5 x 50 mL H_2O . The combined H_2O portions were back-extracted with 25 mL DCM. The two DCM portions were combined and dried over $MgSO_4$ and filtered. Solvent removal by rotary evaporation and drying at rt in a vacuum oven gave 3.29 g of a reddish-gold colored oil (100%). FW = 186.1; 1H NMR ($DMSO-d_6$) δ 3.98 (s, 3H), 2.82 (s, 3H); FTIR (ATR film): 3014, 2961, 2885, 2844, 1752, 1526, 1366 cm^{-1} ; HPLC purity analysis = 98.6%; GC/MS (CI, m/z) 187 ($M^+ + 1$).

Microwave-Assisted Experimental Procedures:

2,6-Difluoro-3-nitropyridine (41): Small Scale: Reacted 0.40 g (3.44 mmol) (99%) **40** with 1.50 equivalents of **3** at 80 °C for 10 min. irradiation, followed by a second 5 min irradiation to obtain an isolated yield of 0.52 g (95%) of a golden-colored oil. FW = 160.1; 1H NMR ($DMSO-d_6$) δ 8.94 (dd, 1H), 7.46 (d, 1H); GC/MS (CI, m/z) 161 ($M^+ + 1$ and base peak); FTIR (ATR film) 3108, 1536, 1348 cm^{-1} ; HPLC purity analysis = 100%. Anal. Calcd for $C_5H_2F_2N_2O_2$: C, 37.52%; H, 1.26%; F, 23.74%; N, 17.50%. Found C, 37.18 %; H, 1.28%; F, 23.85%; N, 17.13%.

Large-Scale: Microwave synthesis of **41** was conducted with the Ethos Milestone instrument using a 250 mL reaction vessel accessory. The 250 mL reaction vessel containing a magnetic stirring bar accessory was charged with 11.50 g (81.1 mmol) 96% **1** and 30 mL DCM. The suspension was stirred at rt under an N_2 gas atmosphere while 23.19 g (82.2 mmol) of neat **2** were weighed out under an N_2 gas blanket. Neat **2** was added with a disposable capillary pipette directly to the stirred suspension followed by 10 mL DCM. The reaction suspension was stirred at rt under an N_2 gas atmosphere for 2 h

to obtain **3** *in-situ*. Using a disposable capillary pipette, 6.72 g (54.5 mmol) liquid **40** were added directly to the stirred reaction suspension followed by a 3 mL DCM addition. Following a 5 min temperature ramp-up time from rt to 80 °C, during which the reaction momentarily exothermed to a 94 °C, the reaction vessel was irradiated at 80 °C for 15 min. The reaction was permitted to cool at rt about 45 min before opening the reaction vessel. The reaction was transferred to a 500 mL Erlenmeyer flask using a 100 mL DCM rinse of the reaction vessel, and the reaction was quenched by adding 150 mL of 5% NaHCO₃ to the stirred reaction mixture bringing the upper aqueous layer to pH 8. The lower DCM layer was separated and washed with 5 x 150 mL H₂O. The combined H₂O portions were back-extracted with 50 mL DCM. The two DCM portions were combined, dried over MgSO₄ and filtered. Solvent removal by rotary evaporation and drying at rt in a vacuum oven to a constant weight gave 8.89 g of **41** as a golden-colored oil (98%). FW = 160.1; ¹H NMR (DMSO-d₆) δ 8.94 (ovlp. dd, 3H), 7.46 (d, 3H); FTIR (ATR film): 3109, 1534, 1347 cm⁻¹; HPLC purity analysis = 100% as compared with a ¹H NMR 98% purity; GC/MS (CI, *m/z*) 161 (M⁺+1). Anal. Calcd for C₅H₂F₂N₂O₂: C, 37.52%; H, 1.26%; F, 23.74; N, 17.50%. Found C, 37.40%; H, 1.36%; F, 17.20%; N, 23.52%.

3,5-Dimethyl-4-nitroisoxazole (43): Reacted 0.33 g (3.36 mmol) (99%) **42** with 1.50 equivalents of **3** at 60 °C for 10 min. irradiation, followed by a second 5 min irradiation to obtain an isolated yield of 0.44 g (92%) a cream-colored solid. FW = 142.1; ¹H NMR (DMSO-d₆) δ 2.80 (s, 3H), 2.49 (s, 3H); GC/MS (CI, *m/z*) 143 (M⁺+1 and base peak); FTIR (ATR film) 3007, 2984, 2940, 2871, 1510, 1361 cm⁻¹; HPLC purity analysis = 99%. Anal. Calcd for C₅H₆N₂O₃: C, 42.26%; H, 4.26%; N, 19.71%. Found C, 41.84%; H, 4.18%; N, 19.41%. Proton NMR and FTIR data were verified by comparison with a commercial sample.

Methyl 5-methyl-4-nitroisoxazole-3-carboxylate (45): Small Scale: Irradiated 0.50 g (3.44 mmol) (97%) **44** with 1.50 equivalents of **3** at 60 °C for 10 min, followed by a second 5 min irradiation to obtain 0.64 g (100%) of a golden-colored oil. FW = 186.1; ¹H NMR (DMSO-d₆) δ 3.98 (s, 3H), 2.82 (s, 3H); FTIR (ATR film): 3018, 2961, 2942, 2885, 2850, 1752, 1526, 1365 cm⁻¹; GC/MS (CI, *m/z*) 187 (M⁺+1); HPLC purity analysis = 99%. Anal. Calcd for C₆H₆N₂O₅: C, 38.72%; H, 3.25%; N, 15.05%. Found C, 38.99%; H, 3.30%; N, 15.10%.

Large Scale: Microwave synthesis of **45** was conducted with the Ethos Milestone instrument using a 100 mL reaction vessel accessory. The 100 ml reaction vessel containing a magnetic stirring bar accessory was charged with 5.75 g (40.5 mmol) 96% **1** and 15 mL DCM. The suspension was stirred at rt under an N₂ gas atmosphere several minutes while 11.52 g (40.8 mmol) of neat **2** were weighed out under an N₂ gas blanket. Neat **2** was added with a disposable capillary pipette directly to the stirred suspension

followed by 5 mL DCM. The reaction suspension was stirred at rt under an N₂ gas atmosphere for 1h and 40 min to obtain **3** *in-situ*. Then, 3.92 g (27.0 mmol) solid **44** were added directly to the stirred reaction suspension followed by a 5 mL DCM addition. Following a 10 min rt to 60 °C temperature ramp-up time, the reaction vessel was irradiated at 60 °C for 15 min. The reaction was permitted to cool at rt about 30 min before opening the reaction vessel. The reaction was transferred to a 250 mL Erlenmeyer flask using a 50 mL DCM rinse of the reaction vessel, and the reaction was quenched by adding 85 mL of 5% NaHCO₃ to the stirred reaction mixture bringing it to pH 8. The lower DCM layer was separated and washed with 5 x 75 mL H₂O. The combined H₂O portions were back-extracted with 25 mL DCM. The two DCM portions were combined, dried over MgSO₄ and filtered. Solvent removal by rotary evaporation and drying at rt in a vacuum oven to a constant weight gave 5.03 g of **45** as a reddish golden-colored oil (100%). FW = 186.1; ¹H NMR (DMSO-d₆) δ 3.98 (s, 3H), 2.82 (s, 3H); FTIR (ATR film): 3018, 2961, 2942, 1750, 1526, 1365 cm⁻¹; GC/MS (CI, *m/z*) 187 (M⁺+1); HPLC purity analysis = 99%. Anal. Calcd for C₆H₆N₂O₅: C, 38.72%; H, 3.25%; N, 15.05%. Found C, 38.86%; H, 3.29%; N, 15.00%.

Methyl phenyl nitrosulfone isomers (6h[o/m/p]): Reacted 0.53 g (3.39 mmol) **5h** with 1.50 equivalents of **3** at 80 °C for 10 min irradiation, followed by a second 5 min irradiation to obtain an isolated yield of 0.64 g (95% mixture of isomers) of white solid. FW = 201.1; ortho-Isomer 6h(o): ¹H NMR (CDCl₃) δ 8.20 (m, 1H), beneath 7.84-7.79 region of **6h(m)** peak (3H), 3.43 (s, 3H); ¹H NMR (CD₃CN) δ 8.14 (d, 1H), beneath 7.90-7.85 region of **6h(m)** peak (3H), 3.37 (s, 3H); ¹H NMR (DMSO-d₆) δ 8.15-8.07 (complex m, 1H), 8.02 partial peak with remainder beneath 7.99-7.93 region of **6h(m)** peak (3H), 3.56 (s, 3H); meta-Isomer 6h(m): ¹H NMR (CDCl₃) δ 8.80 (s, 1H), 8.52 (d, 1H), 8.29 (d, 1H), 7.82 (t, 3H), 3.13 (s, 3H); ¹H NMR (CD₃CN) δ 8.67 (s, 1H), 8.51 (d, 1H), 8.30 (d, 1H), 7.88 (t, 3H), 3.15 (s, 3H); 3.15 (t, 3H); ¹H NMR (DMSO-d₆) δ 8.64 (s, 1H), 8.56 (d, 1H), 8.37 (d, 1H), 7.96 (t, 3H), 3.36 (t, 3H); GC/MS (CI, *m/z*) 202 (M⁺+1 and base peak); FI/MS (ANCI, *m/z*) 201 (M⁻ and base peak); ; para-Isomer 6h(p): ¹H NMR (CDCl₃) δ 8.42 (d, 1H), 8.16 (d, 1H), methyl group beneath 3.13 peak of **6h(m)** isomer (3H); ¹H NMR (CD₃CN) δ 8.40 (d, 1H), group beneath 8.14 doublet of **6h(o)** isomer (1H), group beneath 3.36 peak of **6h(m)** isomer (3H); ¹H NMR (DMSO-d₆) δ 8.45 (d, 1H), 8.56 (d, 1H), 8.21 (d, 1H), beneath 3.36 triplet of **6h(m)** isomer (3H). Anal. Calcd for C₇H₇NO₄S isomeric mixture: C, 41.79%; H, 3.51%; N, 6.96%; S, 15.94%. Found C, 41.94%; H, 3.50%; N, 7.03%; S, 15.90%.

Continued References

27. Schwartz, K. J.; Nakagawa, Y.; Kaiser E. T. *J. Am. Chem. Soc.*, **1976**, 98, 6369-6378. Two recrystallizations from chloroform-petroleum ether were conducted prior to determining the melting point.