Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting information for

Exploring the Generation and use of Acylketenes with Continuous Flow Processes

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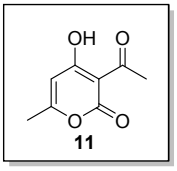
1. General Methods

Commercially available reagents and solvents were used without further purification, unless otherwise stated. Progress of the reactions was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 sheet and visualized with ultraviolet light or potassium permanganate stain. Flash column chromatography (FCC) was performed with Sigma Aldrich silica gel 40-60 Å as the stationary phase and solvents employed were analytical grade. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVX500 (500 MHz) and AVX400 (400 MHz) spectrometers at ambient temperature. Chemical shifts (δ) are given in parts per million, referenced to the residual peak of $CDCl_3$, δ = 7.26 (^{1}H NMR) and δ = 77.0 (^{13}C NMR) as internal references. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets and m = multiplet. NMR spectra were processed using MestReNova version 6.0.2-5475 software. Infrared spectra were recorded on a Shimadzu IR-Affinity-1S ATR-FTIR spectrometer with the intensities of the characteristic signals being reported as weak (w, <30% of tallest signal), medium (m, 31–70% of tallest signal) or strong (s, >71% of tallest signal). Mass spectra (ESI) data were analysed using Waters LCT Premier TOF Mass spectrometer. Melting points were measured on a Gallenkamp melting point apparatus and are reported corrected by linear calibration to benzophenone (47 - 49 °C) and benzoic acid (121 - 123 °C). The flow setup consisted of PFA tubing of an 0.8 mm ID and one HPLC pump. Residence coils were made from the tubing by taking the appropriate length for the desired volume (0,8 mm ID PFA tube, length 20.21 m, volume 10 mL). Sample loop of 1 or 5 mL (PFA) were used to load the reagents. The temperature of the flow residence coil was controlled using a CRD Polar Bear Plus device. Compounds **12a** – **12h** are designed to fragment and afford acylketene materials, we have been unable to observe a mass ion corresponding to these materials under the MS methods tried – in every case we have however seen the acylketene molecular ion at 84.02 m/z. Owing to the sensitive and volatile nature of these materials, some of the NMR spectra contain trace impurities that have not been removed using a drying pistol or high-vacuum line.

2. Experimental Procedures

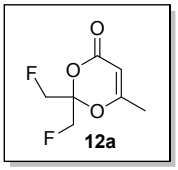
2.1 General procedure for the synthesis of TMD derivatives.

TMD (3.25 mmol, 1 equiv.) and the corresponding ketone (16.25 mmol, 5 equiv.) were mixed in EtOAc (6.5 mL) or toluene (0.5 M) and filled into a 5 mL loading loop. The loop was injected into a stream of EtOAc or toluene at 0.5 mL min^{-1} using a PFA coil reactor of 10 mL at 150 °C; pressurised to 250 psi using a back-pressure regulator. In the case of synthesising dehydroacetic acid (**11**), just TMD was filled into the loop and the product was obtained by recrystallization using $CHCl_3$. The products were isolated by column chromatography using EtOAc/Hexane as solvent elution.



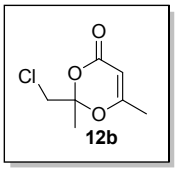
11

Dehydroacetic acid (**11**). Obtained in 68% yield (1.7 mmol, 285 mg) as a brown solid. **M.p.** = 111 - 113 °C. **IR** (ATR, cm^{-1}): 3084 (w), 2980 (w), 1716 (m), 1635 (m), 1541 (s), 1369 (m), 993 (s), 854 (m), 777 (m), 567 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 16.62 (s, 1H), 5.87 (s, 1H), 2.60 (s, 3H), 2.20 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.3, 181.1, 169.1, 161.3, 101.5, 99.9, 30.1, 20.7 ppm. NMR data is consistent with literature values.[1] **HRMS** (EI) calc. for $[M]^+$ $C_8H_8O_4$: 168.0421, found: 168.0423



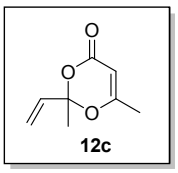
12a

2,2-bis(fluoromethyl)-6-methyl-4H-1,3-dioxin-4-one. Obtained in 55% yield (1.4 mmol, 244 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2970 (w), 2924 (w), 1743 (s), 1643 (s), 1342 (s), 1039 (s), 966 (m), 810 (w), 671 (w), 641 (w), 545 (w) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.22 (d, *J* = 0.9 Hz, 1H), 4.71 (dd, *J* = 10.4, 2.7 Hz, 1H), 4.65 – 4.55 (m, 2H), 4.50 (dd, *J* = 10.4, 2.3 Hz, 1H), 2.00 (d, *J* = 0.9 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 157.7, 102.36 (t, *J* = 20.3 Hz, acetal carbon), 94.4, 79.89 (d, *J* = 181.6 Hz, methyl-F carbon), 78.09 (d, *J* = 181.6 Hz, methyl-F carbon), 19.7 ppm.



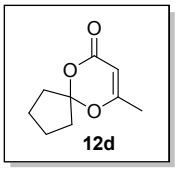
12b

2-(chloromethyl)-2,6-dimethyl-4H-1,3-dioxin-4-one. Obtained in 85% yield (2.2 mmol, 374 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2980 (w), 1732 (s), 1637 (s), 1386 (s), 1350 (s), 1240 (s), 806 (m), 765 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.21 (s, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.58 (d, *J* = 12.1 Hz, 1H), 1.97 (s, 3H), 1.71 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.7, 159.5, 105.3, 94.2, 45.3, 21.9, 19.8 ppm.

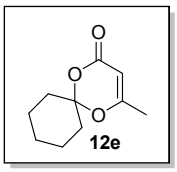


12c

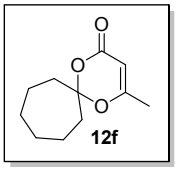
2,6-dimethyl-2-vinyl-4H-1,3-dioxin-4-one. Obtained in 15% yield (0.4 mmol, 58 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2970 (w), 2926 (w), 2852 (w), 1734 (s), 1716 (s), 1495 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.44 (d, *J* = 17.3 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 0.8 Hz, 1H), 1.92 (d, *J* = 0.8 Hz, 3H), 1.65 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.6, 161.3, 135.6, 118.4, 105.1, 95.3, 26.2, 19.9 ppm.



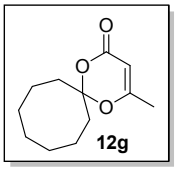
9-methyl-6,10-dioxaspiro[4.5]dec-8-en-7-one. Obtained in 80% yield (2 mmol, 336 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2964 (w), 2877 (w), 1724 (s), 1635 (s), 1388 (s), 1350 (s), 1190 (m), 1093 (s), 906 (m), 806 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 2.18 – 2.02 (m, 4H), 1.97 (s, 3H), 1.85 – 1.63 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.9, 162.0, 115.9, 94.9, 36.7, 23.1, 19.9 ppm. NMR data is consistent with literature values.[2]



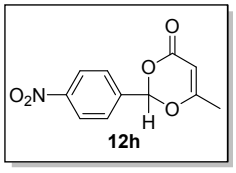
4-methyl-1,5-dioxaspiro[5.5]undec-3-en-2-one. Obtained in 95% yield (2.37 mmol, 431 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2939 (w), 2864 (w), 1720 (s), 1637 (m), 1388 (s), 1346 (s), 1217 (m), 1066 (s), 912 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 2.06 – 1.88 (m, 7H), 1.74 – 1.65 (m, 2H), 1.64 – 1.54 (m, 2H), 1.52 – 1.41 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4, 161.2, 107.0, 94.0, 33.7, 24.6, 22.2, 19.9 ppm. NMR data is consistent with literature values.[2]



4-methyl-1,5-dioxaspiro[5.6]dodec-3-en-2-one. Obtained in 65% yield (1.6 mmol, 318 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2980 (w), 2929 (w), 2860 (w), 1718 (s), 1637 (s), 1388 (m), 1348 (s), 1068 (m), 804 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.13 (d, *J* = 0.7 Hz, 1H), 2.18 – 2.02 (m, 4H), 1.91 (d, *J* = 0.7 Hz, 3H), 1.63 – 1.42 (m, 8H). ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4, 161.3, 111.1, 93.9, 37.4, 28.7, 21.37, 20.0 ppm.



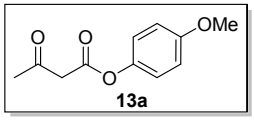
4-methyl-1,5-dioxaspiro[5.7]tridec-3-en-2-one. Obtained in 16% yield (0.4 mmol, 84 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2980 (m), 2926 (m), 2858 (m), 1722 (s), 1697 (s), 1637 (m), 1390 (m), 1350 (m), 1097 (m), 947 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.12 (s, 1H), 2.00 – 2.20 (m, 4H), 1.90 (s, 3H), 1.72 – 1.44 (m, 10H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.2, 161.2, 110.7, 93.8, 32.6, 27.6, 24.4, 21.07, 20.0 ppm.



6-methyl-2-(4-nitrophenyl)-4H-1,3-dioxin-4-one. Obtained in 74% yield (1.85 mmol, 435 mg) as a white powder. **M.p.** = 141 - 143 °C. **IR** (ATR, cm^{-1}): 3097 (w), 2980 (w), 1724 (s), 1624 (s), 1527 (s), 1330 (m), 1220 (m), 1058 (s), 698 (s), 576 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 5.50 (s, 1H), 2.18 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.8, 161.0, 149.1, 139.9, 127.7, 123.9, 98.3, 96.9, 19.5 ppm.

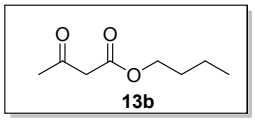
2.2 General procedure for the synthesis of β-dicarbonyls products.

TMD (3.25 mmol, 1 equiv.) and the corresponding nucleophile (3.57 mmol, 1.1 equiv.) were mixed in EtOAc (6.5 mL) or toluene (0.5 M) and filled into a 5 mL loading loop (1 mL for β-ketoamides). The loop was injected into a stream of EtOAc or toluene at 0.5 mL min^{-1} using a PFA coil reactor of 10 mL at 150 °C; pressurised to 250 psi. The products were isolated by column chromatography using EtOAc/Hexane as solvent elution. Some of these compounds are volatile and should not be left for a long time in the vacuum line.



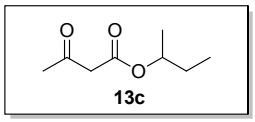
13a

4-methoxyphenyl 3-oxobutanoate. Obtained in 97% yield (2.42 mmol, 504 mg) as a clear yellow solid. **M.p.** = 56 - 58 °C. **IR** (ATR, cm^{-1}): 2970 (w), 2835 (w), 1749 (m), 1716 (m), 1506 (s), 1232 (s), 1192 (s), 1031 (m), 827 (m), 732 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.99 – 6.85 (m, 2H), 6.83 – 6.71 (m, 2H), 3.66 (s, 3H), 3.54 (s, 2H), 2.19 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.4, 166.2, 157.5, 143.9, 122.2, 114.5, 55.5, 49.8, 30.2. NMR data is consistent with literature values.[3]



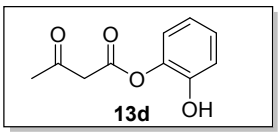
13b

Butyl 3-oxobutanoate. Obtained in 99% yield (2.47 mmol, 391 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2960 (w), 2935 (w), 2873 (w), 1714 (s), 1411 (w), 1359 (w), 1147 (s), 1029 (m), 542 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.08 (t, *J* = 6.7 Hz, 2H), 3.38 (s, 2H), 2.20 (s, *J* = 8.4 Hz, 3H), 1.62 – 1.49 (m, 2H), 1.39 – 1.25 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.7, 167.2, 65.3, 50.2, 30.5, 30.2, 19.1, 13.7 ppm. NMR data is consistent with literature values.[4] **HRMS** (EI) calc. for $[M]^+$ $C_8H_{14}O_3$: 158.0943, found: 158.0936



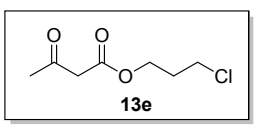
13c

***Sec*-butyl 3-oxobutanoate**. Obtained in 99% yield (2.47 mmol, 391 mg) as a clear liquid. **IR** (ATR, cm^{-1}): 2974 (w), 2937 (w), 2881 (w), 1712 (s), 1359 (m), 1313 (m), 1112 (w), 748 (m), 698 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.83 (sext, *J* = 6.4 Hz, 1H), 3.36 (s, 2H), 2.20 (s, 3H), 1.62 – 1.42 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.8, 166.8, 73.6, 50.5, 30.1, 28.7, 19.3, 9.6 ppm. NMR data is consistent with literature values.[5] **HRMS** (EI) calc. for $[M]^+$ $C_8H_{14}O_3$: 158.0943 found: 158.0945



13d

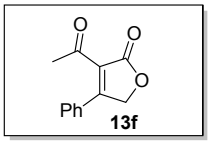
2-hydroxyphenyl 3-oxobutanoate. Obtained in 95% yield (2.37 mmol, 460 mg) as a brown viscous liquid. **IR** (ATR, cm^{-1}): 3373 (m), 2922 (w), 1762 (m), 1699 (s), 1494 (s), 1361 (s), 1253 (s), 1136 (s), 1095 (s), 744 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.19 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.06 (ddd, *J* = 12.5, 8.1, 1.6 Hz, 2H), 6.91 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 3.84 (s, 2H), 2.39 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.6, 165.1, 147.9, 137.5, 127.8, 122.5, 120.1, 117.5, 50.1, 30.3 ppm. **HRMS** (ESI) calc. for $[M+H]^+$ $C_{10}H_{11}O_4^+$: 195.0657, found: 195.0661



13e

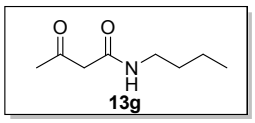
3-chloropropyl 3-oxobutanoate. Obtained in 95% yield (2.37 mmol, 422 mg) as a clear yellow liquid. **IR** (ATR, cm^{-1}): 2966 (w), 2927 (w), 1739 (s), 1712 (s), 1369

(m), 1313 (m), 1259 (m), 1147 (s), 1035 (m), 653 (w), 542 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.1 Hz, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.41 (s, 2H), 2.20 (s, 3H), 2.05 (quint, *J* = 6.2 Hz, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.4, 167.0, 62.0, 50.0, 41.0, 31.4, 30.2 ppm. NMR data is consistent with literature values.[6]



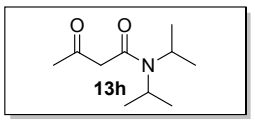
13f

3-acetyl-4-phenylfuran-2(5*H*)-one. Obtained in 45% yield (0.22 mmol, 45 mg) as a viscous yellow liquid. **IR** (ATR, cm^{-1}): 3057 (w), 2980 (w), 2929 (w), 1716 (s), 1597 (m), 1444 (m), 1238 (s), 1157 (w), 1053 (w), 752 (s), 696 (s), 476 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 5H), 5.08 (s, 2H), 2.50 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.1, 170.9, 164.9, 132.2, 129.4, 129.1, 128.1, 126.0, 70.8, 30.7 ppm. NMR data is consistent with literature values.[7]



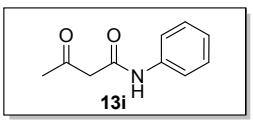
13g

***N*-butyl-3-oxobutanamide**. Obtained in 92% yield (0.46 mmol, 72 mg) as a clear yellow liquid. **IR** (ATR, cm^{-1}): 3307 (w), 2958 (w), 2931 (w), 2873 (w), 1716 (m), 1645 (s), 1550 (s), 1357 (m), 1159 (m), 540 (w) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 3.42 (s, 2H), 3.29 (q, *J* = 6.4 Hz, 2H), 2.28 (s, 3H), 1.52 (quint, *J* = 7.0, 2H), 1.37 (quint, *J* = 6.8, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.0, 165.3, 49.5, 39.3, 31.4, 31.1, 20.1, 13.7 ppm. NMR data is consistent with literature values.[8] **HRMS** (EI) calc. for $[M]^+$ $C_8H_{15}NO_2$: 157.1105 found: 157.1103.



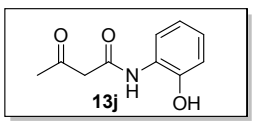
13h

***N*-(2,4-dimethylpentan-3-yl)-3-oxobutanamide**. Obtained in 90% yield (0.45 mmol, 83 mg) as a clear yellow liquid. **IR** (ATR, cm^{-1}) 2999 (w), 2968 (w), 2933 (w), 1716 (m), 1629 (s), 1444 (m), 1336 (m), 1201 (w), 1153 (m), 1043 (m), 605 (w), 555 (w) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.02 – 3.77 (m, 1H), 3.51 (s, 3H), 2.28 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 6H), 1.20 (d, *J* = 6.5 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.2, 165.4, 52.5, 46.1, 29.9, 20.8, 20.4 ppm. NMR data is consistent with literature values.[9] **HRMS** (ESI) calc. for $[M+H]^+$ $C_{10}H_{20}NO_2^+$: 186.1489, found:186.1499.



13i

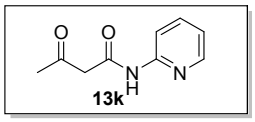
3-oxo-*N*-phenylbutanamide. Obtained in 75% yield (0.37 mmol, 66 mg) as a clear yellow liquid. **IR** (ATR, cm^{-1}): 3304 (m), 2962 (w), 2924 (w), 2872 (w), 1716 (m), 1662 (s), 1598 (s), 1544 (s), 1444 (m), 1330 (m), 1157 (m), 754 (s), 692 (s) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 3.62 (s, *J* = 16.5 Hz, 2H), 2.35 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.4, 163.3, 137.5, 129.0, 124.6, 120.2, 49.6, 31.4 ppm. NMR data is consistent with literature values.[8] **HRMS** (ESI) calc. for $[M+H]^+$ $C_{10}H_{12}NO_2^+$: 178.0863, found: 178.0868



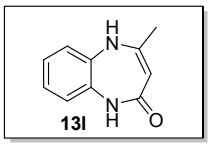
13j

***N*-(2-hydroxyphenyl)-3-oxobutanamide**. Obtained in 61% yield (1.52 mmol, 294 mg) as an orange solid. **M.p.** = 112 - 114 °C. **IR** (ATR, cm^{-1}): 3064 (w), 2877 (w), 2740 (w), 2628 (w), 1710 (s), 1454 (s), 1359 (m), 1278 (m), 1203 (m), 754 (s), 569 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.67 (s, 1H), 7.19 – 7.12 (m, 2H), 7.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.90 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 3.67 (s, 2H), 2.36 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ

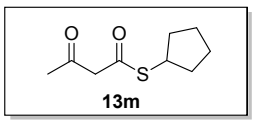
205.1, 165.2, 148.7, 127.4, 125.25, 122.7, 120.5, 119.7, 47.8, 31.2 ppm. **HRMS** (ESI) calc. for $[M+H]^+$ $C_{10}H_{12}NO_3^+$: 194.0812, found: 194.0817.



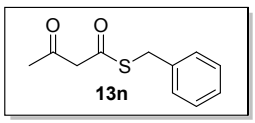
3-oxo-N-(pyridin-2-yl)butanamide. Obtained in 99% yield (0.495 mmol, 88 mg) as a white solid. **M.p.** = 113 - 115 °C. **IR** (ATR, cm^{-1}): 3304 (m), 2962 (w), 2924 (w), 2872 (w), 1716 (m), 1662 (s), 1598 (s), 1544 (s), 1444 (m), 1330 (m), 1157 (m), 754 (s), 692 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.32 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.72 (m, 1H), 7.07 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 3.63 (s, 2H), 2.34 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.3, 164.2, 151.1, 147.9, 138.4, 120.1, 114.4, 50.9, 31.0 ppm. NMR data is consistent with literature values.[10] **HRMS** (ESI) calc. for [M+H]+ $C_9H_{11}N_2O_2^+$: 179.0821, found: 179.0829



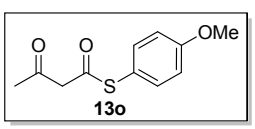
4-methyl-1*H*-benzo[*b*][1,4]diazepin-2(5*H*)-one. Obtained in 21% yield (0.105 mmol, 18 mg) as a yellow solid. **M.p.** = 123 - 125 °C. **IR** (ATR, cm^{-1}): 3066 (w), 3014 (w), 1687 (s), 1654 (m), 1477 (s), 1384 (s), 1255 (m), 1188 (m), 1120 (m), 906 (m), 738 (s), 677 (s), 553 (m), 493 (m), 422 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.09 – 7.04 (m, 1H), 7.03 – 6.97 (m, 3H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.18 (d, *J* = 0.6 Hz, 1H), 2.18 (d, *J* = 0.5 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6, 137.8, 130.0, 128.3, 121.9, 121.4, 114.0, 109.9, 109.1, 20.3 ppm. NMR data is consistent with literature values.[11] **HRMS** (ESI) calc. for $[M+H]^+$ $C_{10}H_{11}N_2O^+$: 175.0871, found: 175.0872



***S*-cyclopentyl 3-oxobutanethioate**. Obtained as a mixture of tautomers (65:35 enol) in 90% yield (2.25 mmol, 418 mg) as a clear orange liquid. **IR** (ATR, cm^{-1}): 2956 (m), 2868 (w), 1718 (m), 1674 (s), 1618 (s), 1396 (w), 1357 (w), 1192 (m), 1085 (s), 977 (m), 837 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (quint, *J* = 6.8, 1H), 3.64 (s, 2H), 2.27 (s, 3H), 2.17 – 2.05 (m, 4H), 1.76 – 1.52 (m, 4H) ppm. **Enol proton** δ 5.14 (s, 1H), 12.80 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.1, 192.6, 58.4, 43.1, 33.0, 30.3, 24.7 ppm. **Enol carbon** δ 195.4, 172.9, 99.9, 41.7, 33.3, 30.6, 24.7, 21.0 ppm. **HRMS** (EI) calc. for $[M]^+$ $C_9H_{14}O_2S$:, found: 186.0715, 186.0710.



***S*-benzyl 3-oxobutanethioate**. Obtained as a mixture of tautomers (75:25 enol) in 99% yield (2.47 mmol, 515 mg) as a clear orange liquid. **IR** (ATR, cm^{-1}): 3062 (w), 3062 (w), 2920 (w), 1718 (m), 1676 (s), 1618 (s), 1396 (w), 1192 (m), 1085 (s), 831 (m), 698 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 4.20 (s, 2H), 3.70 (s, 2H), 2.27 (s, 3H) ppm. **Enol proton** δ 5.46 (s, 1H), 12.70 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.7, 191.4, 136.8, 128.9, 128.8, 127.5, 58.0, 33.8, 30.3 ppm. **Enol carbon** δ 193.5, 173.6, 137.6, 128.7, 127.3, 99.7, 32.27, 21.1 ppm. NMR data is consistent with literature values.[12]

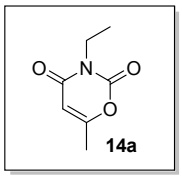


***S*-(4-methoxyphenyl) 3-oxobutanethioate**. Obtained as a mixture of tautomers (65:35 enol) in 99% yield (2.47 mmol, 554 mg) as a clear yellow solid. **IR** (ATR, cm^{-1}): 3003 (w), 2960 (w), 2837 (w), 1718 (s), 1591 (s), 1492 (s), 1288 (s), 1246 (s), 1026 (m), 823 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 1H), 7.38 – 7.34 (m, 2H), 7.00 – 6.95 (m, 1H), 3.86 (s, 3H), 3.76 (s, 2H), 2.31 (s, 3H) ppm. **Enol proton** δ 5.50 (s, 1H), 12.65 (s,

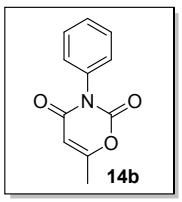
1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.7, 191.6, 136.7, 136.1, 115.1, 114.9, 57.6, 55.4, 30.3 ppm. **Enol carbon** δ 194.35, 174.57, 160.87, 117.72, 117.61, 98.66, 55.38, 30.34, 21.18 ppm. NMR data is consistent with literature values.[13] **HRMS** (EI) calc. for $[M]^+$ $C_{11}H_{12}O_3S$: 224.0507, found: 224.0513.

2.3 General procedure for the synthesis of 1,3-oxazine-2,4-diones.

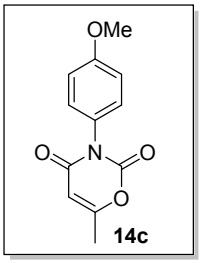
TMD (3.25 mmol, 1 equiv.) and the corresponding isocyanate (16.25 mmol, 5 equiv.) were mixed in EtOAc or THF (6.5 mL, 0.5 M) and filled into a 5 mL loading loop. The loop was injected into a stream of EtOAc or THF at 0.5 mL min^{-1} using a 10 mL PFA coil reactor at 150 °C pressurised at 250 psi. The products were isolated by column chromatography using EtOAc/Hexane as solvent elution.



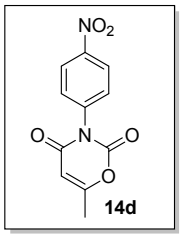
3-ethyl-6-methyl-*2H*-1,3-oxazine-2,4(*3H*)-dione. Obtained in 97% yield (2.42 mmol, 375 mg) as a white solid. **M.p.** = 81 - 83 °C. M.p. data is consistent with literature values.[14] **IR** (ATR, cm^{-1}): 3095 (w), 2981 (m), 1739 (s), 1697 (s), 1654 (s), 1396 (m), 1346 (s), 1128 (m), 950 (m), 856 (s), 761 (s), 624 (m), 530 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 3.86 (qd, *J* = 7.1, 1.3 Hz, 2H), 2.14 – 2.11 (m, 3H), 1.19 – 1.13 (m, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5, 161.1, 148.8, 101.4, 37.1, 19.1, 12.5 ppm. **HRMS** (ESI) calc. for $[M+H]^+$ $C_7H_{10}NO_3^+$: 156.0661, found: 156.0656



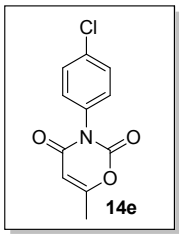
6-methyl-3-phenyl-*2H*-1,3-oxazine-2,4(*3H*)-dione. Obtained in 80% yield (2 mmol, 406 mg) as a white solid. **M.p.** = 153 - 157 °C. M.p. data is consistent with literature values.[14] **IR** (ATR, cm^{-1}): 2980 (m), 1770 (m), 1695 (s), 1683 (s), 1386 (m), 1334 (m), 1151 (w), 952 (m), 752 (s), 628 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.41 (m, 3H), 7.41 – 7.09 (m, 2H), 5.92 (s, 1H), 2.28 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.2, 161.2, 148.7, 133.7, 129.6, 129.3, 128.0, 101.7, 19.3 ppm. **HRMS** (EI) calc. for $[M]^+$ $C_{11}H_9NO_3^+$: 203.0575, found: 203.0582



3-(4-methoxyphenyl)-6-methyl-*2H*-1,3-oxazine-2,4(*3H*)-dione. Obtained in 65% yield (1.62 mmol, 378 mg) as a white solid. **M.p.** = 194 - 198 °C. M.p. data is consistent with literature values.[14] **IR** (ATR, cm^{-1}): 3084 (w), 2980 (m), 2970 (w), 1749 (m), 1697 (s), 1516 (s), 1236 (m), 1170 (m), 825 (m), 758 (m), 626 (m) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 2H), 7.05 – 7.01 (m, 2H), 5.92 (d, *J* = 0.9 Hz, 1H), 3.86 (s, 3H), 2.29 (d, *J* = 0.9 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.1, 161.5, 160.0, 149.0, 128.9, 126.1, 114.9, 101.7, 55.5, 19.3 ppm. **HRMS** (EI) calc. for $[M]^+$ $C_{12}H_{11}NO_4^+$: 233.0688, found: 233.0692



6-methyl-3-(4-nitrophenyl)-*2H*-1,3-oxazine-2,4(*3H*)-dione. Obtained in 57% yield (1.42 mmol, 353 mg) as a yellow solid. **M.p.** = 219 - 221 °C. M.p. data is consistent with literature values.[14] **IR** (ATR, cm^{-1}): 3082 (w), 2980 (m), 1766 (m), 1697 s), 1519 (m), 1332 (s), 1242 (w), 1209 (w), 1001 (m), 860 (s), 756 (s) 694 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 – 8.32 (m, 2H), 7.57 – 7.42 (m, 2H), 5.96 (d, *J* = 0.9 Hz, 1H), 2.33 (d, *J* = 0.8 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.8, 160.5, 148.0, 147.9, 139.1, 129.5, 124.7, 101.5, 19.4 ppm.



3-(4-chlorophenyl)-6-methyl-*2H*-1,3-oxazine-2,4(*3H*)-dione. Obtained in 67% yield (1.67 mmol, 397 mg) as a yellow solid. **M.p.** = 190 - 195 °C. M.p. data is consistent with literature values.[14] **IR** (ATR, cm^{-1}): 3082 (w), 2980 (m), 2972 (m), 1768 (s), 1689 (s), 1394 (s), 1336 (s), 1085 (m), 953 (m), 858 (m), 829 (s), 754 (s), 528 (s) cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.25 – 7.17 (m, 2H), 5.92 (d, *J* = 1.0 Hz, 1H), 2.30 (d, *J* = 0.9 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4, 160.9, 148.4, 135.4, 132.0, 129.8, 129.4, 101.6, 19.3 ppm. **HRMS** (EI) calc. for $[M]^+$ $C_{11}H_8ClNO_3$: 237.0193, found: 237.0182

3. Flow equipment picture

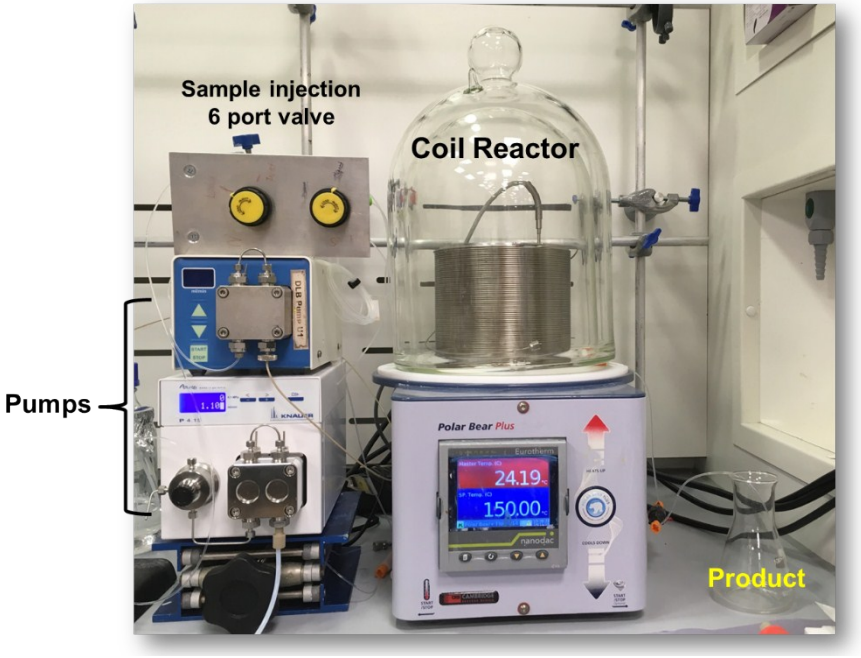
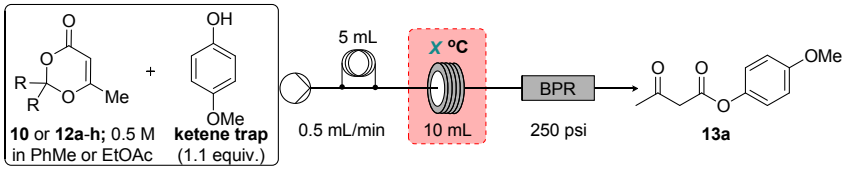
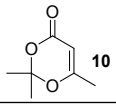
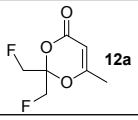
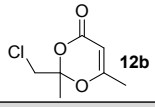
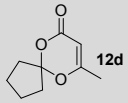
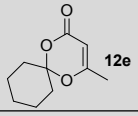
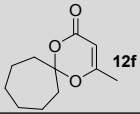
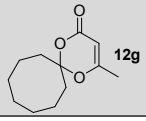
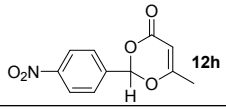


Figure S1. Flow equipment setup

4. Acylketene formation using TMD derivatives

Table S1. Reaction between TMD derivatives and 4-methoxyphenol in order to evaluate the stability of them.



Entry	Dioxinones	Temperature (°C)	Dioxinone/13a ratio (%)[a]
1	 **10**	100	82/18
2		120	10/90
3		150	0/100
2	 **12a**	100	100/0
3		120	95/5
4		150	0/100
5	 **12b**	100	95/5
6		120	75/25
7		150	0/100
8	 **12d**	100	51/45
9		120	18/82
10		150	7/93
10	 **12e**	100	95/5
11		120	70/30
12		150	13/87
13	 **12f**	100	11/89
14		120	5/95
15		150	0/100
16	 **12g**	100	10/90
17		120	5/95
18		150	0/100
19	 **12h**	100	98/2
20		120	83/17
21		150	0/100

[a] Determined by ^{1}H NMR using mesitylene as an internal standard.

Both Toluene and Ethyl Acetate have been used in these reactions and they can be used interchangeable with essentially the same results oberserved.

5. ^{1}H and ^{13}C NMR data

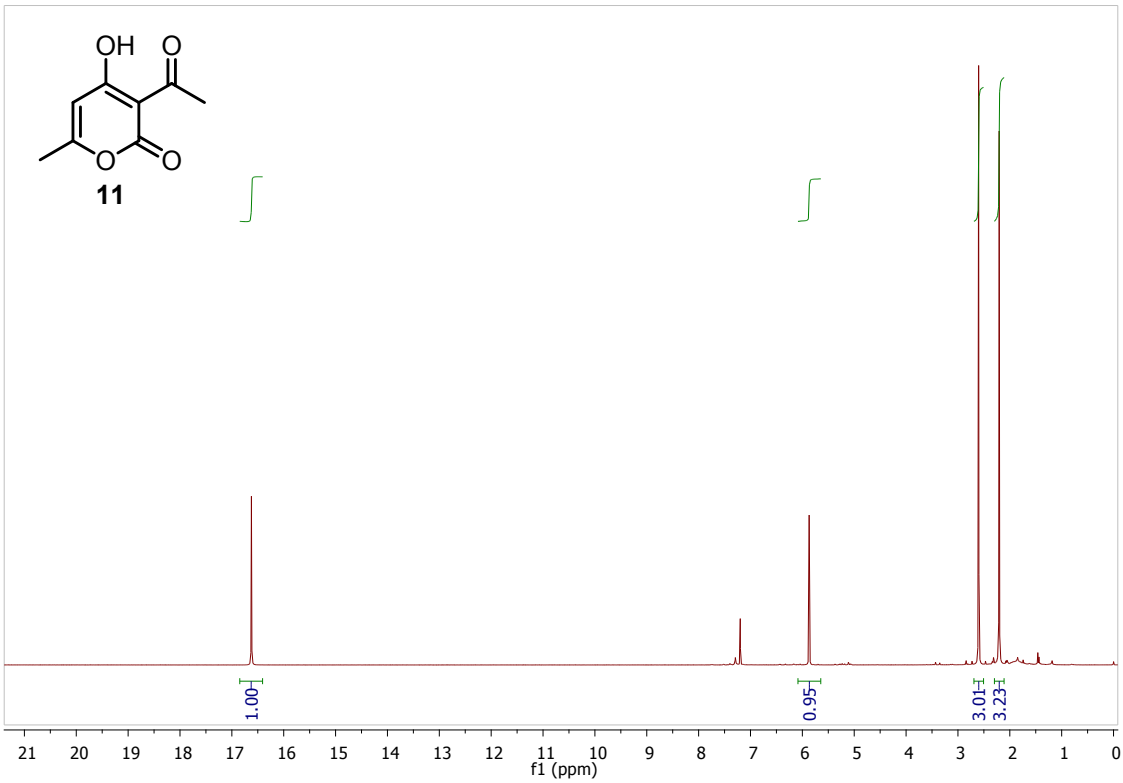


Fig S2. ^{1}H NMR spectrum for dehydroacetic acid (**11**).

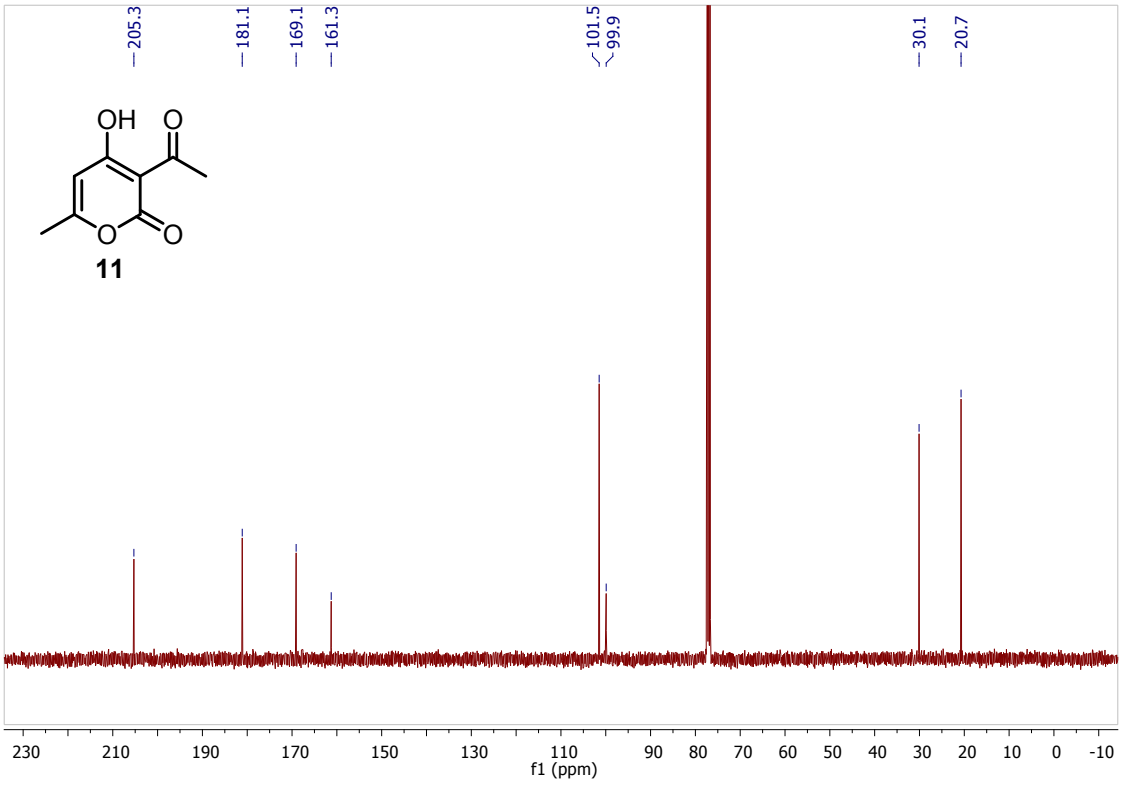


Fig S3. ^{13}C NMR spectrum for dehydroacetic acid (**11**).

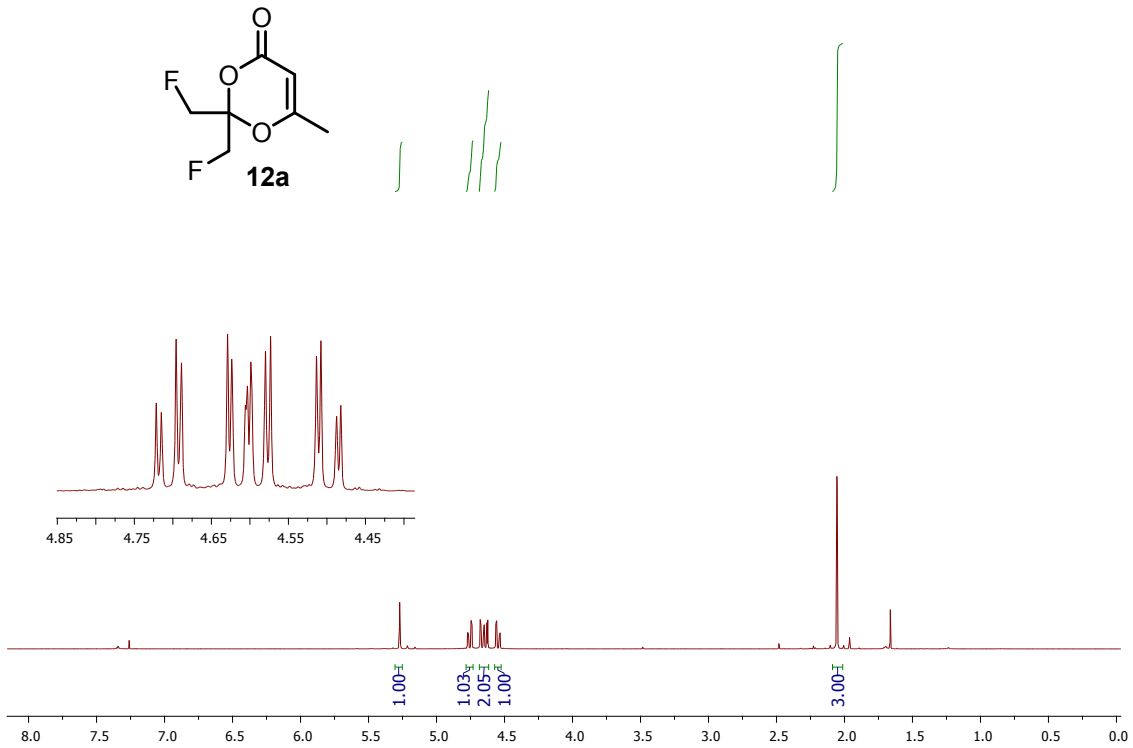


Fig S4. ^{1}H NMR spectrum for dioxinone **12a**.

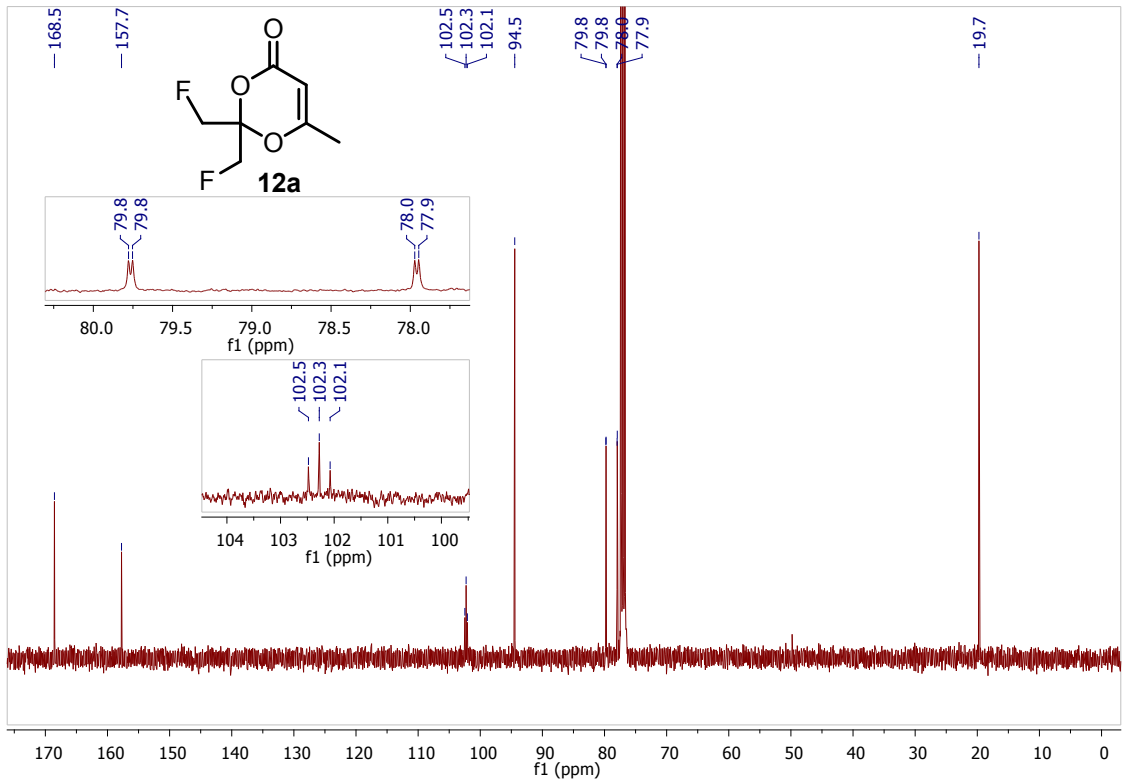


Fig S5. ^{13}C NMR spectrum for dioxinone **12a**.

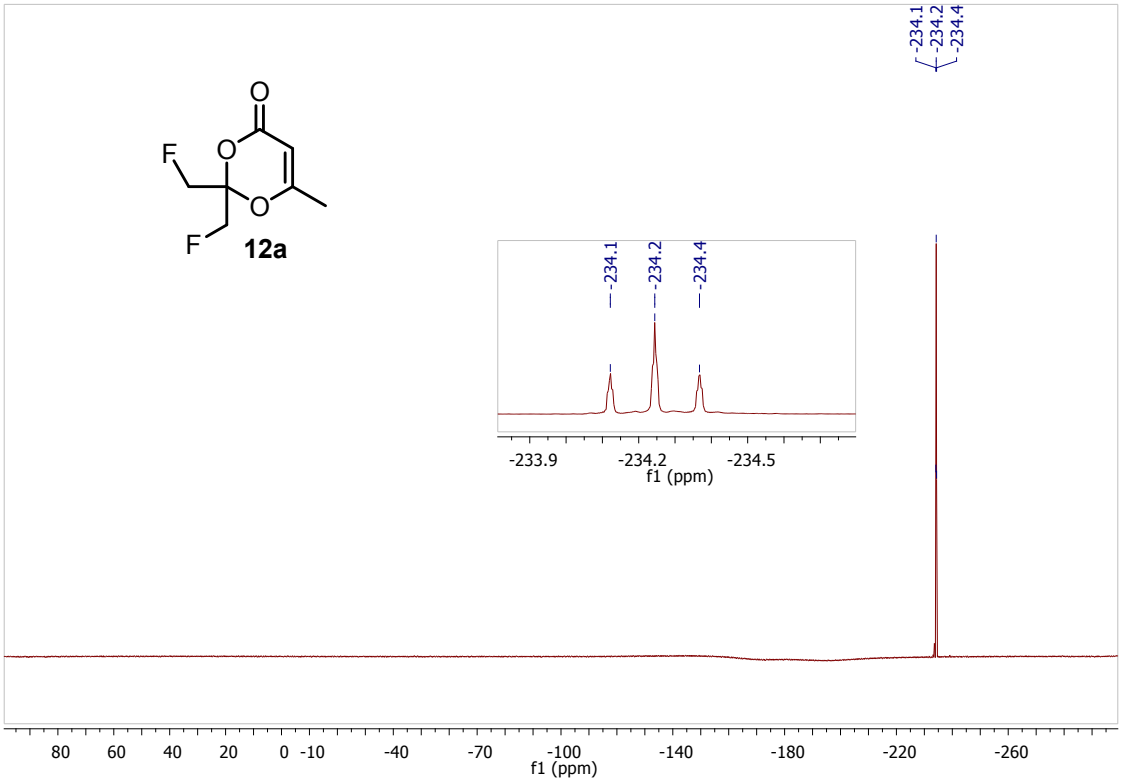


Fig S6. ^{1}H-coupled ^{19}F NMR spectrum for dioxinone **12a**.

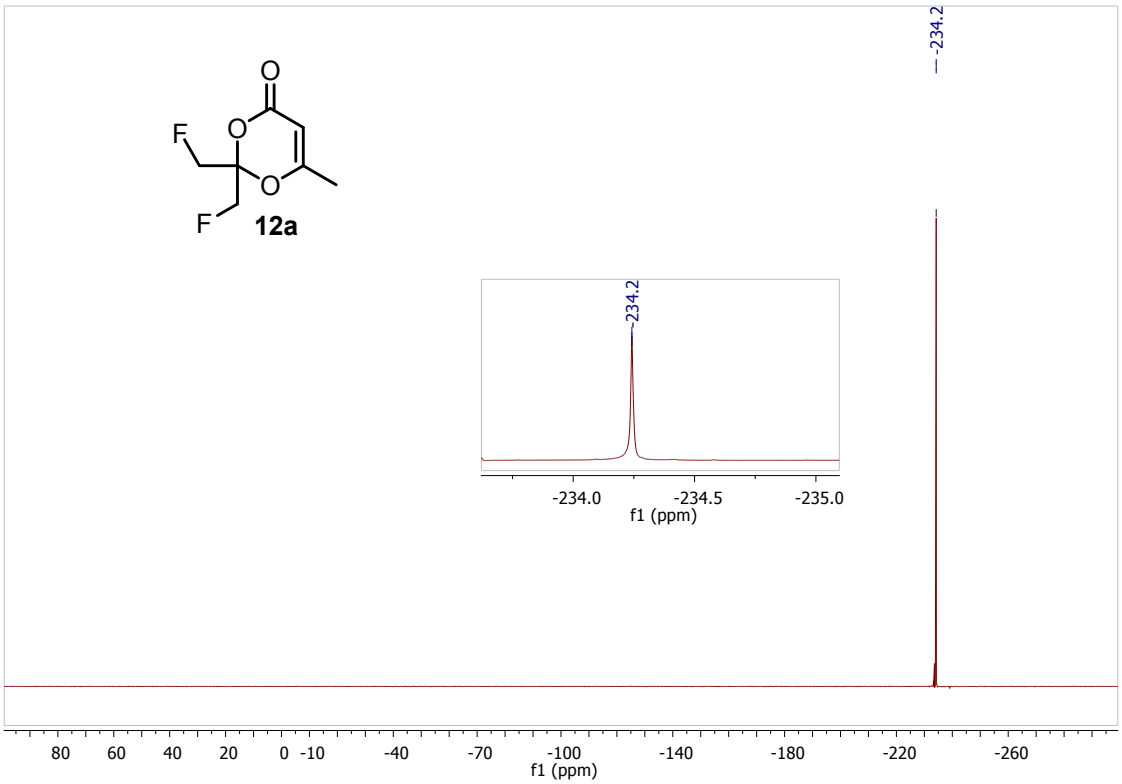


Fig S7. ^{1}H-Decoupled ^{19}F NMR spectrum for dioxinone **12a**.

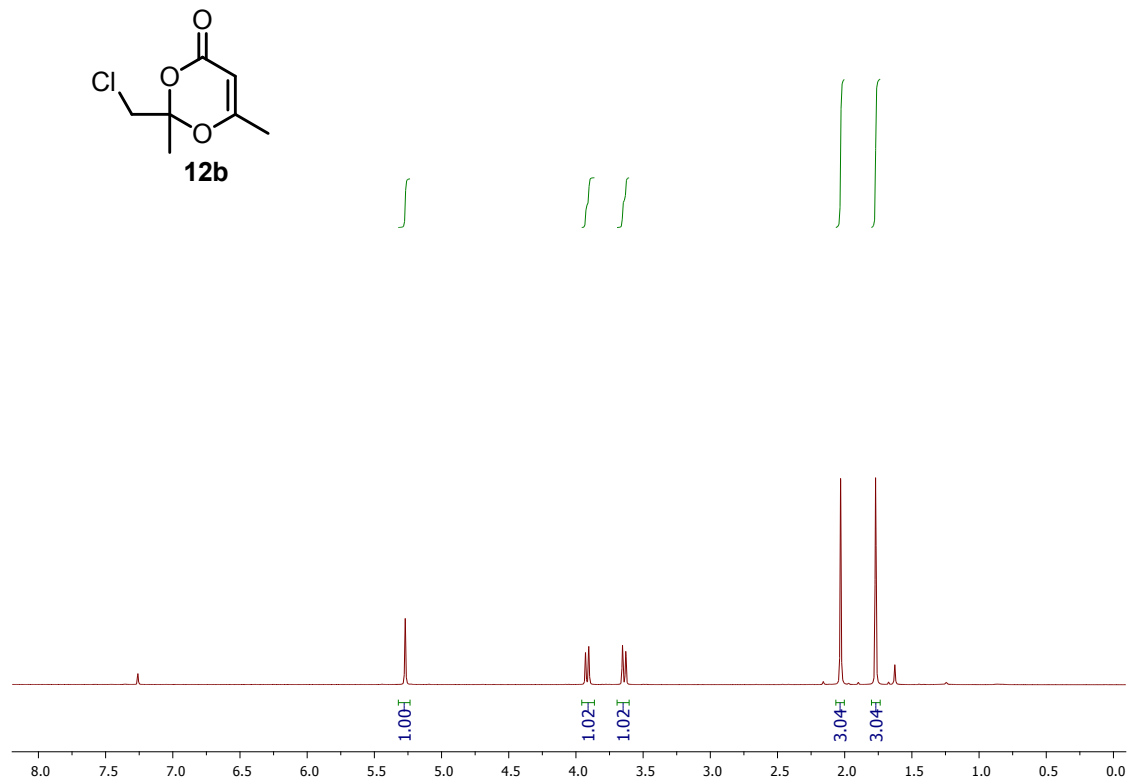


Fig S8. ^{1}H NMR spectrum for dioxinone **12b**.

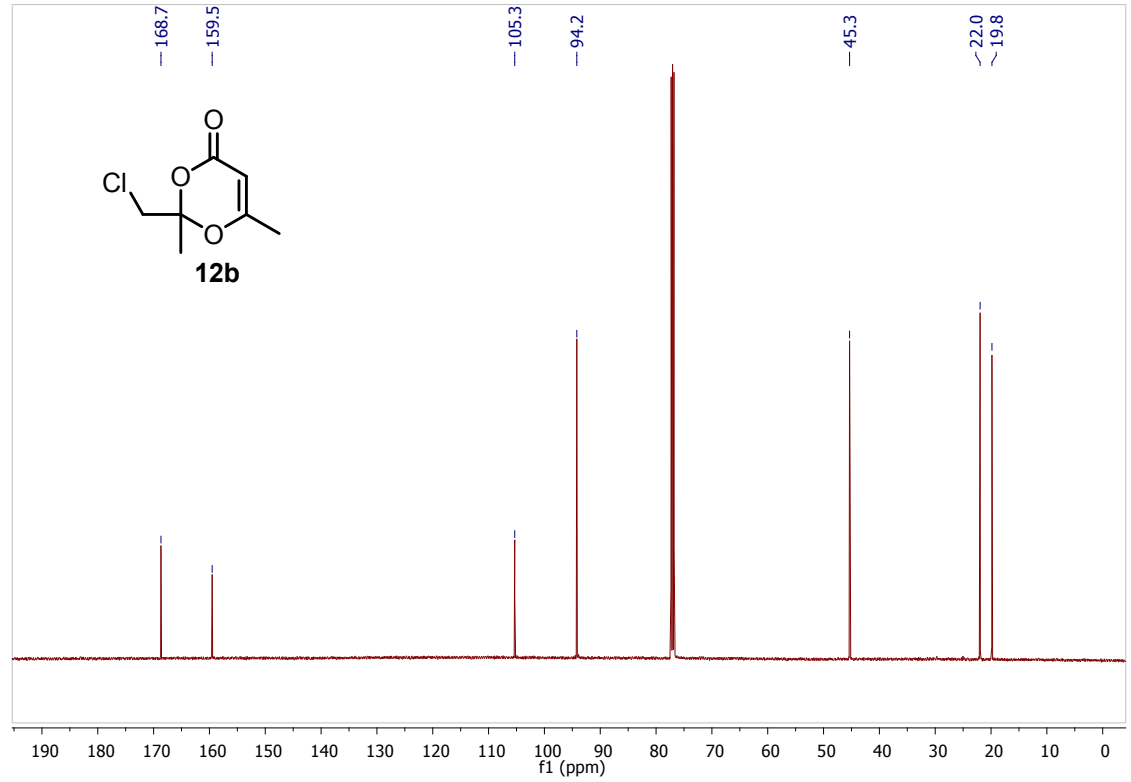


Fig S9. ^{13}C NMR spectrum for dioxinone **12b**.

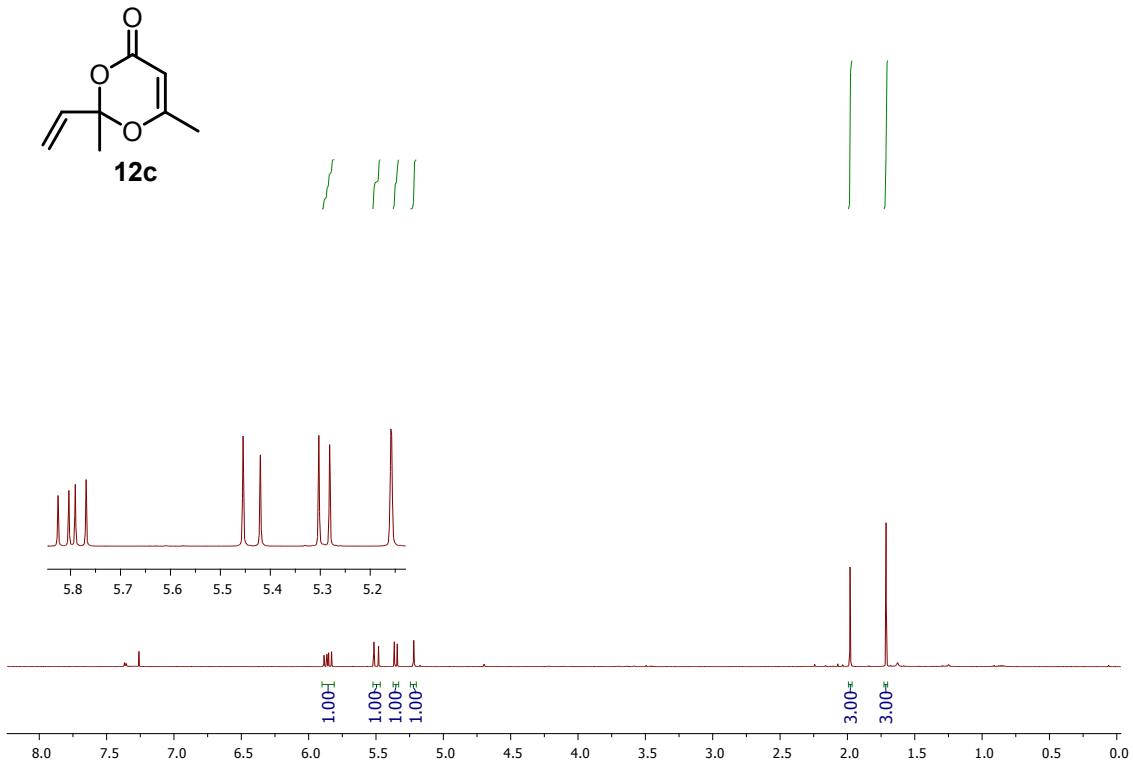


Fig S10. ^{1}H NMR spectrum for dioxinone **13c**.

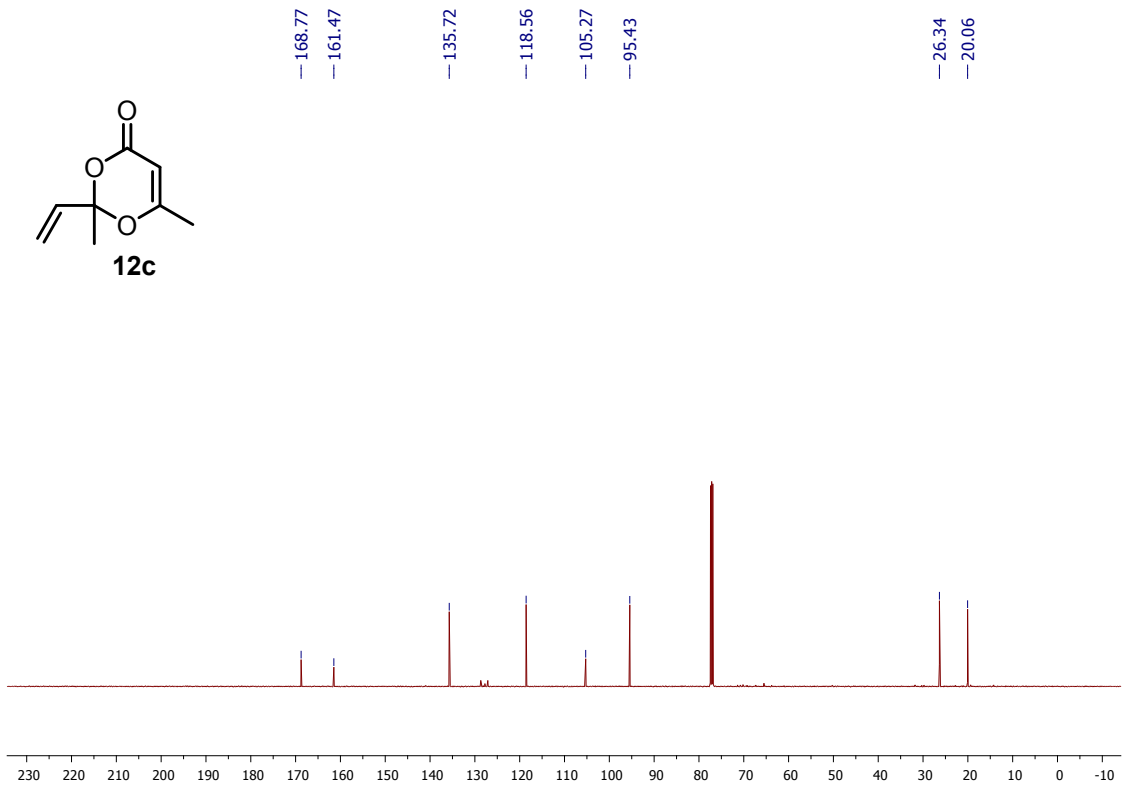


Fig S11. ^{13}C NMR spectrum for dioxinone **12c**.

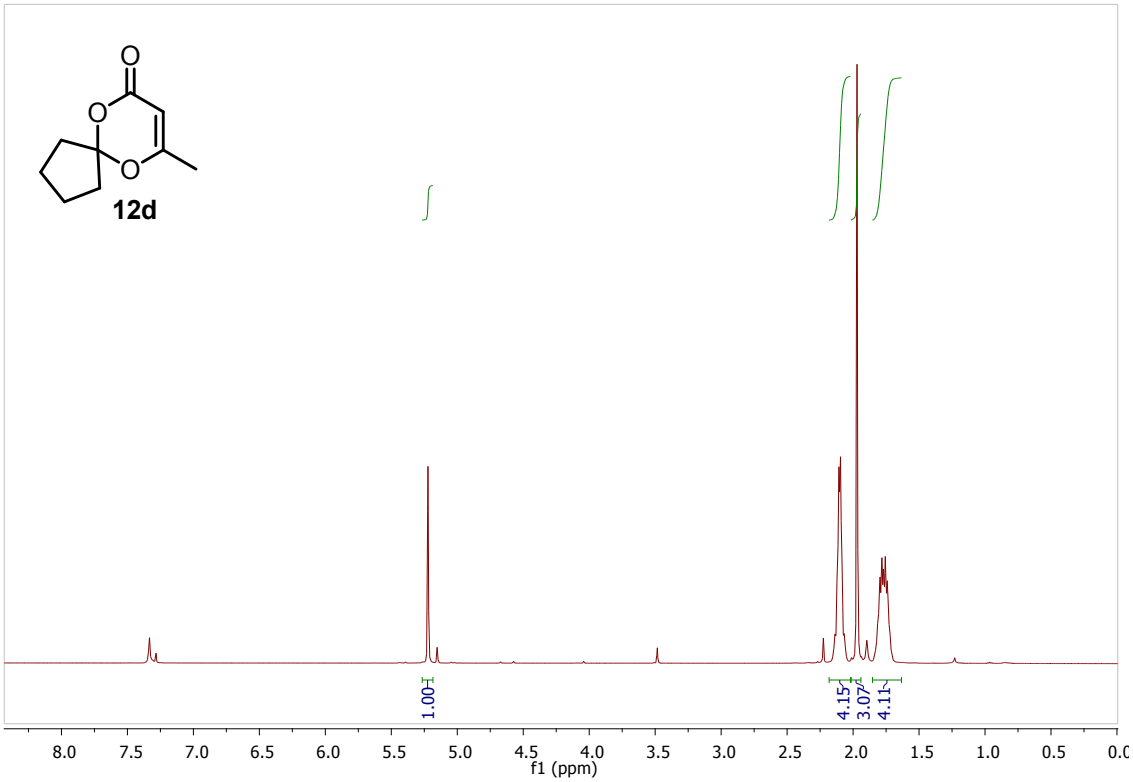


Fig S12. ^{1}H NMR spectrum for dioxinone **12d**.

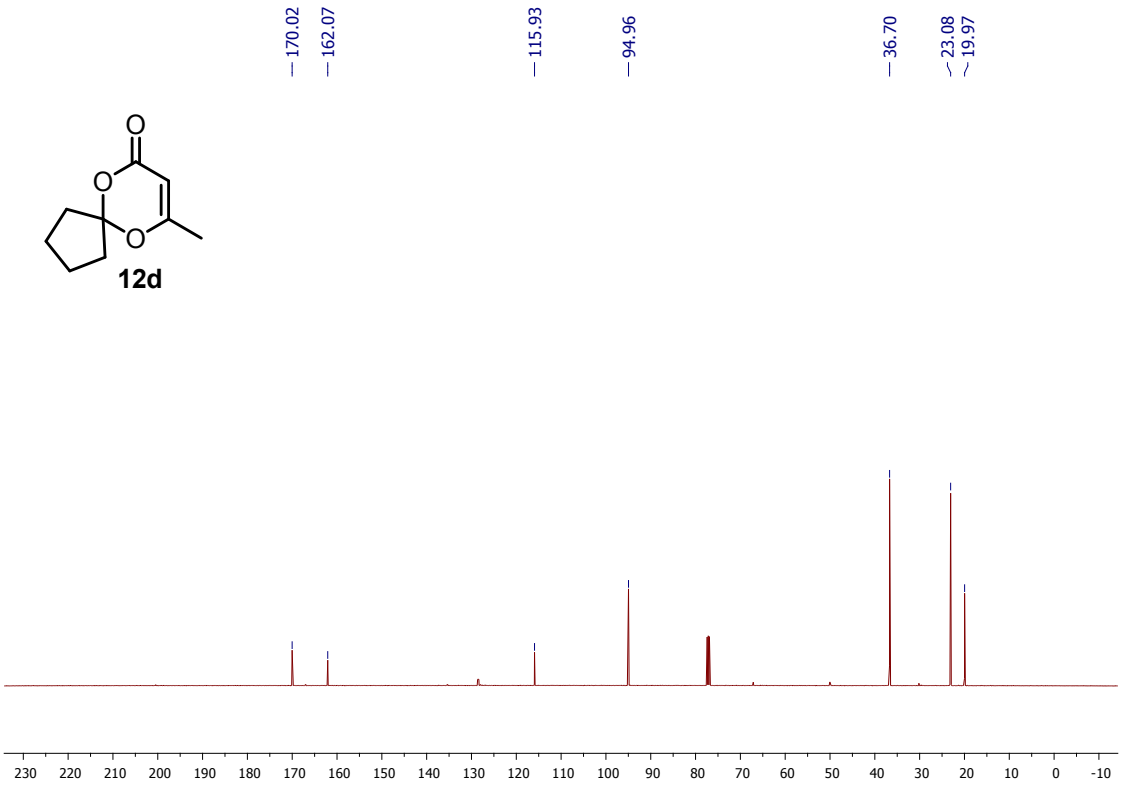


Fig S13. ^{13}C NMR spectrum for dioxinone **12d**.

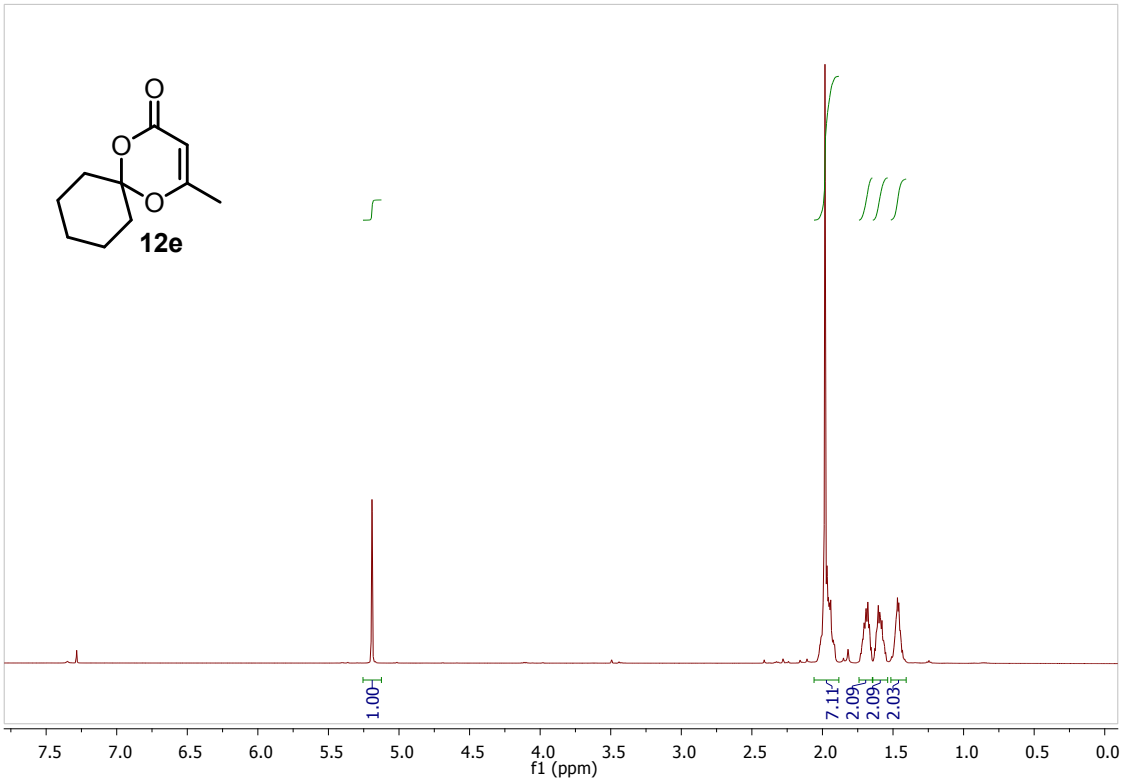


Fig S14. ^{1}H NMR spectrum for dioxinone **12e**.

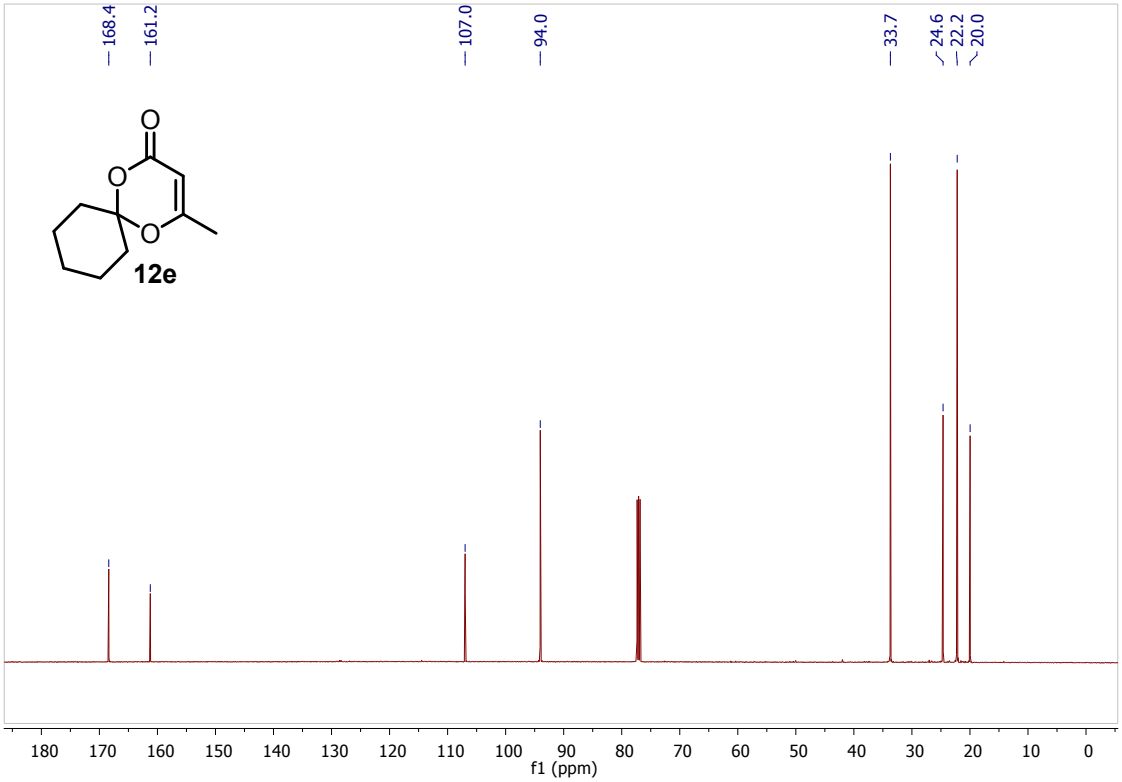


Fig S15. ^{13}C NMR spectrum for dioxinone **12e**.

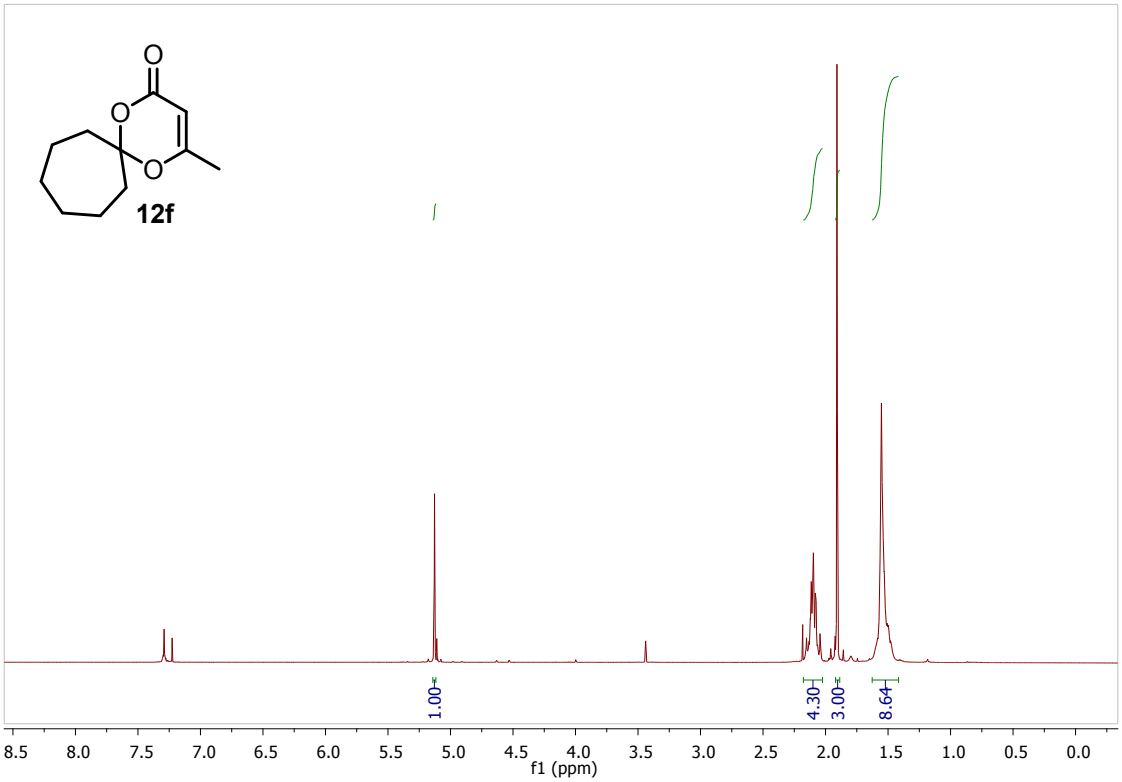


Fig S16. ^{1}H NMR spectrum for dioxinone **12f**.

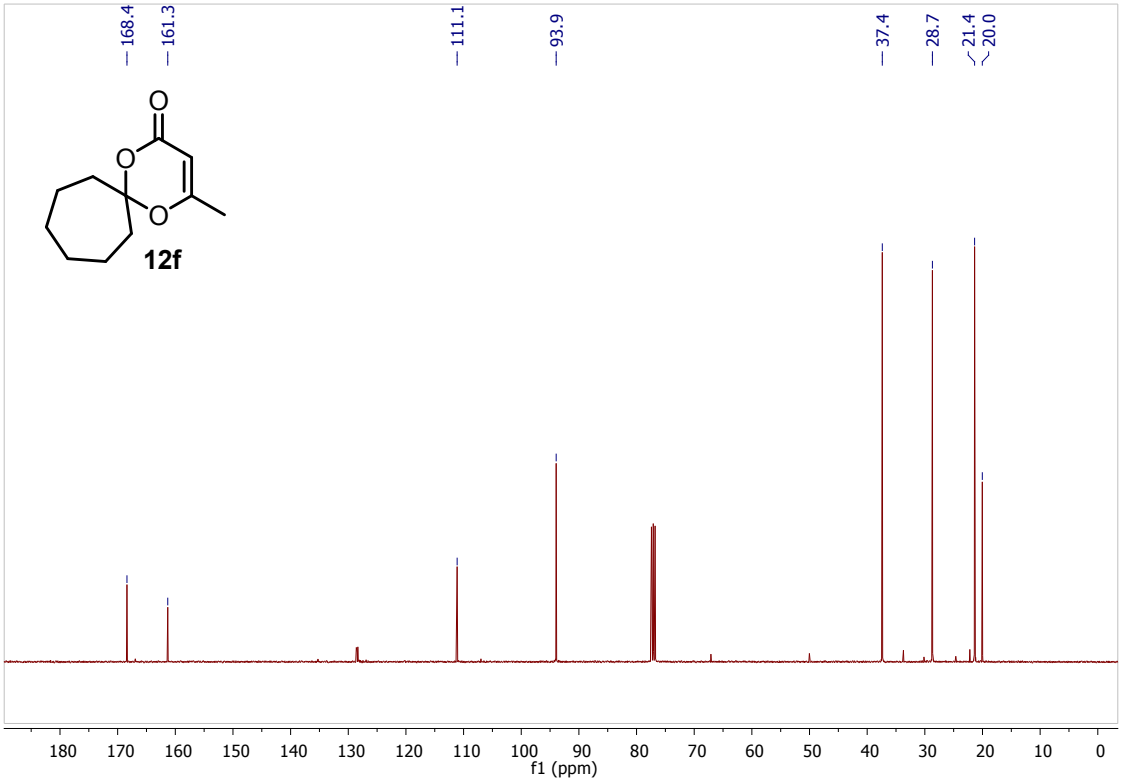


Fig S17. ^{13}C NMR spectrum for dioxinone **12f**.

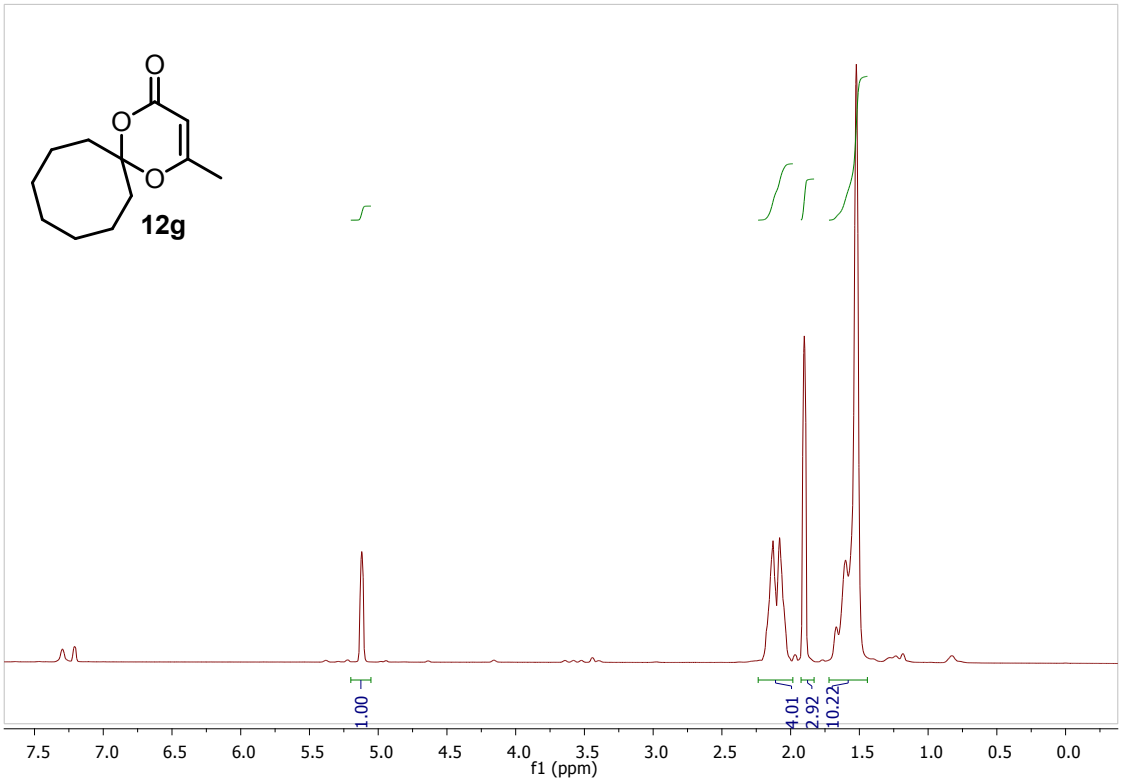


Fig S18. ^{1}H NMR spectrum for dioxinone **12g**.

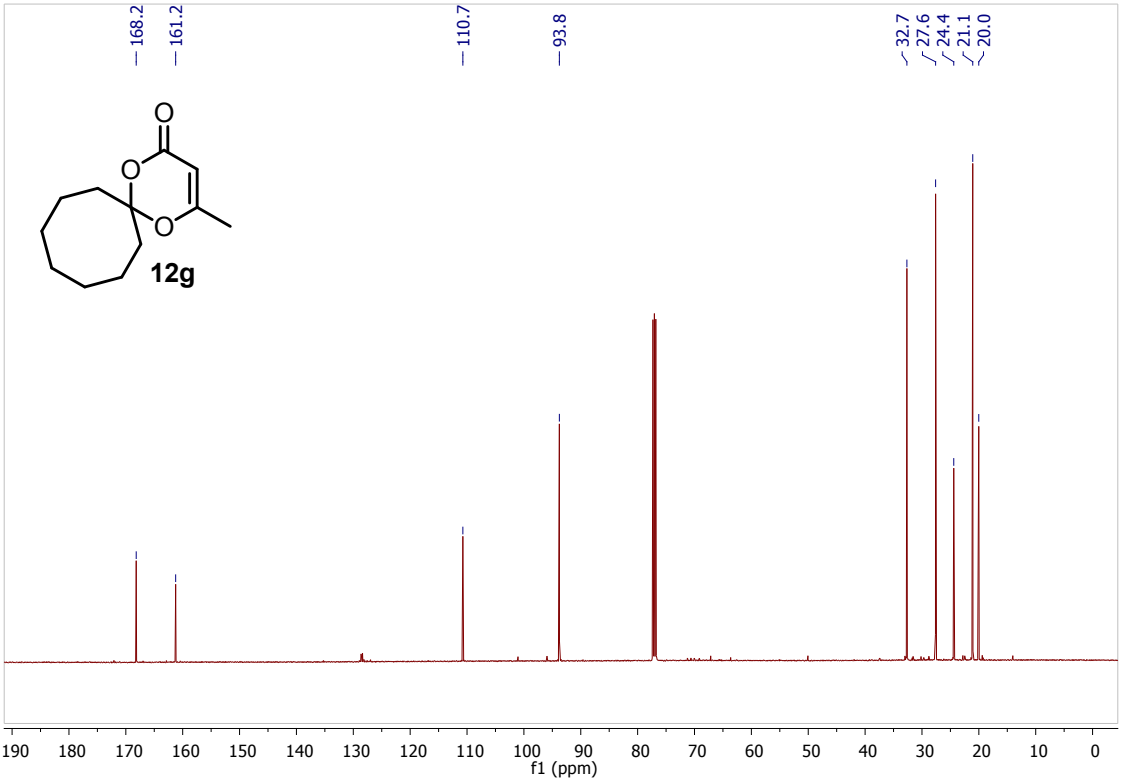


Fig S19. ^{13}C NMR spectrum for dioxinone **12g**.

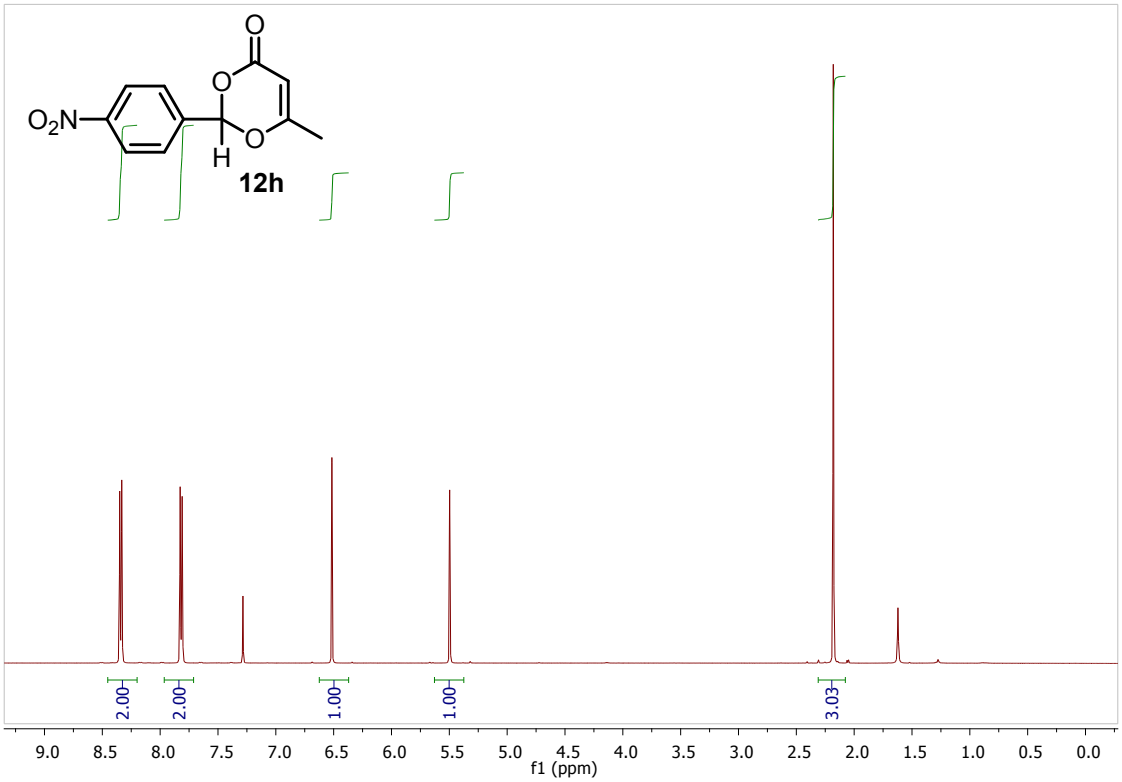


Fig S20. ^{1}H NMR spectrum for dioxinone **12h**.

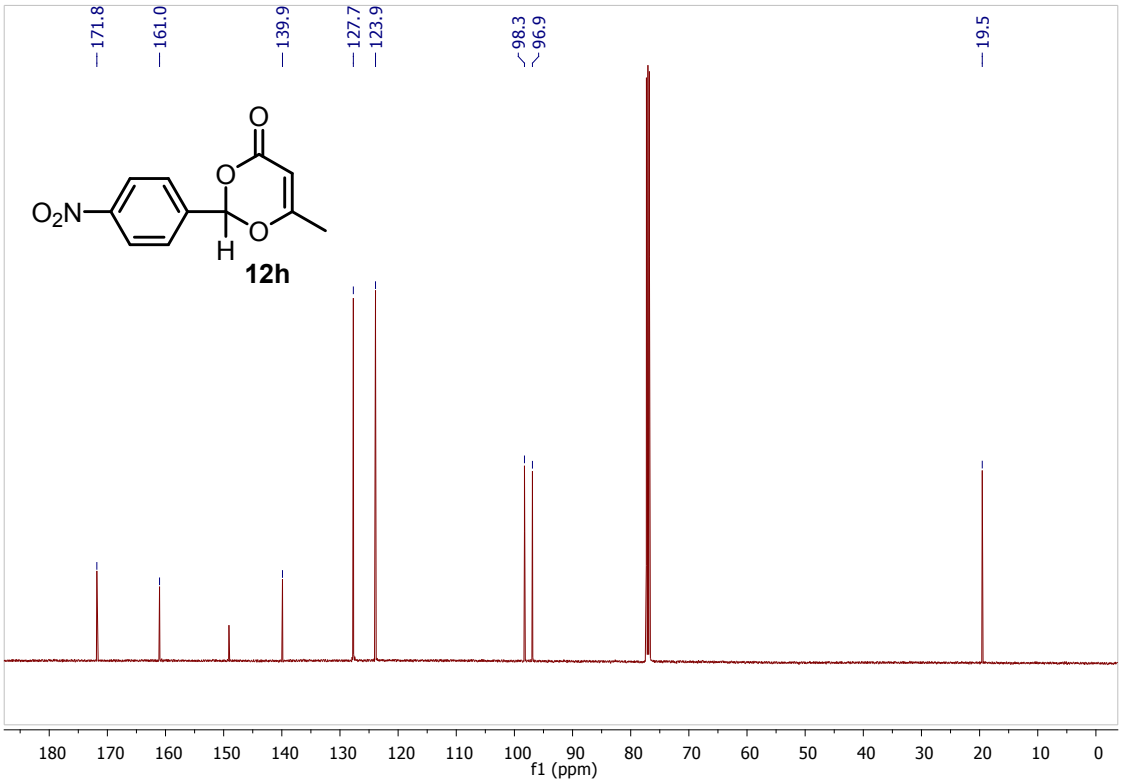


Fig S21. ^{13}C NMR spectrum for dioxinone **12h**.

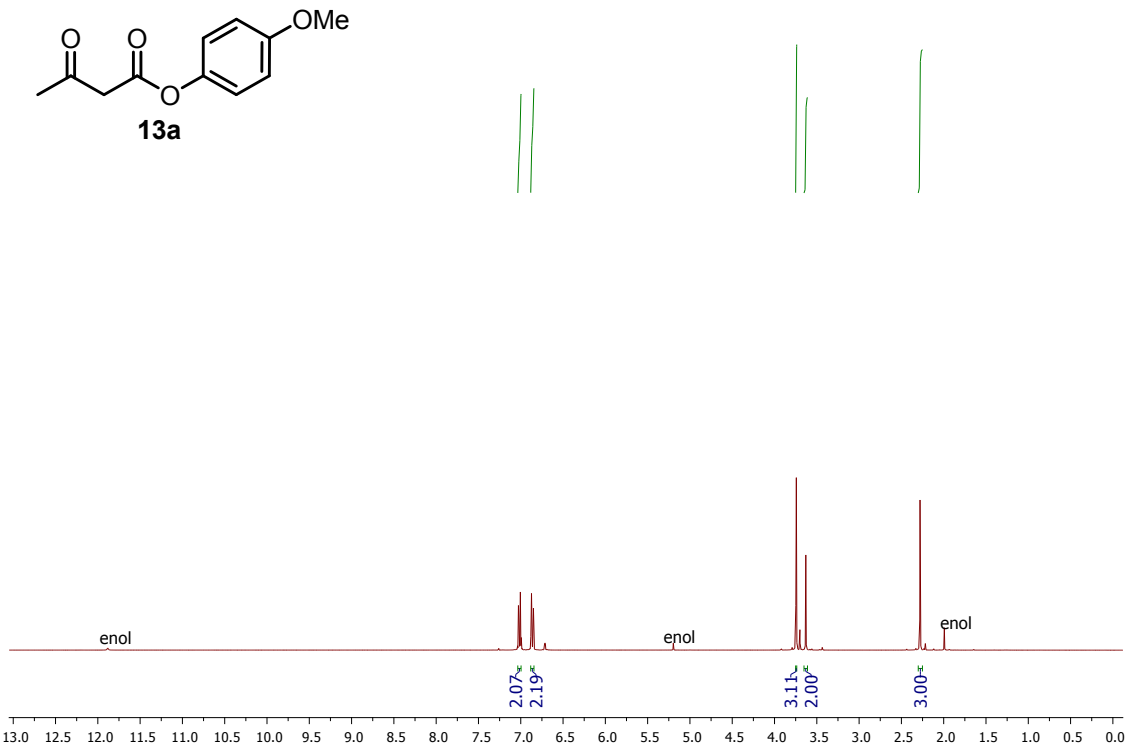


Fig S22. ^{1}H NMR spectrum for β-ketoester **13a**.

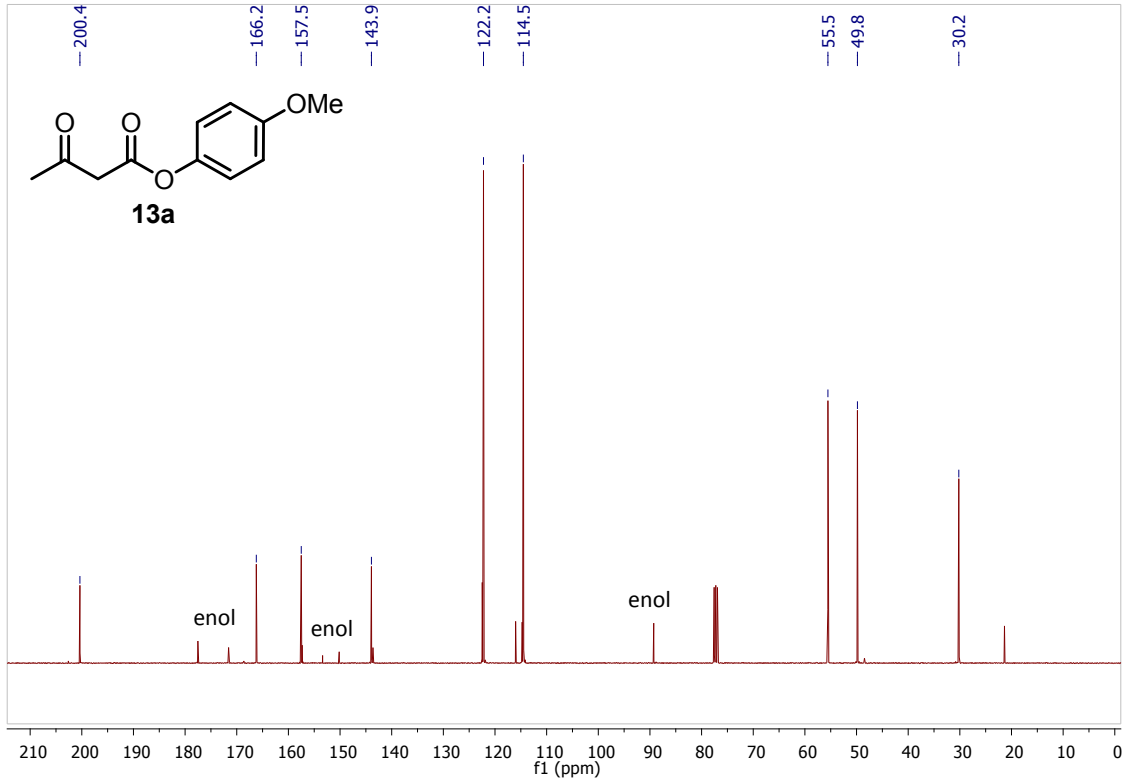


Fig S23. ^{13}C NMR spectrum for β-ketoester **13a**.

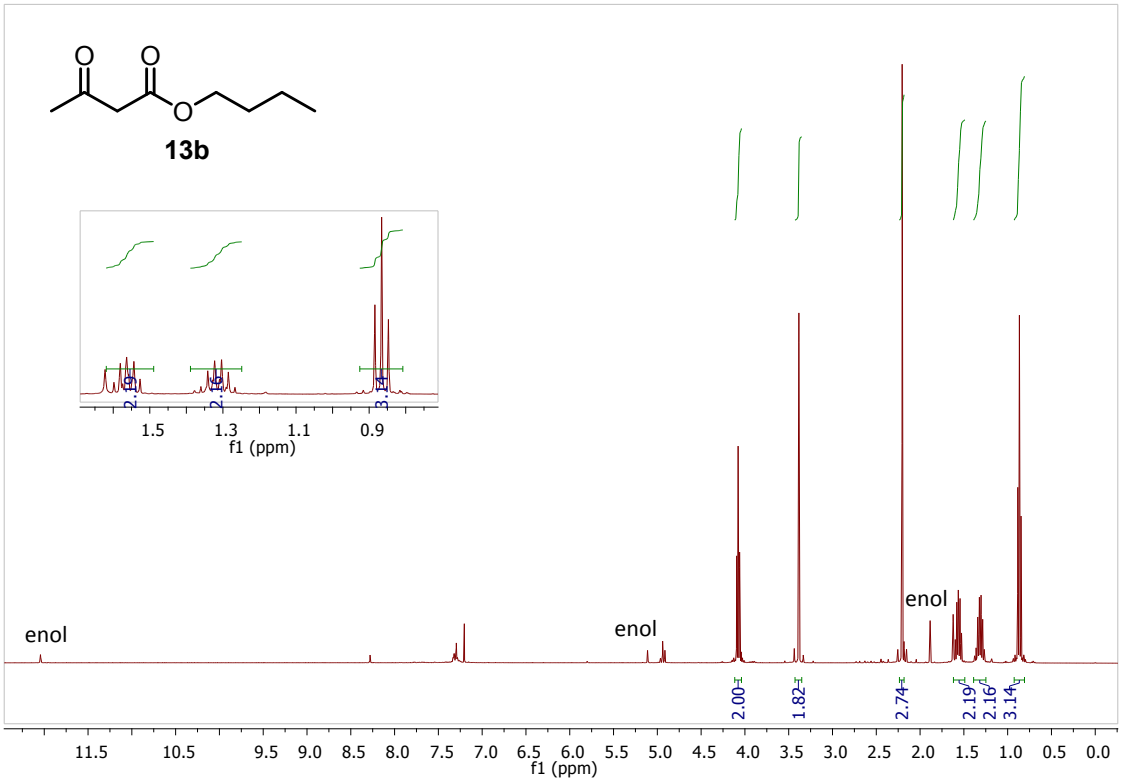


Fig S24. ^{1}H NMR spectrum for β-ketoester **13b**.

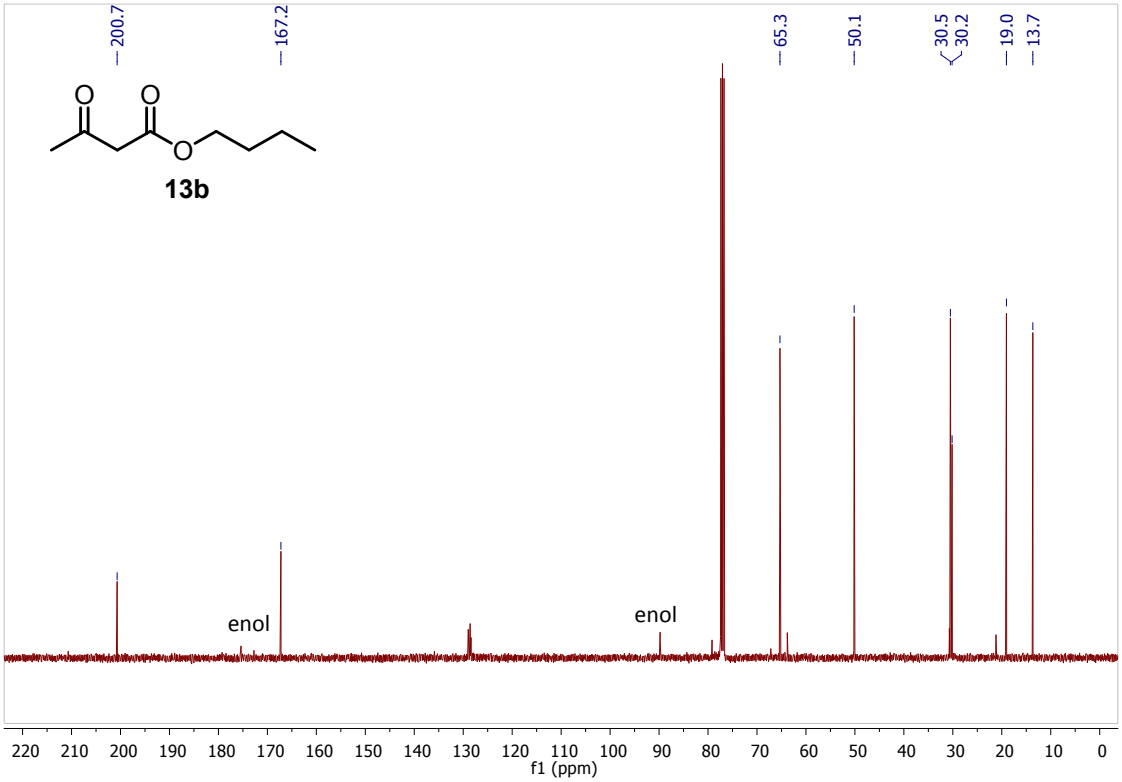


Fig S25. ^{13}C NMR spectrum for β-ketoester **13b**.

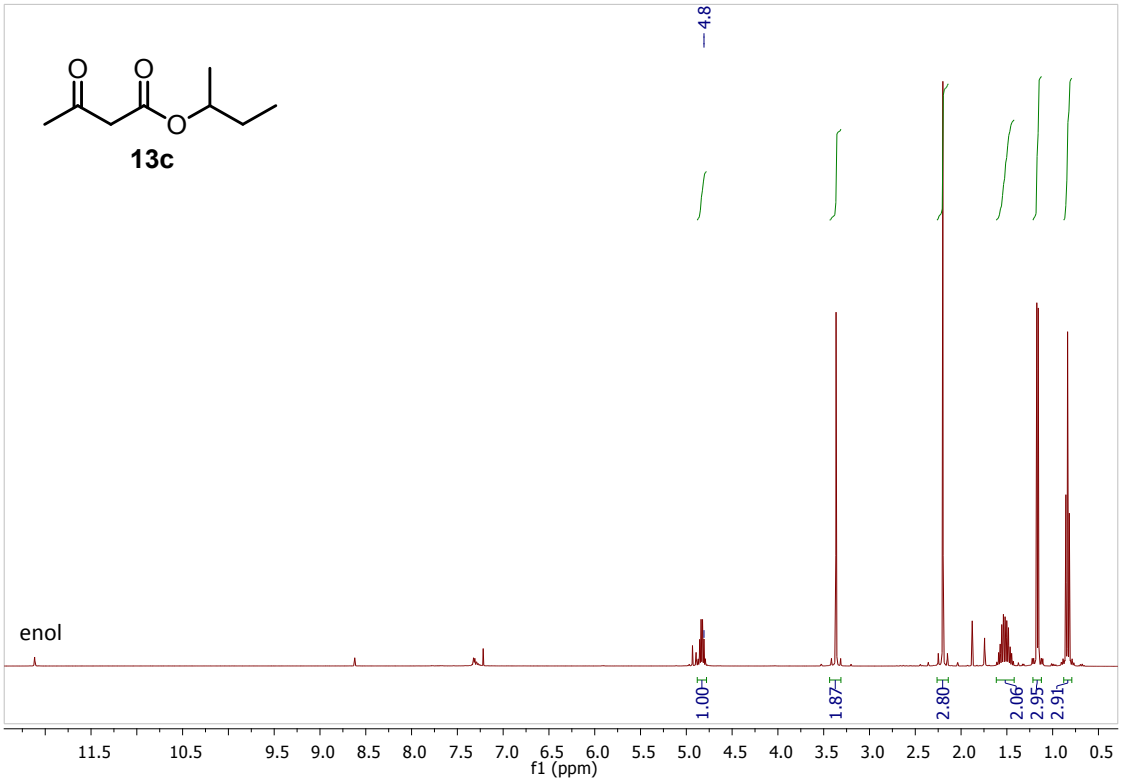


Fig S26. ^{1}H NMR spectrum for β-ketoester **13c**.

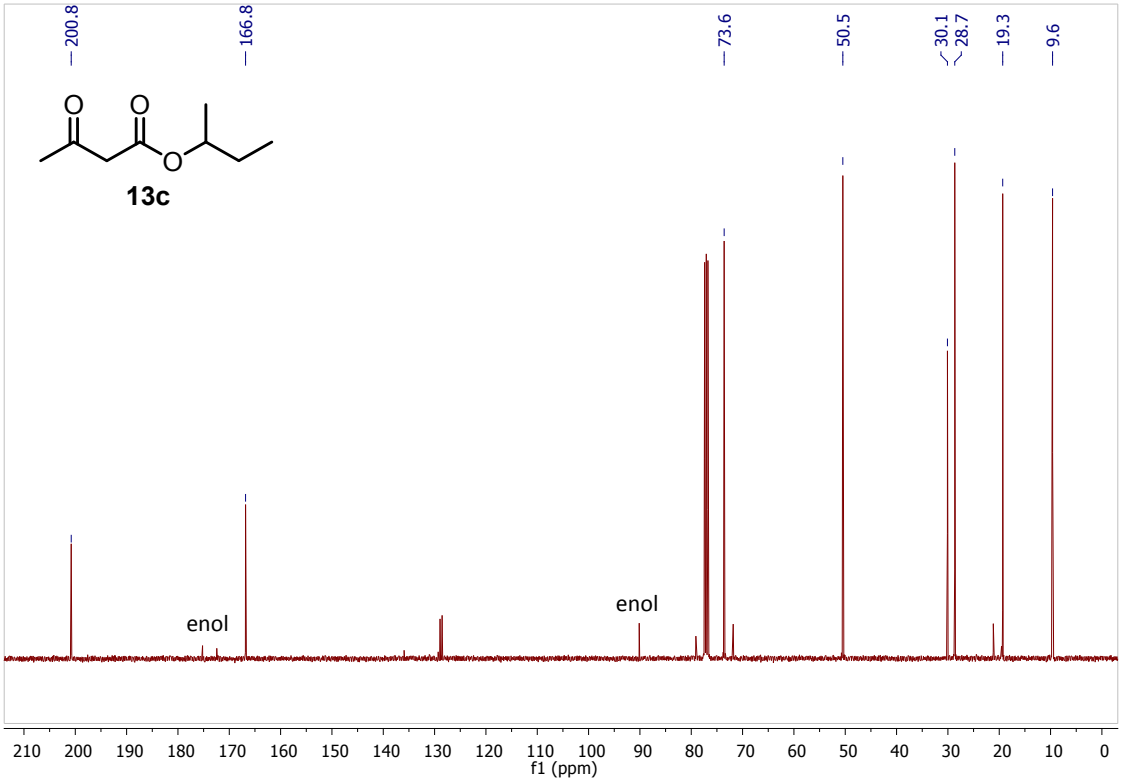


Fig S27. ^{13}C NMR spectrum for β-ketoester **13c**.

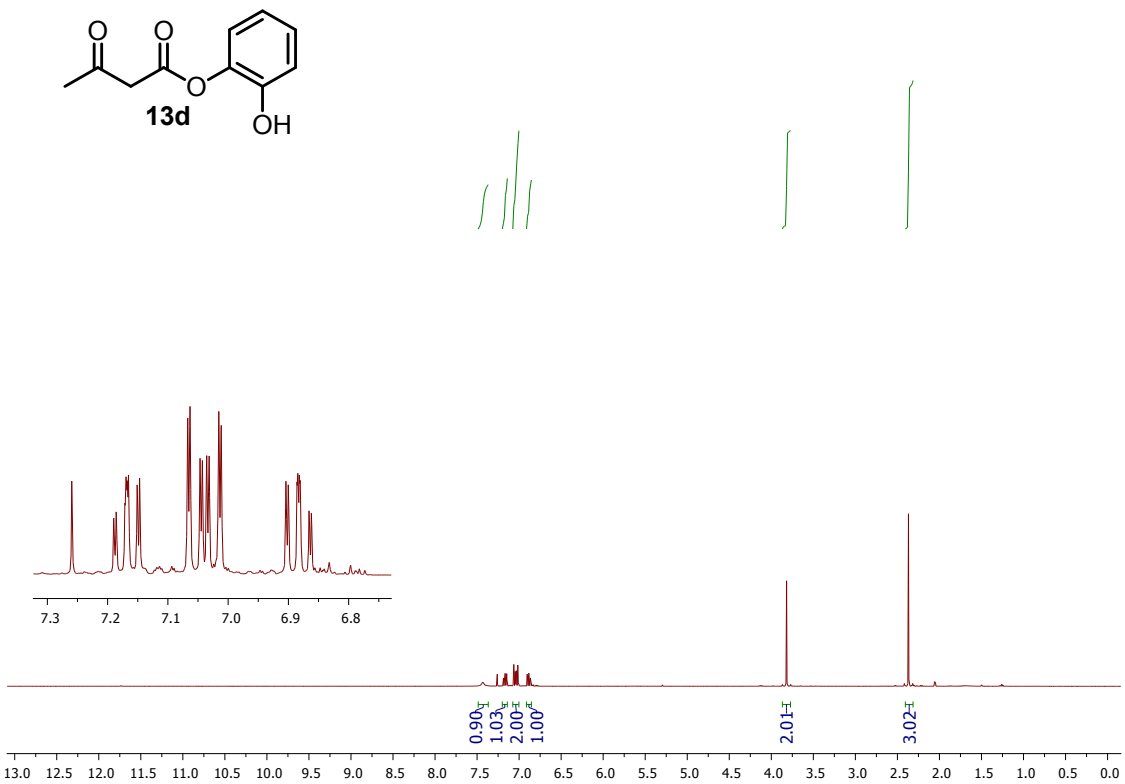


Fig S28. ^{1}H NMR spectrum for β-ketoester **13d**.

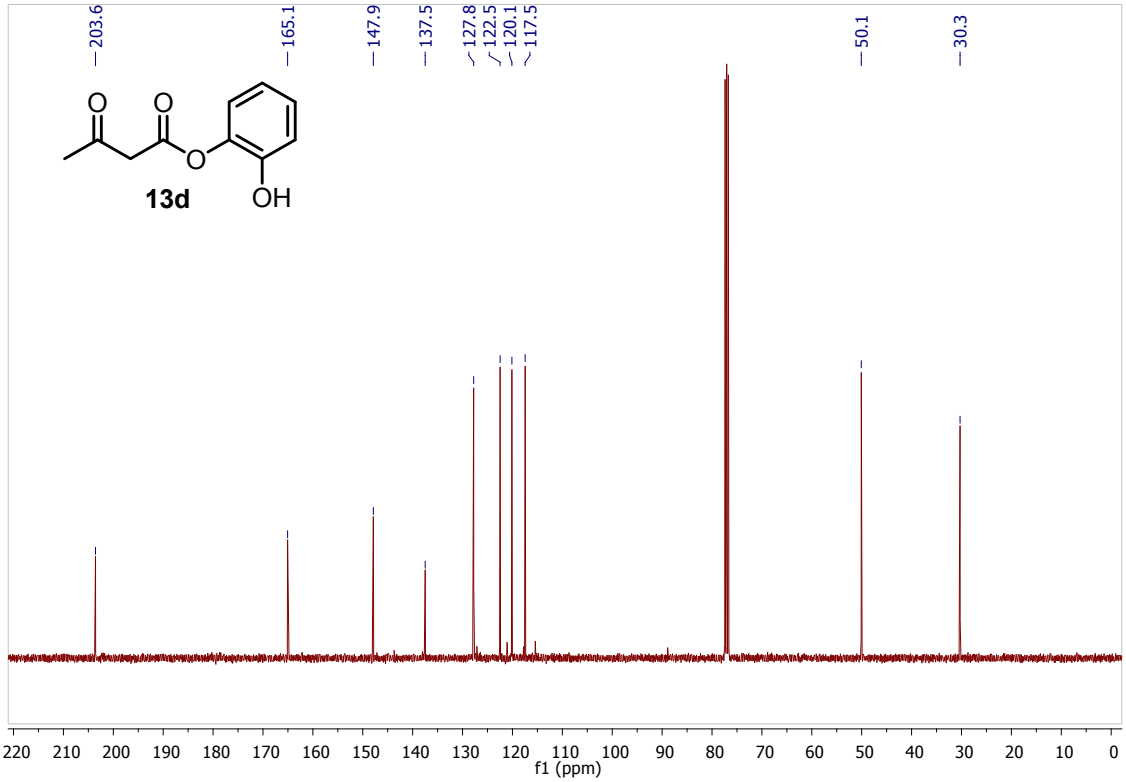


Fig S29. ^{13}C NMR spectrum for β-ketoester **13d**.

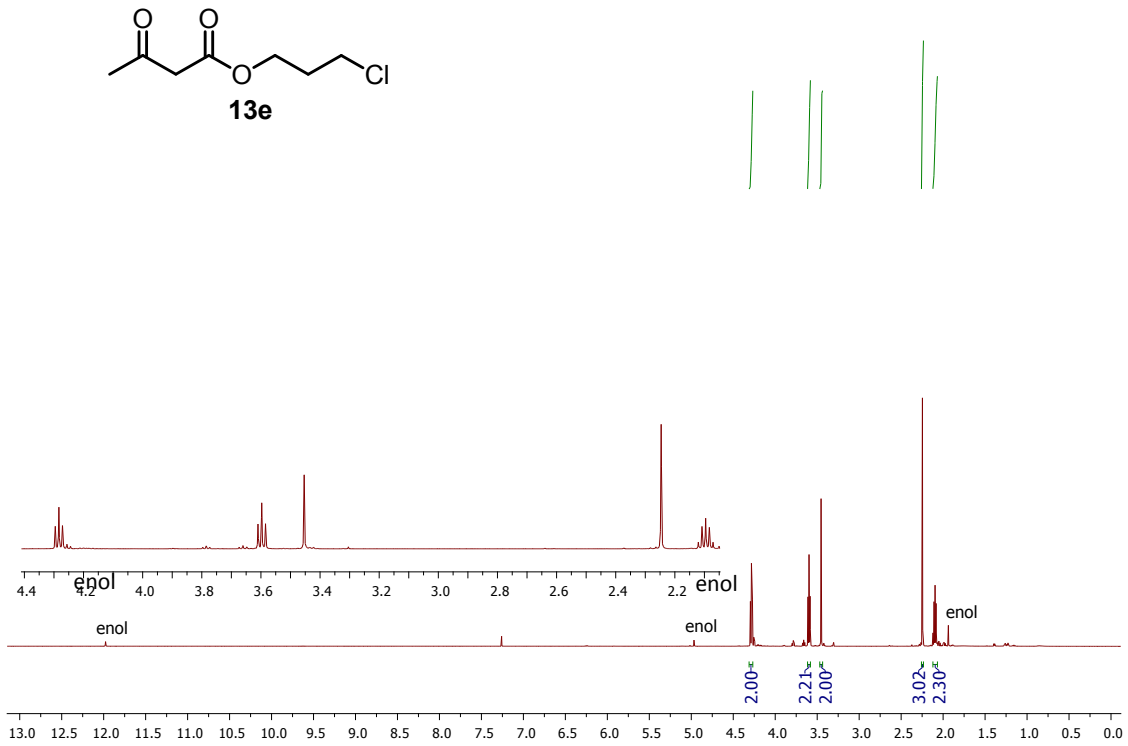


Fig S30. ^{1}H NMR spectrum for β-ketoester **13e**.

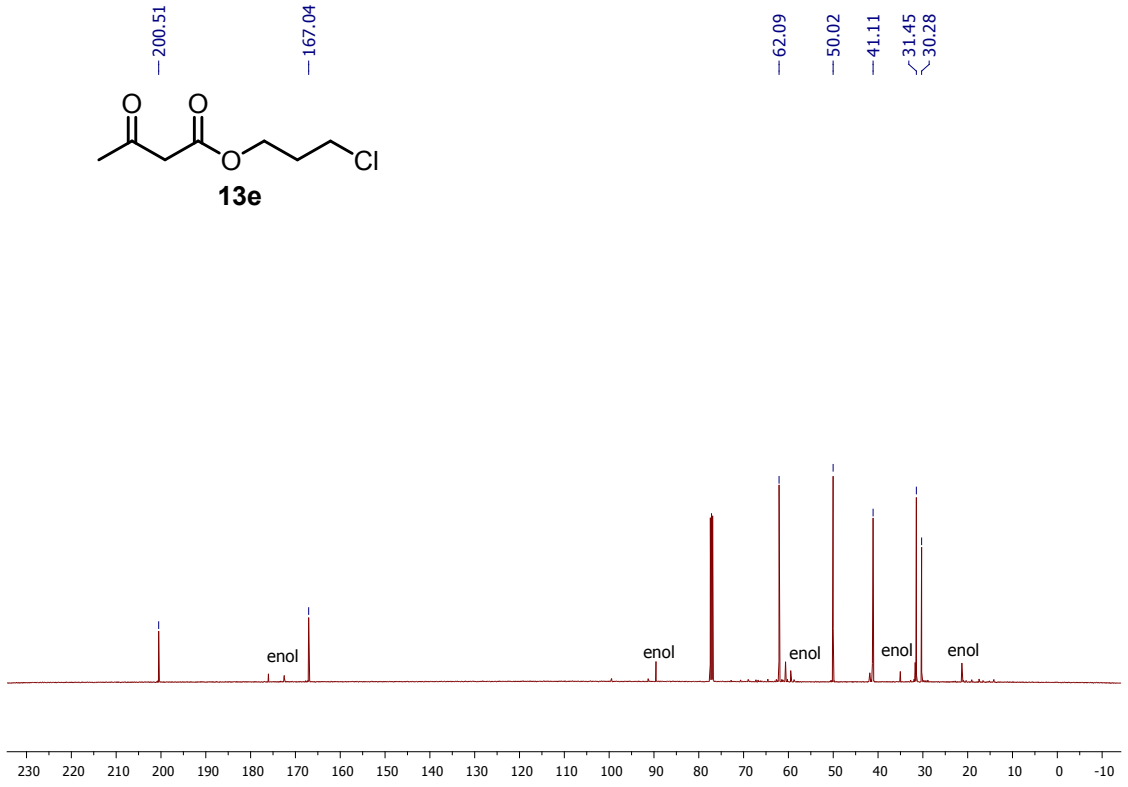


Fig S31. ^{13}C NMR spectrum for β-ketoester **13e**.

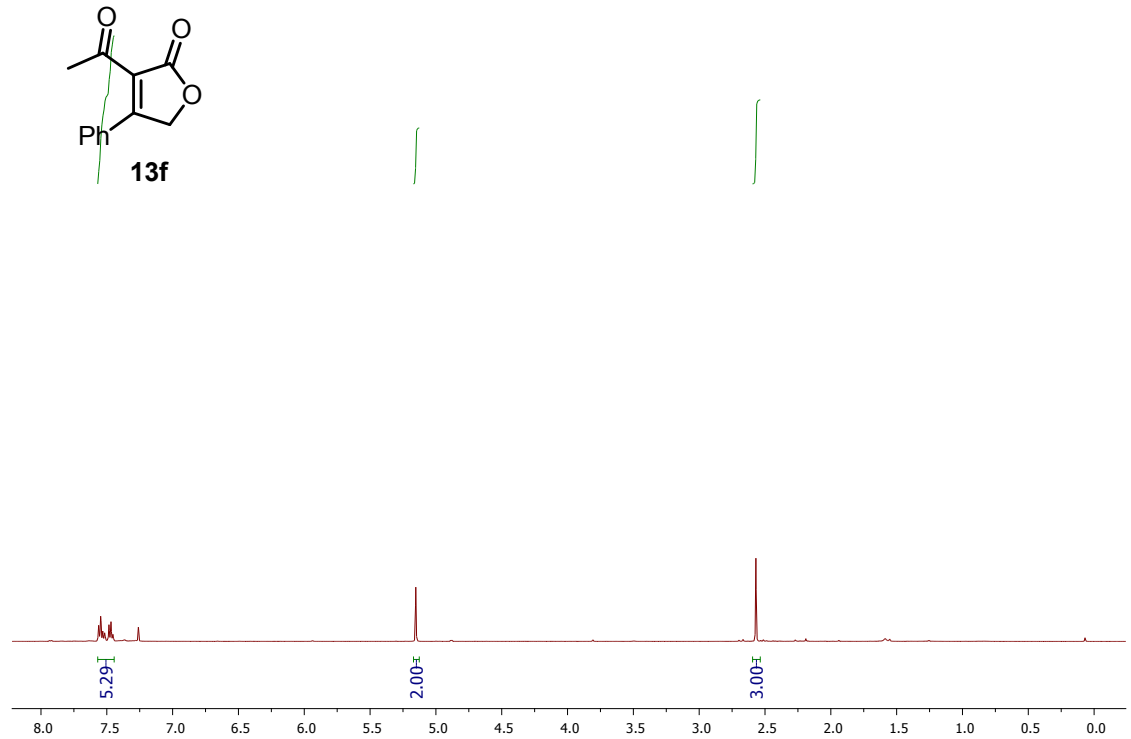


Fig S32. ^{1}H NMR spectrum for β-ketoester **13f**.

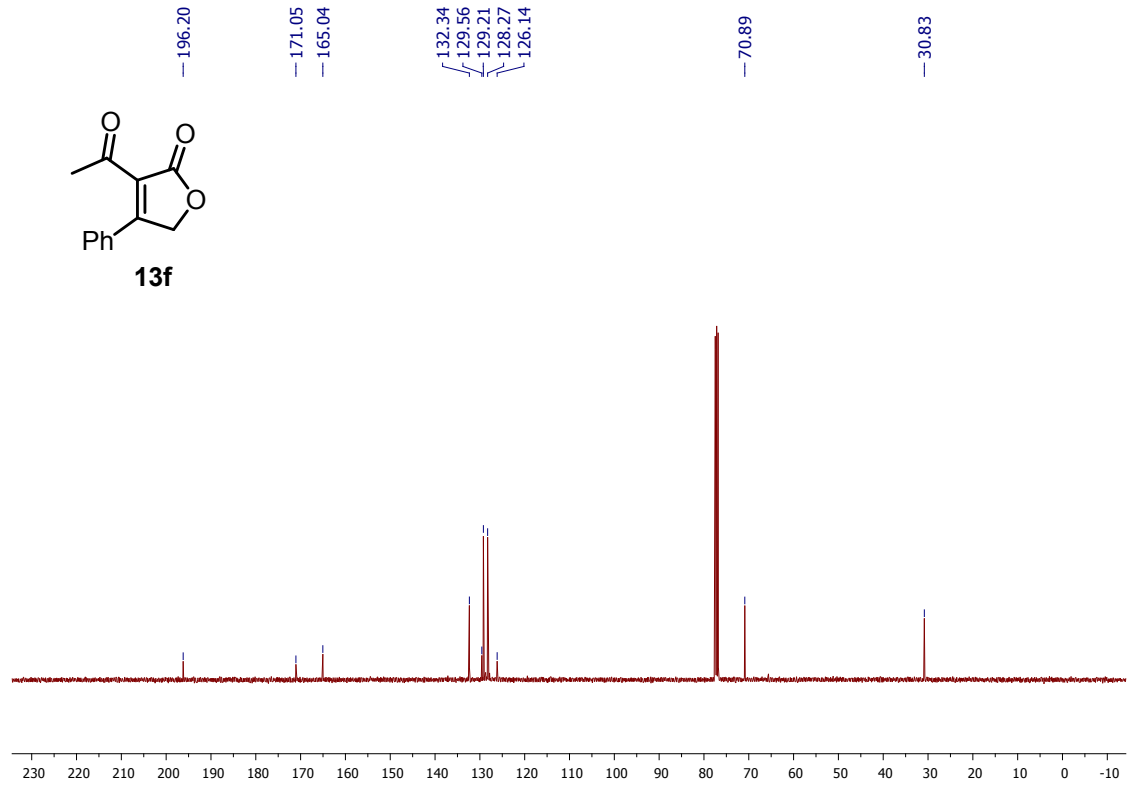


Fig S33. ^{13}C NMR spectrum for β-ketoester **13f**.

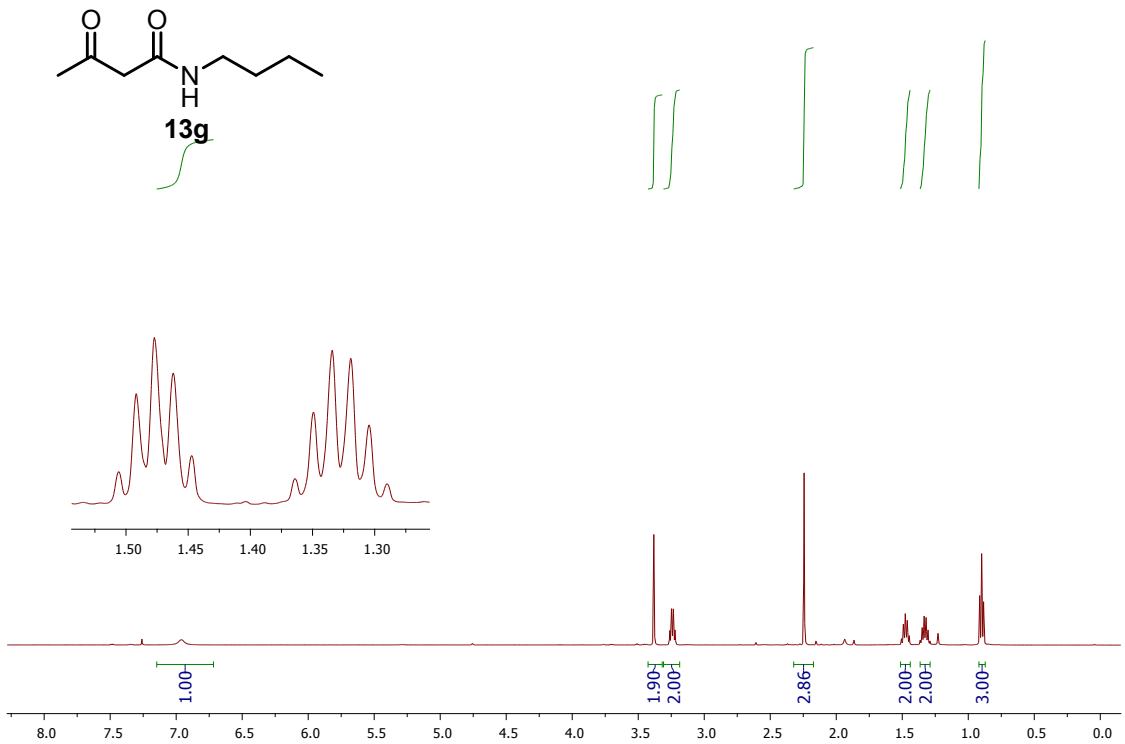


Fig S30. ^{1}H NMR spectrum for β-ketoamide **13g**.

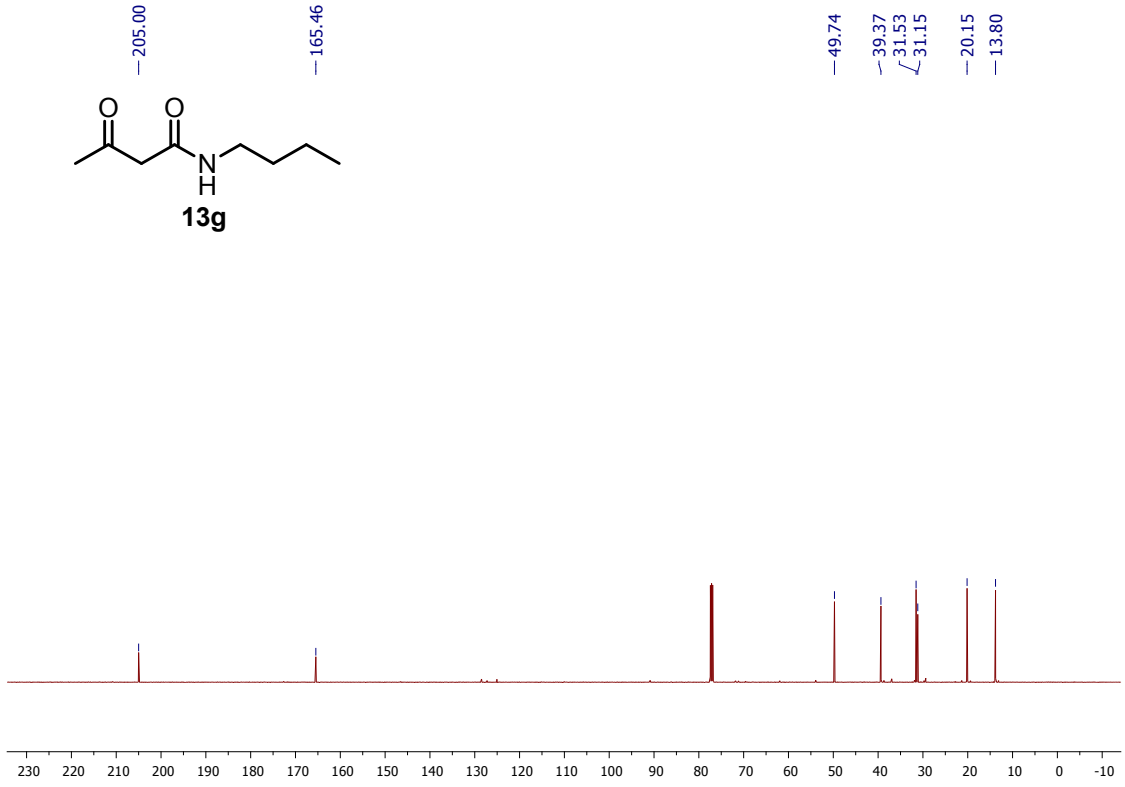


Fig S31. ^{13}C NMR spectrum for β-ketoamide **13g**.

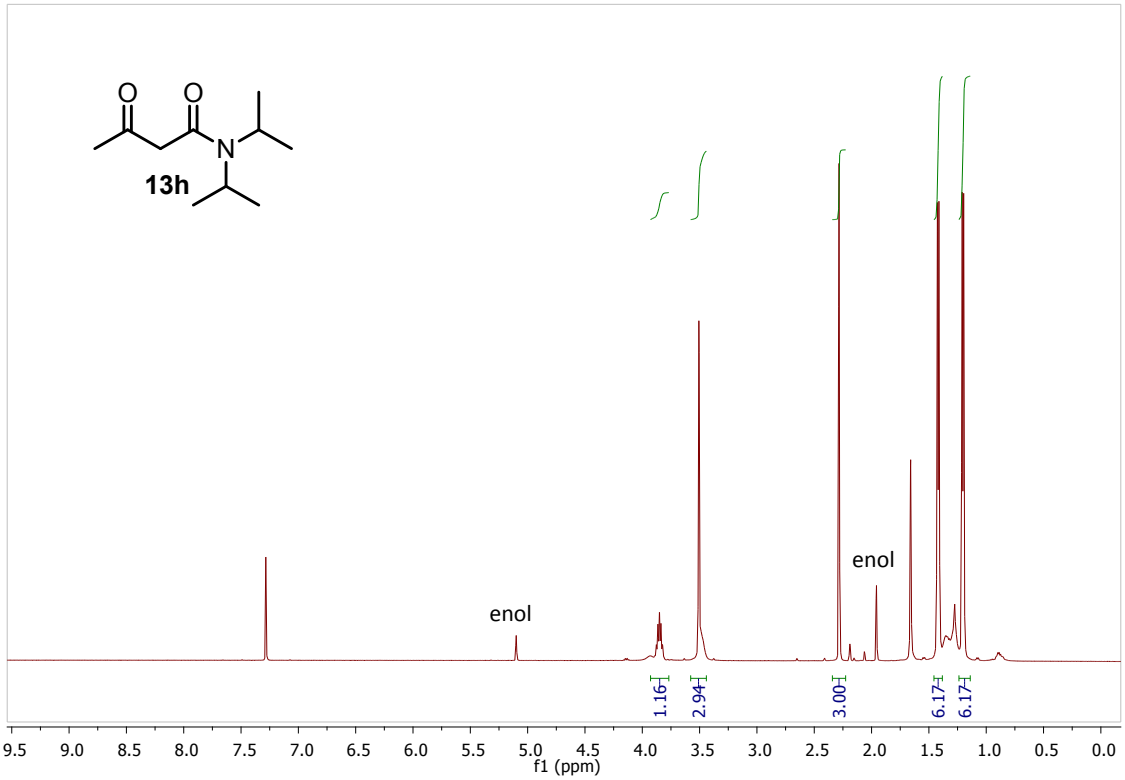


Fig S32. ^{1}H NMR spectrum for β-ketoamide **13h**.

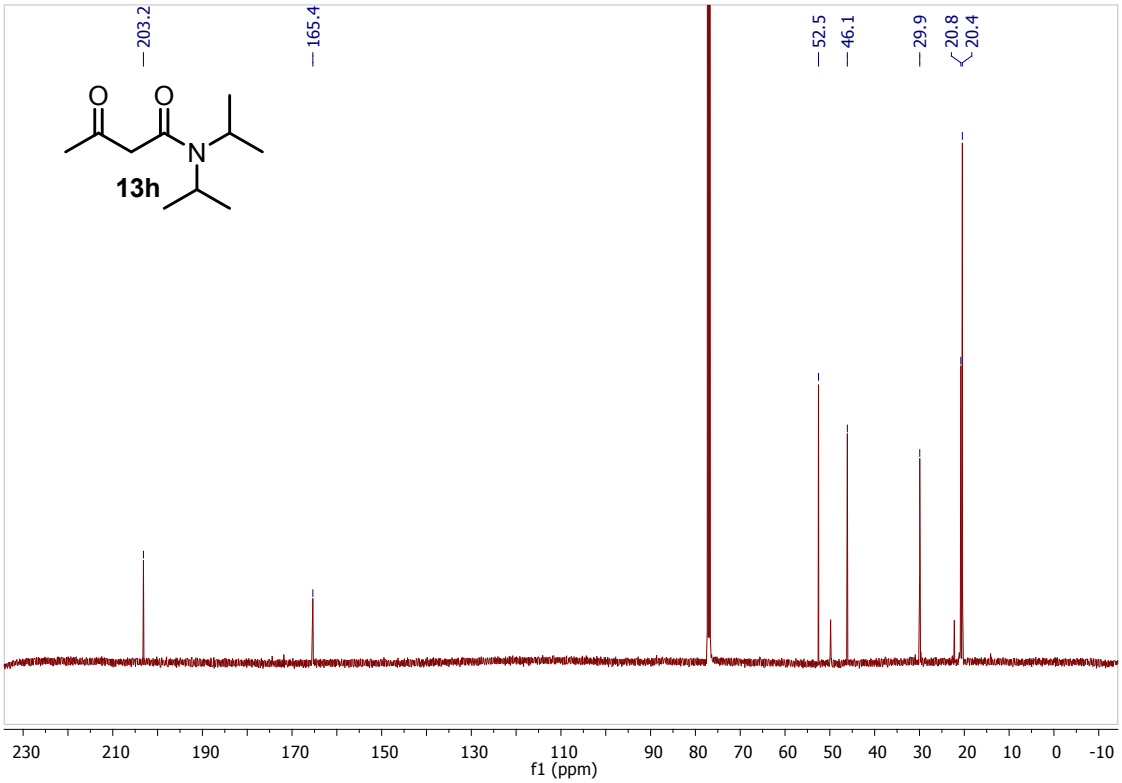


Fig S33. ^{13}C NMR spectrum for β-ketoamide **13h**.

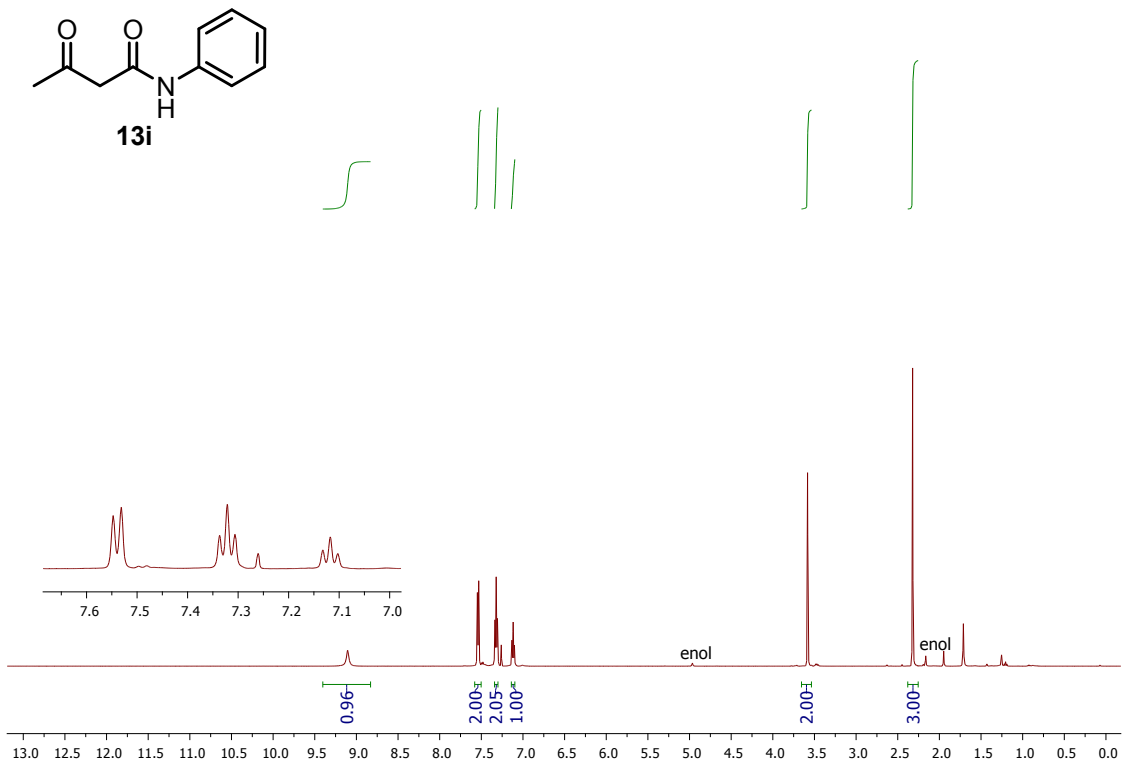


Fig S34. ^{1}H NMR spectrum for β-ketoamide **13i**.

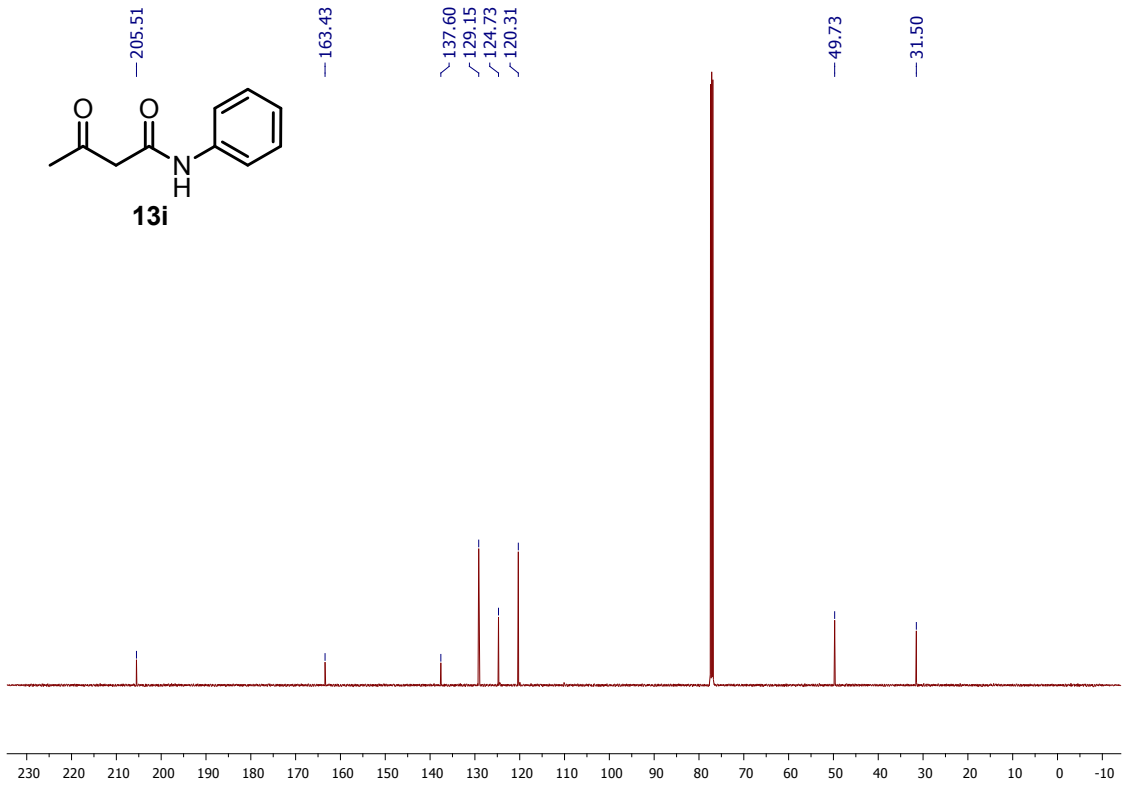


Fig S35. ^{13}C NMR spectrum for β-ketoamide **13i**.

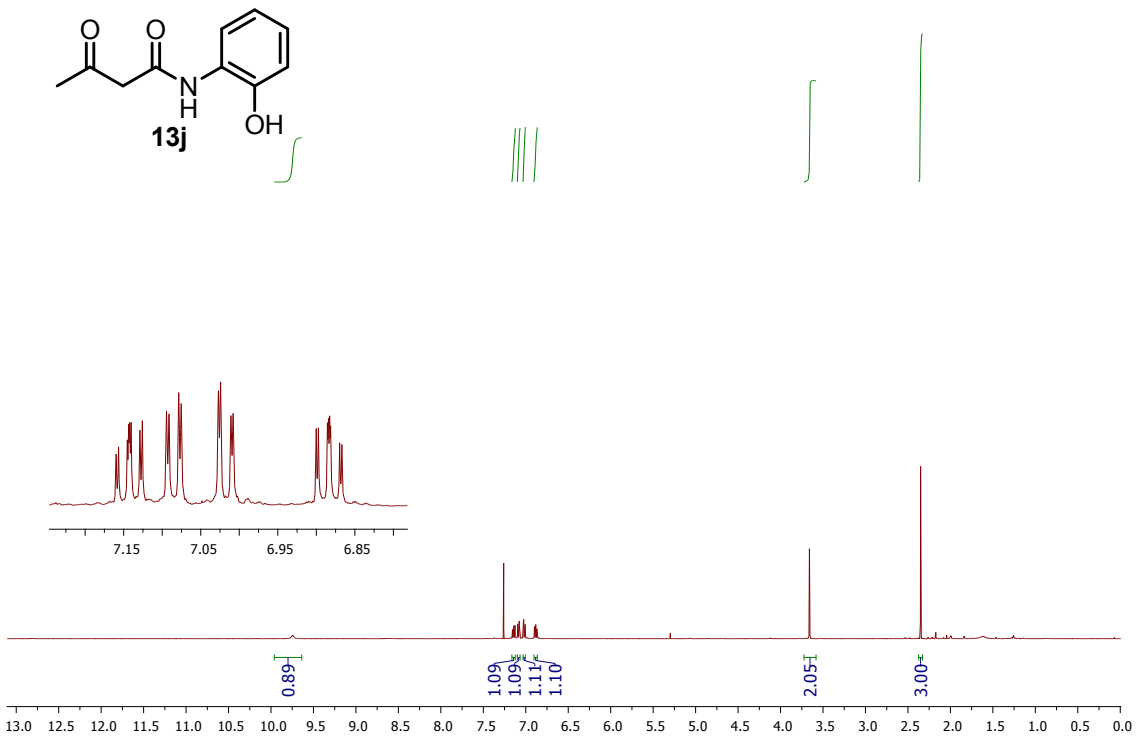


Fig S36. ^{1}H NMR spectrum for β-ketoamide **13j**.

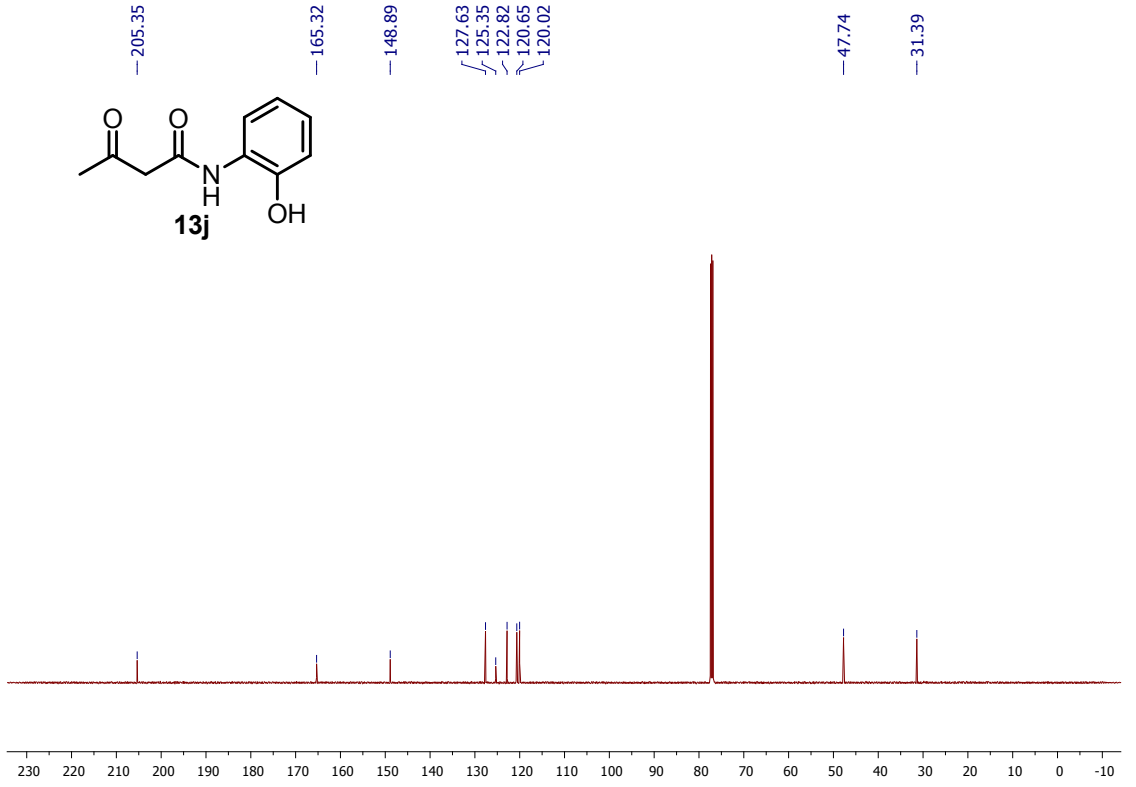


Fig S37. ^{13}C NMR spectrum for β-ketoamide **13j**.

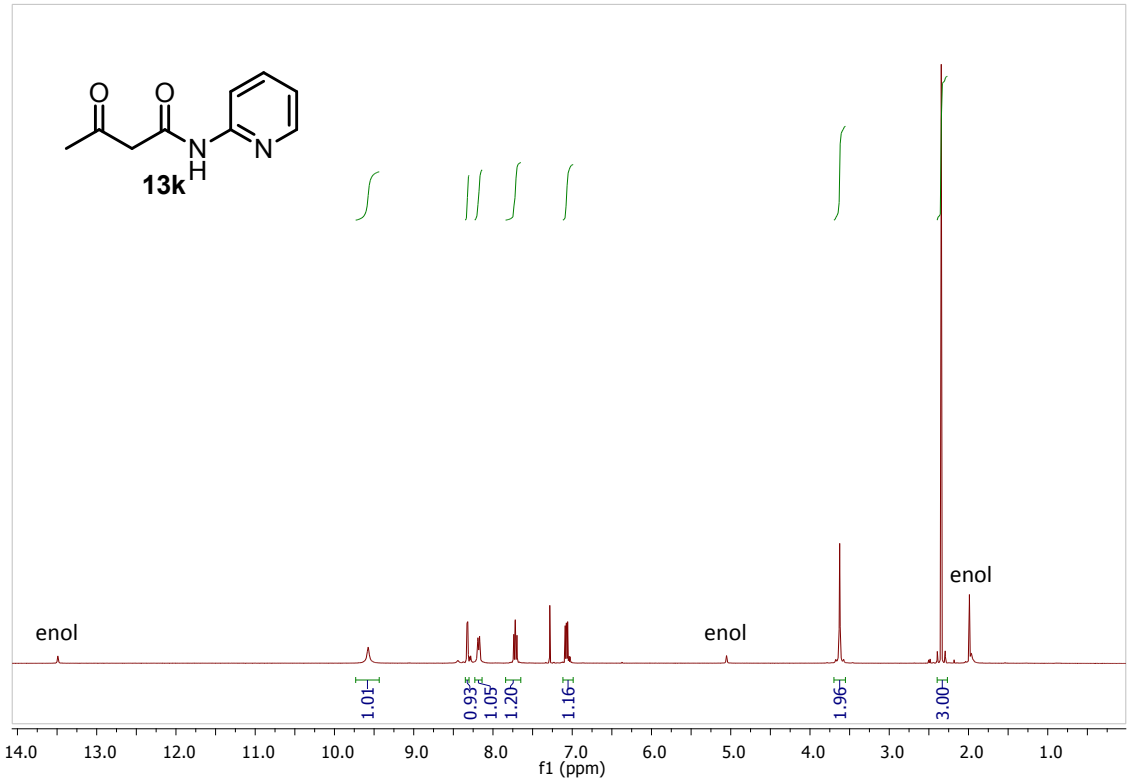


Fig S38. ^{1}H NMR spectrum for β-ketoamide **13k**.

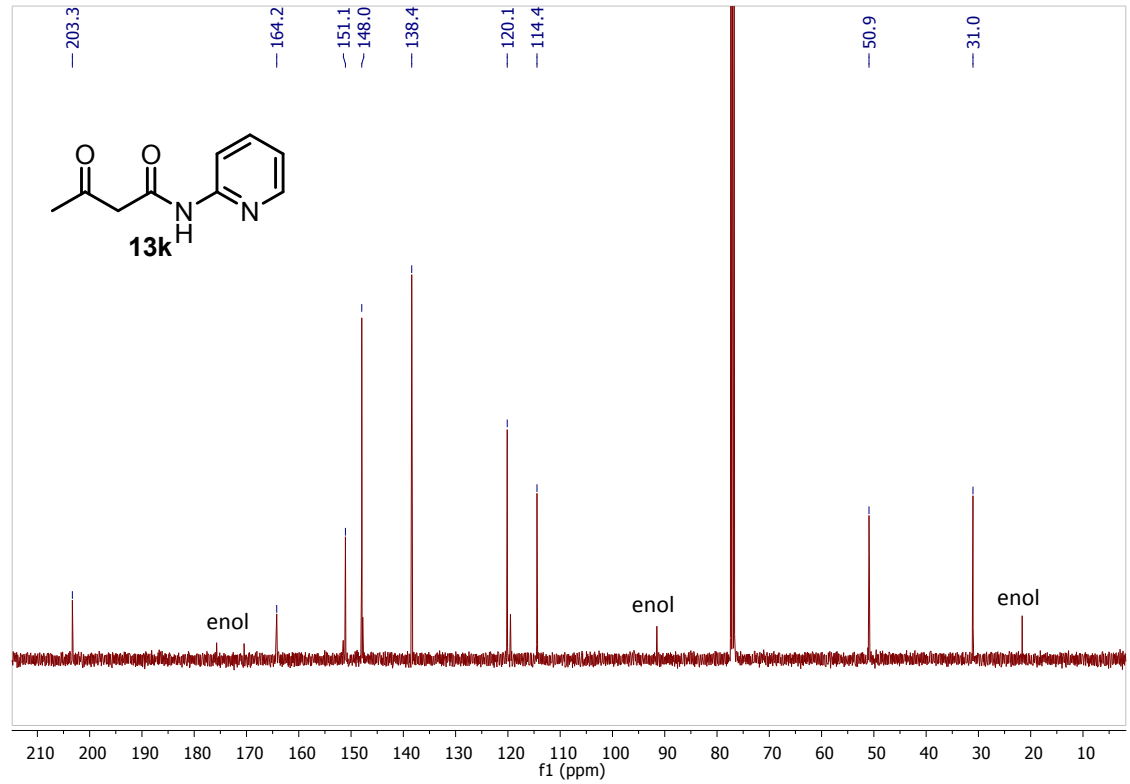


Fig S39. ^{13}C NMR spectrum for β-ketoamide **13k**.

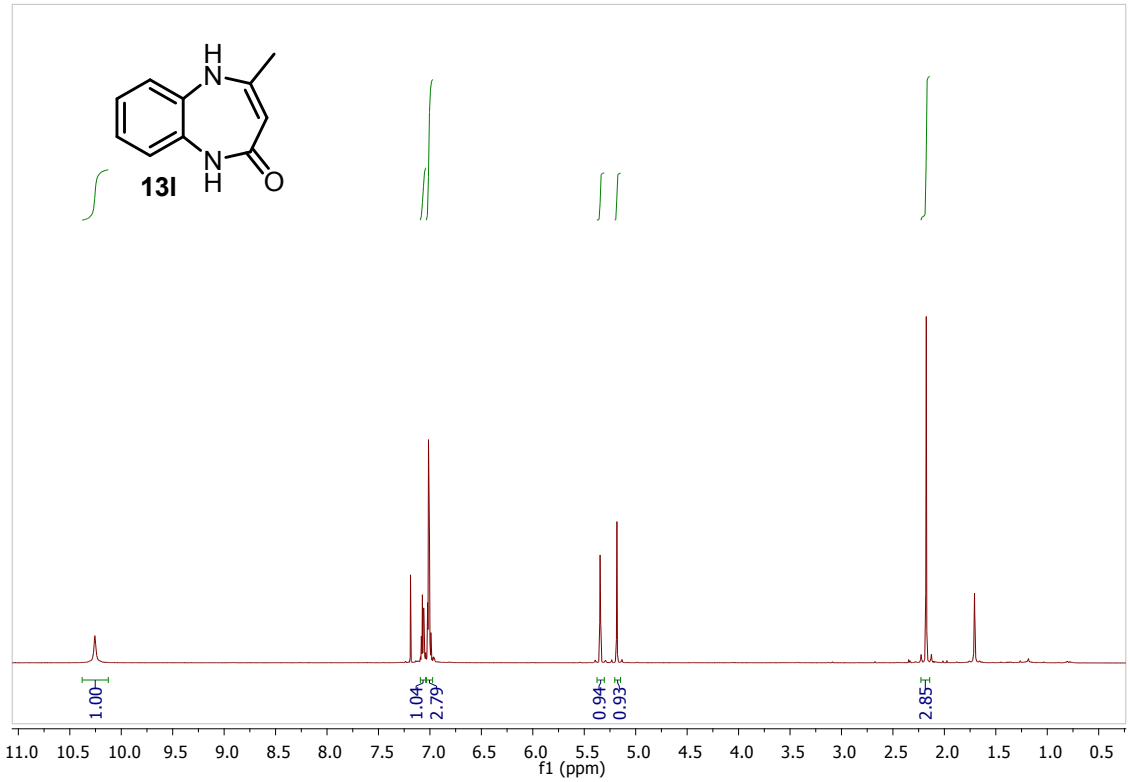


Fig S38. ^{1}H NMR spectrum for benzodiazepine **13l**.

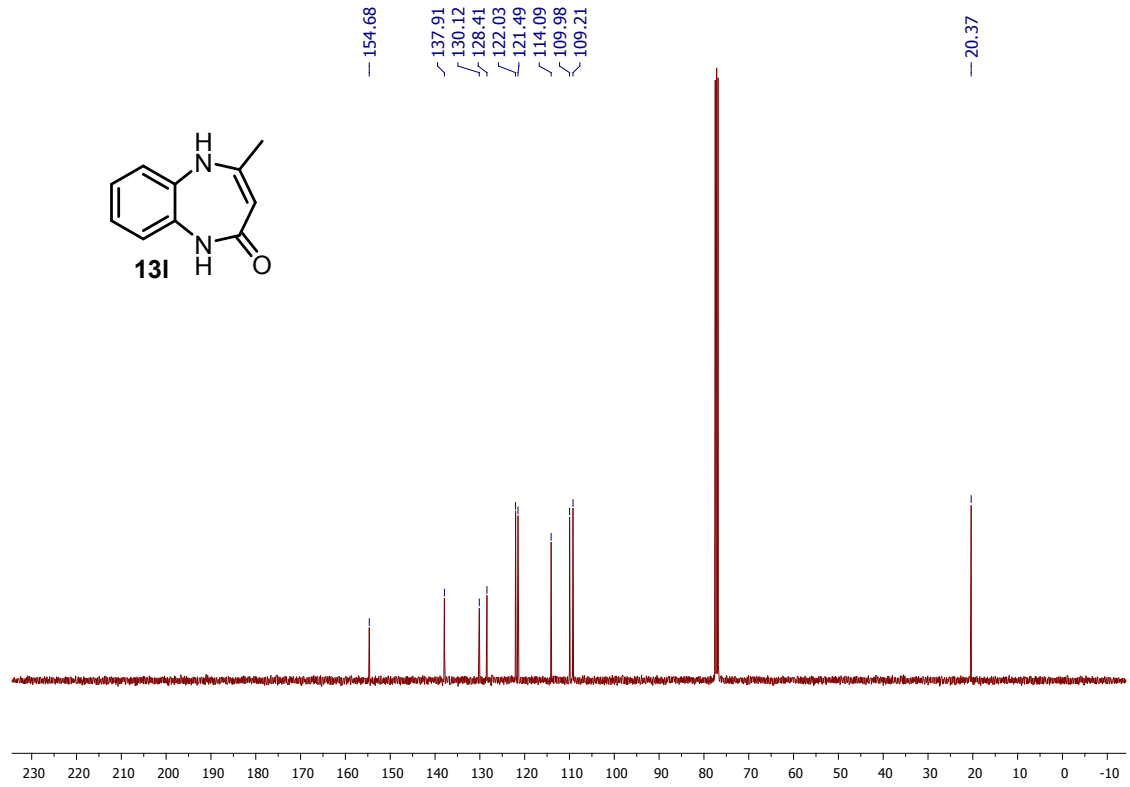


Fig S39. ^{13}C NMR spectrum for benzodiazepine **13l**.

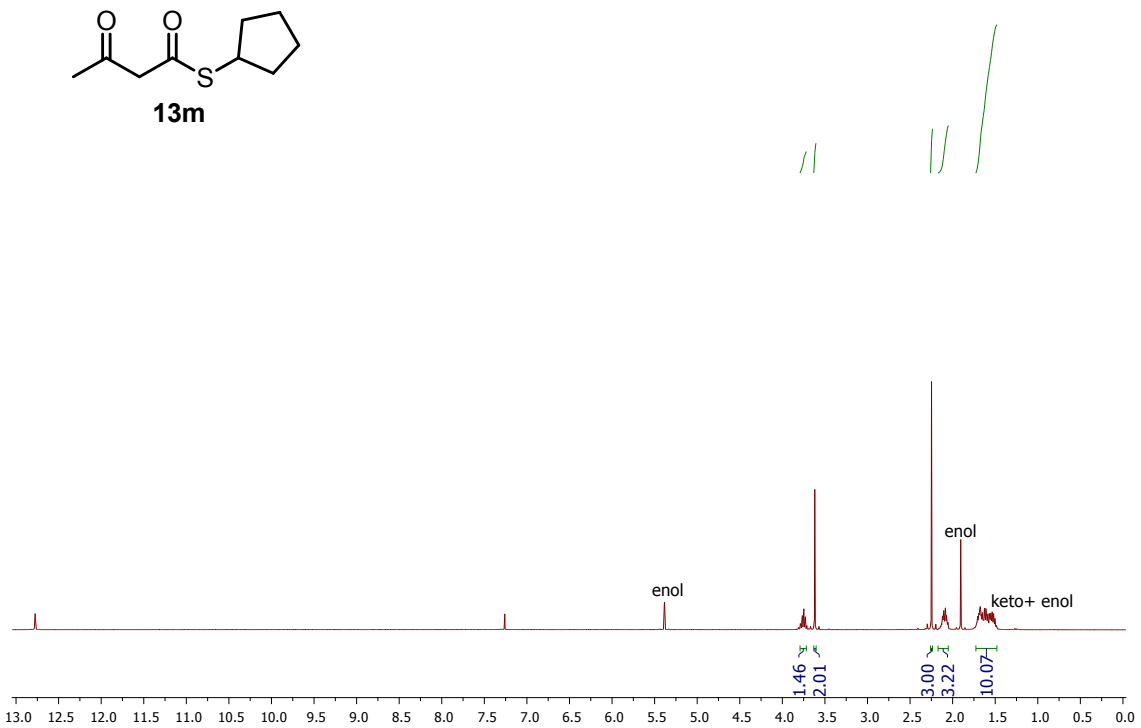


Fig S38. ^{1}H NMR spectrum for β-ketothioate **13m**.

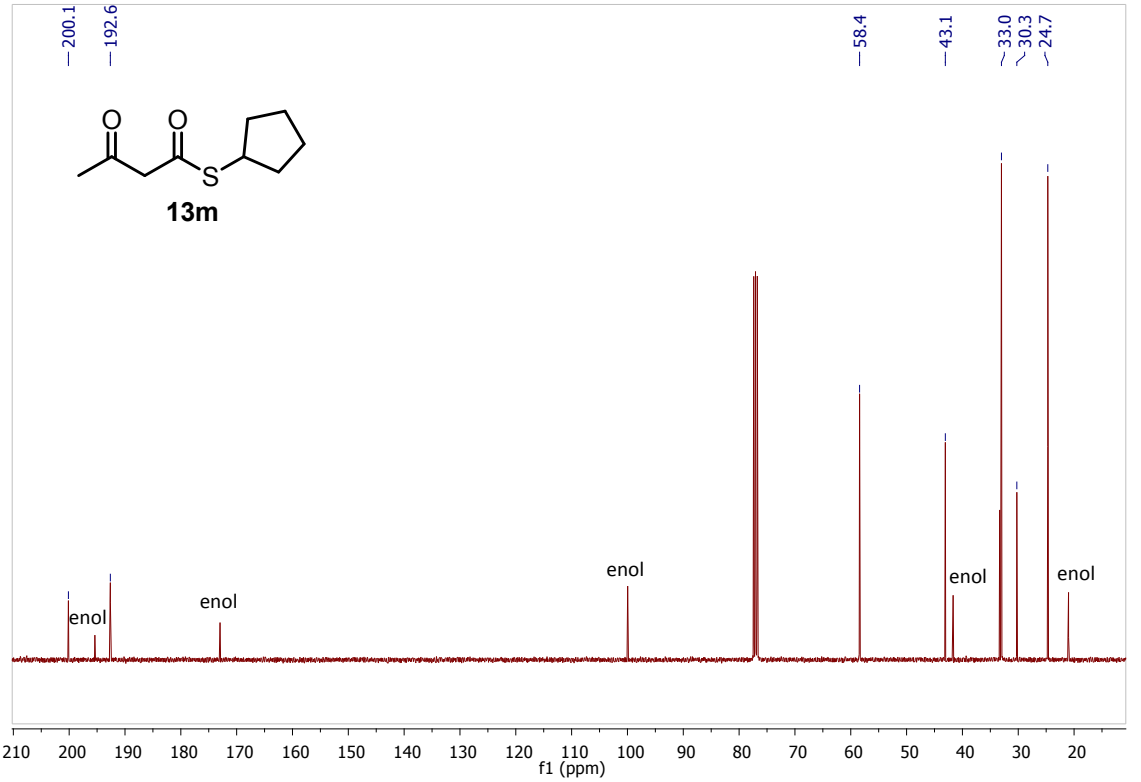


Fig S39. ^{13}C NMR spectrum for β-ketothioate **13m**.

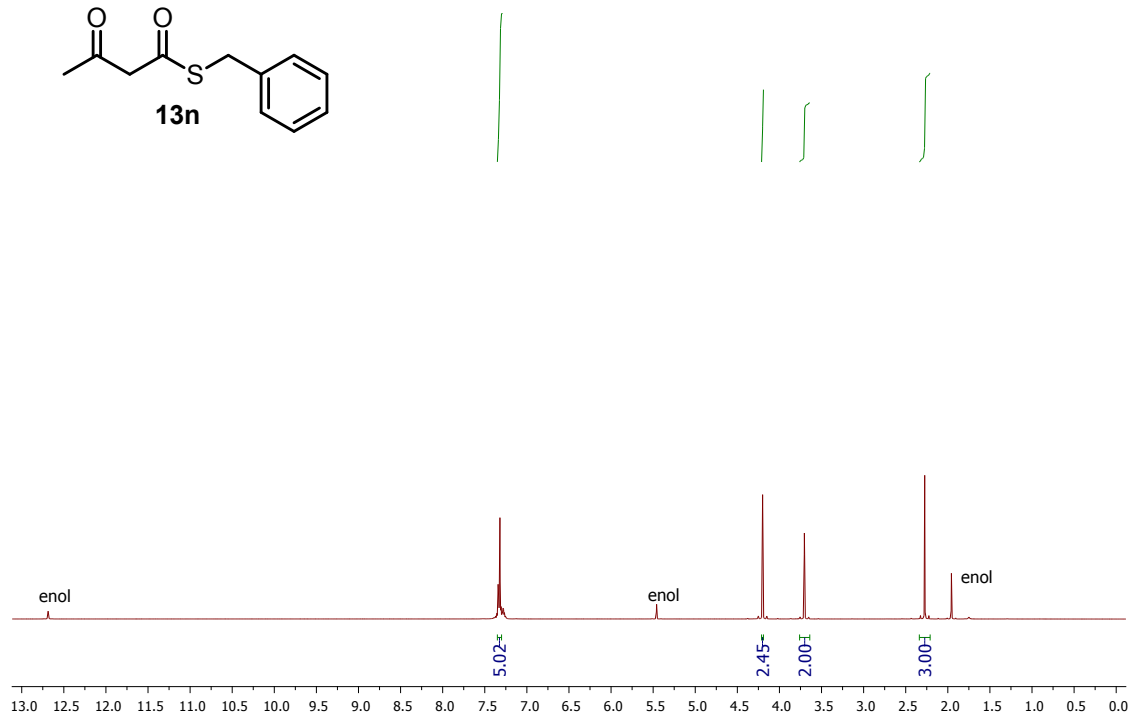


Fig S40. ^{1}H NMR spectrum for β-ketothioate **13n**.

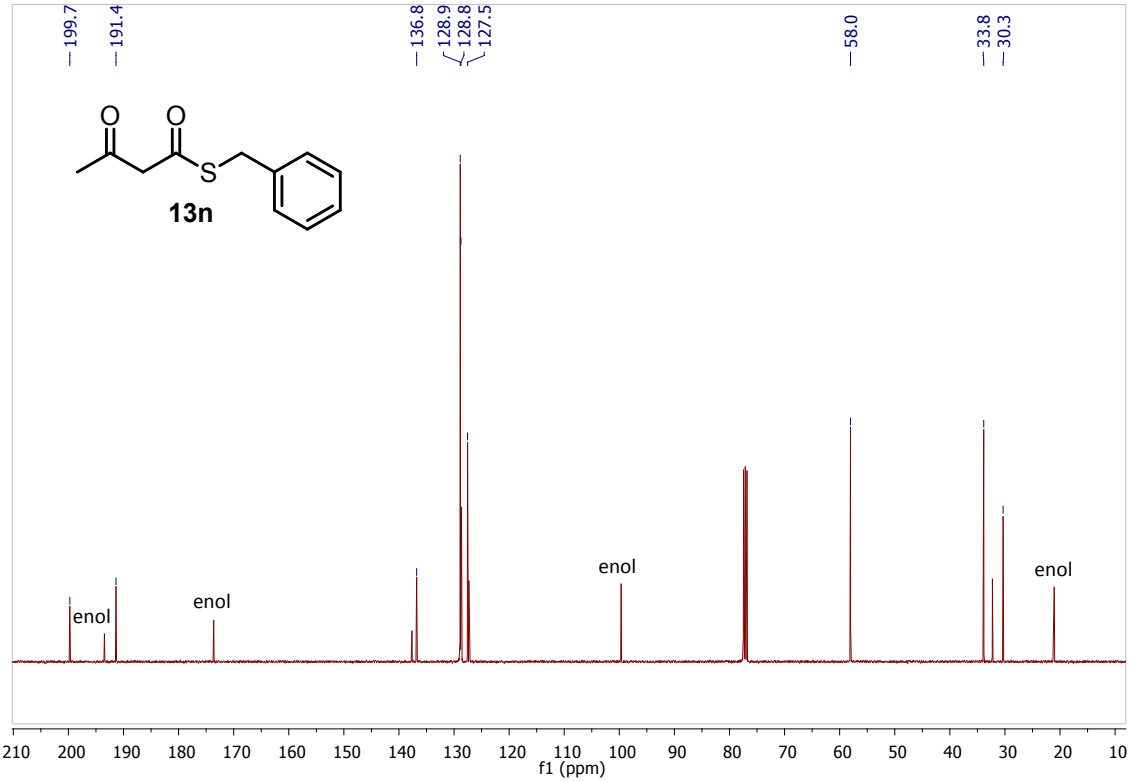


Fig S41. ^{13}C NMR spectrum for β-ketothioate **13n**.

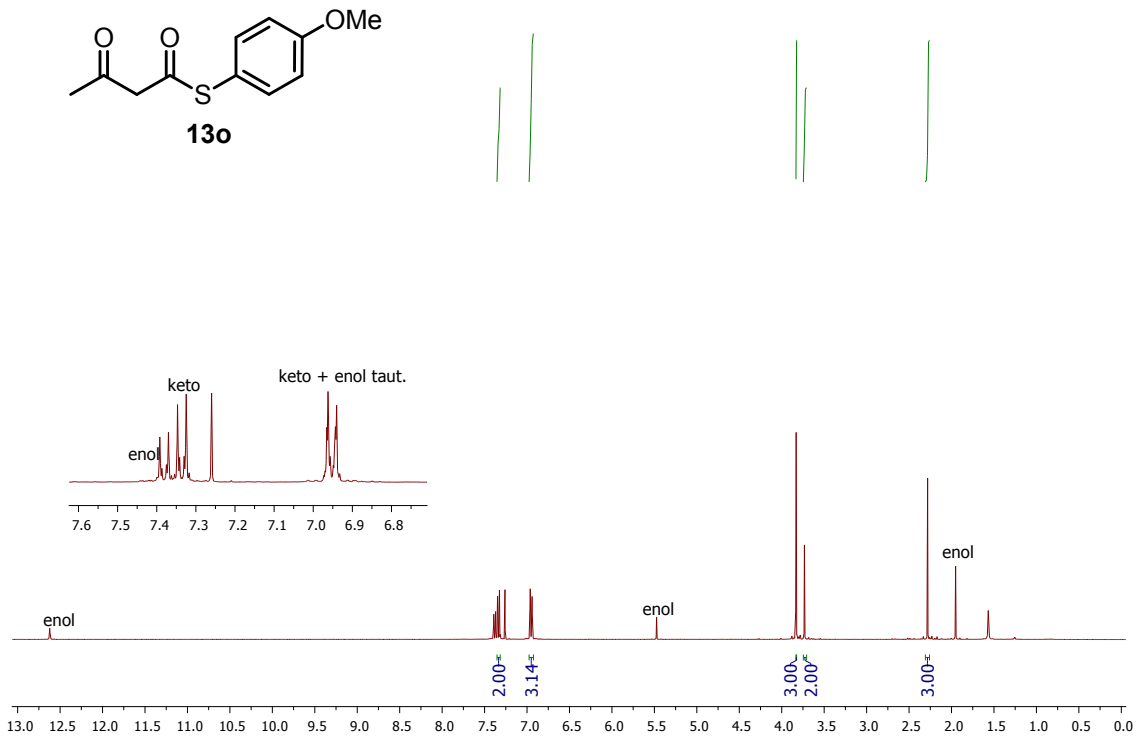


Fig S42. ^{1}H NMR spectrum for β-ketothioate **13o**.

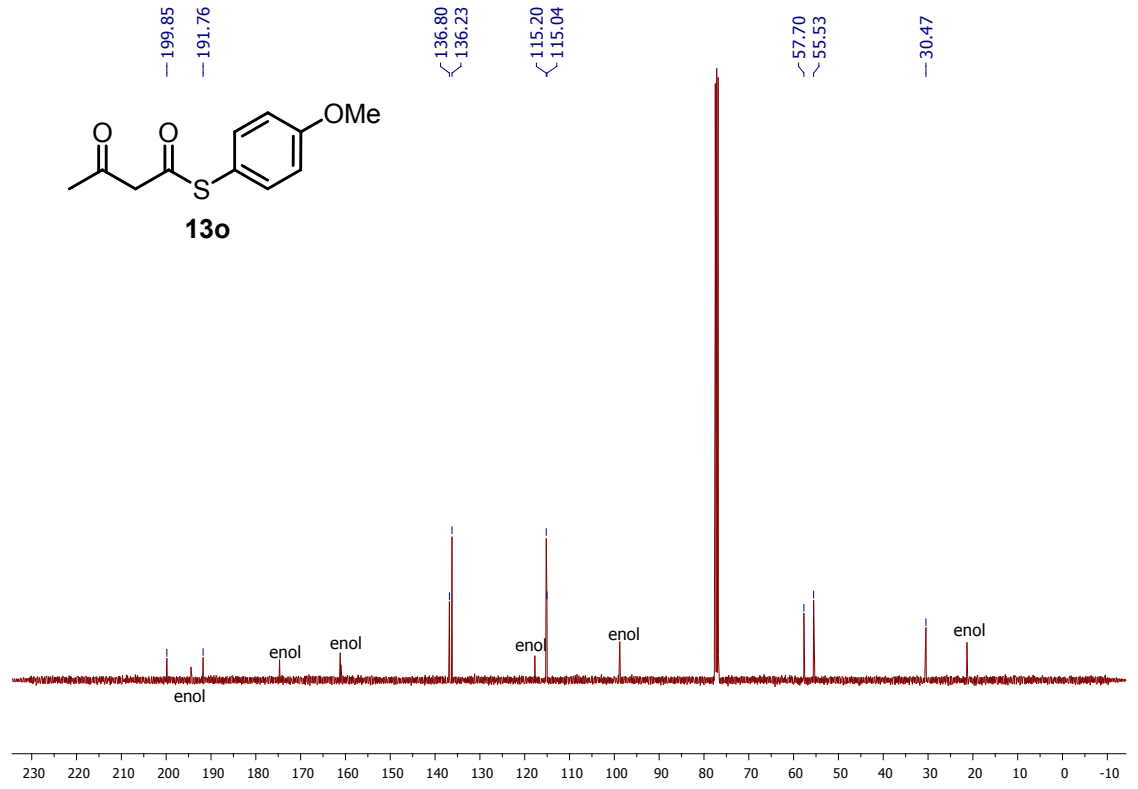


Fig S43. ^{13}C NMR spectrum for β-ketothioate **13o**.

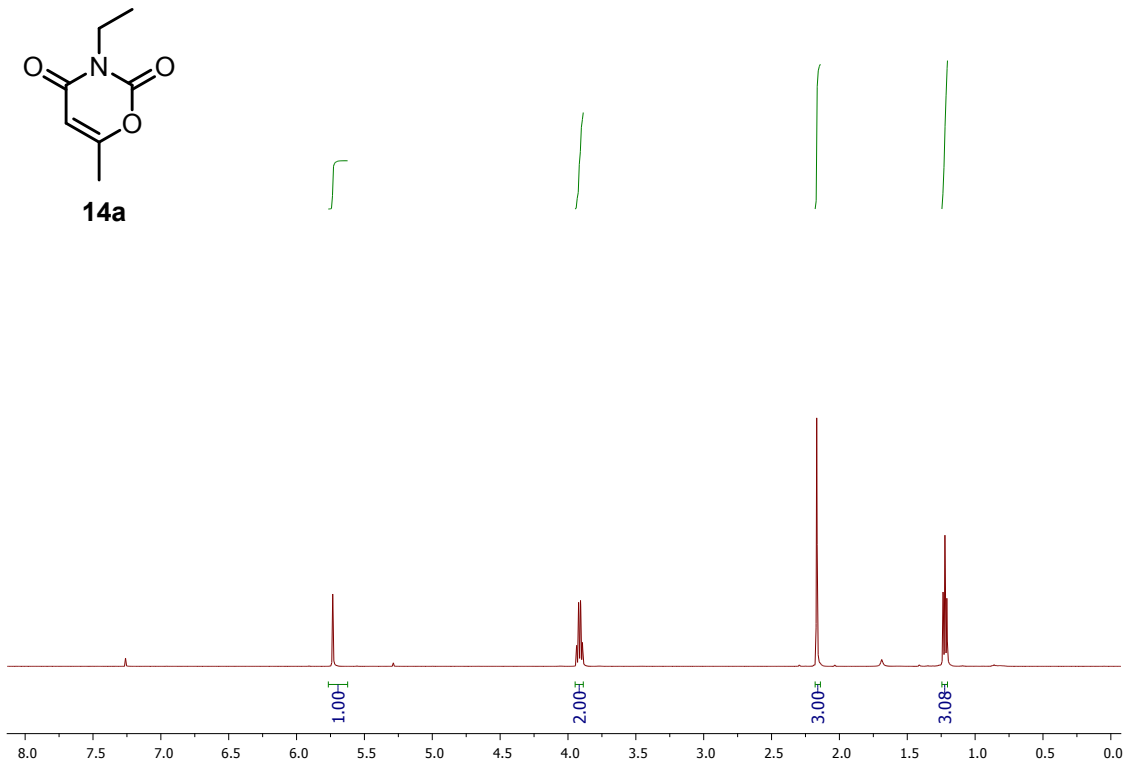


Fig S44. ^{1}H NMR spectrum for 1,3-oxazine-2,4-dione **14a**.

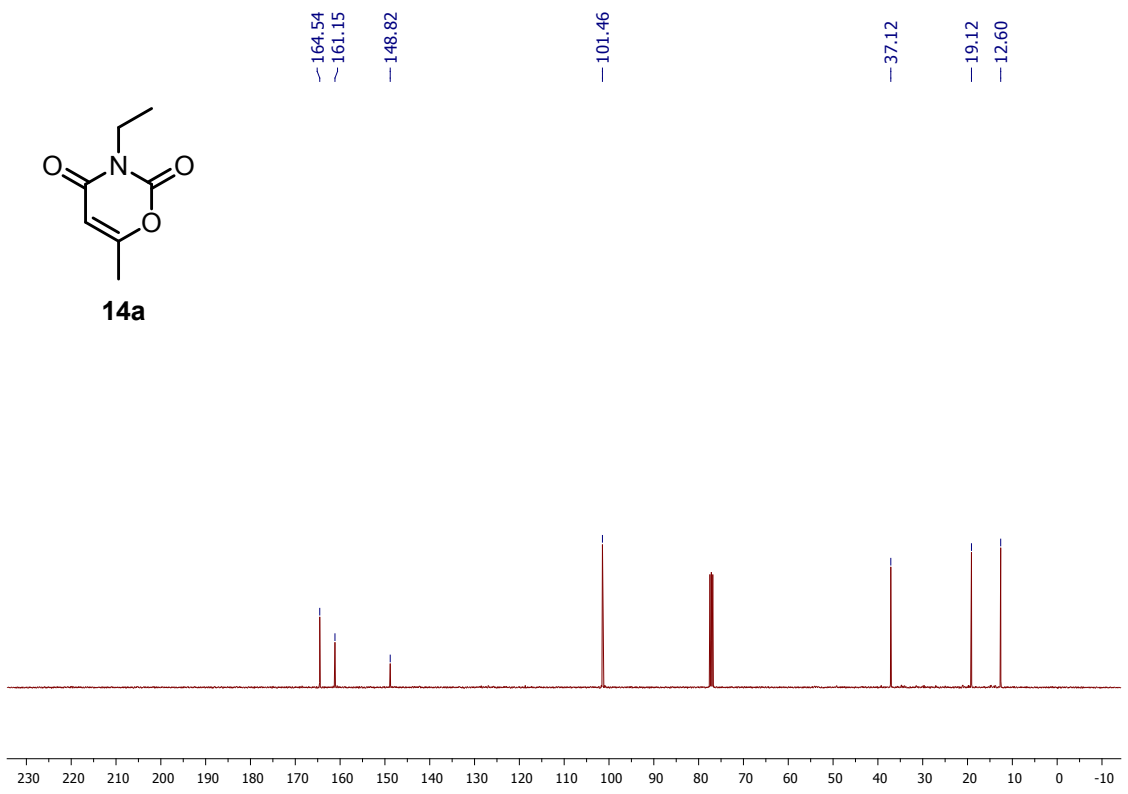


Fig S45. ^{13}C NMR spectrum for 1,3-oxazine-2,4-dione **14a**.

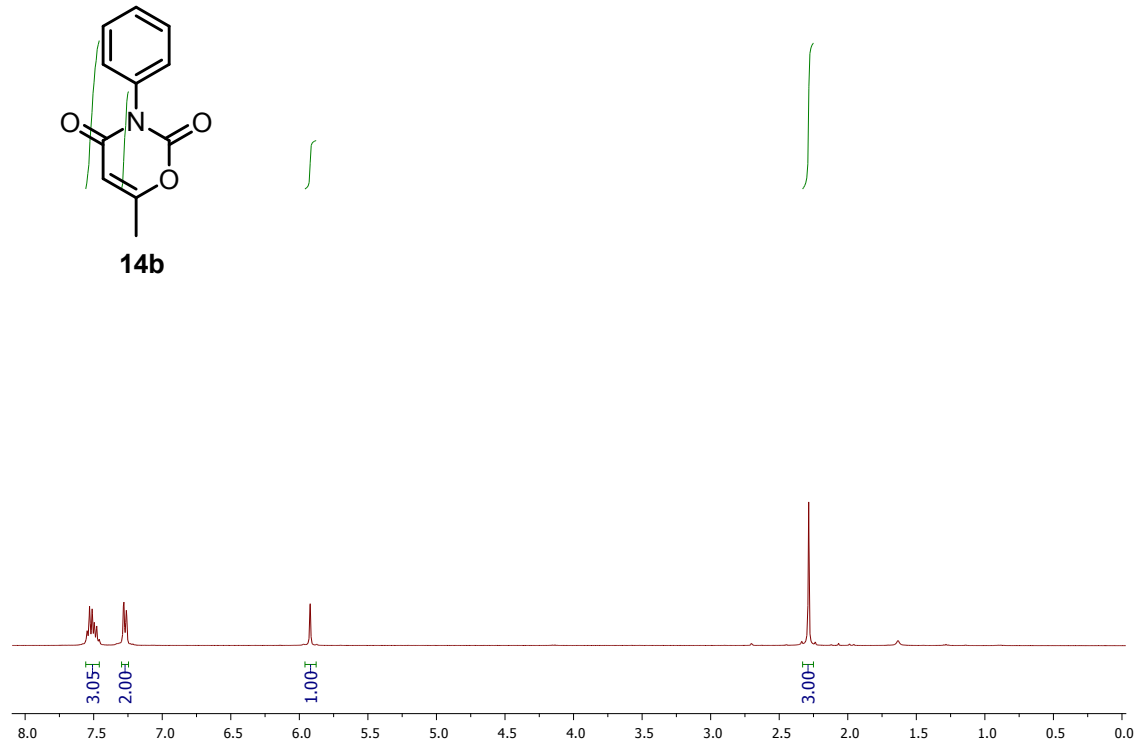


Fig S46. ^{1}H NMR spectrum for 1,3-oxazine-2,4-dione **14b**.

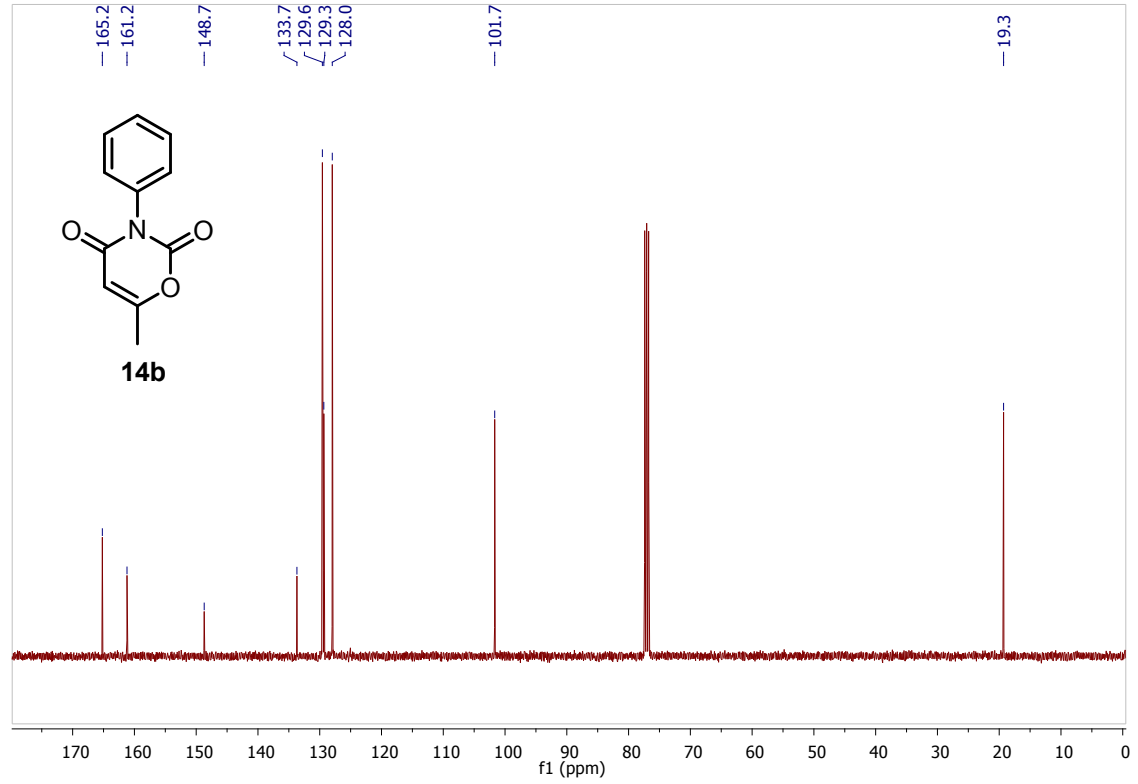


Fig S47. ^{13}C NMR spectrum for 1,3-oxazine-2,4-dione **14b**.

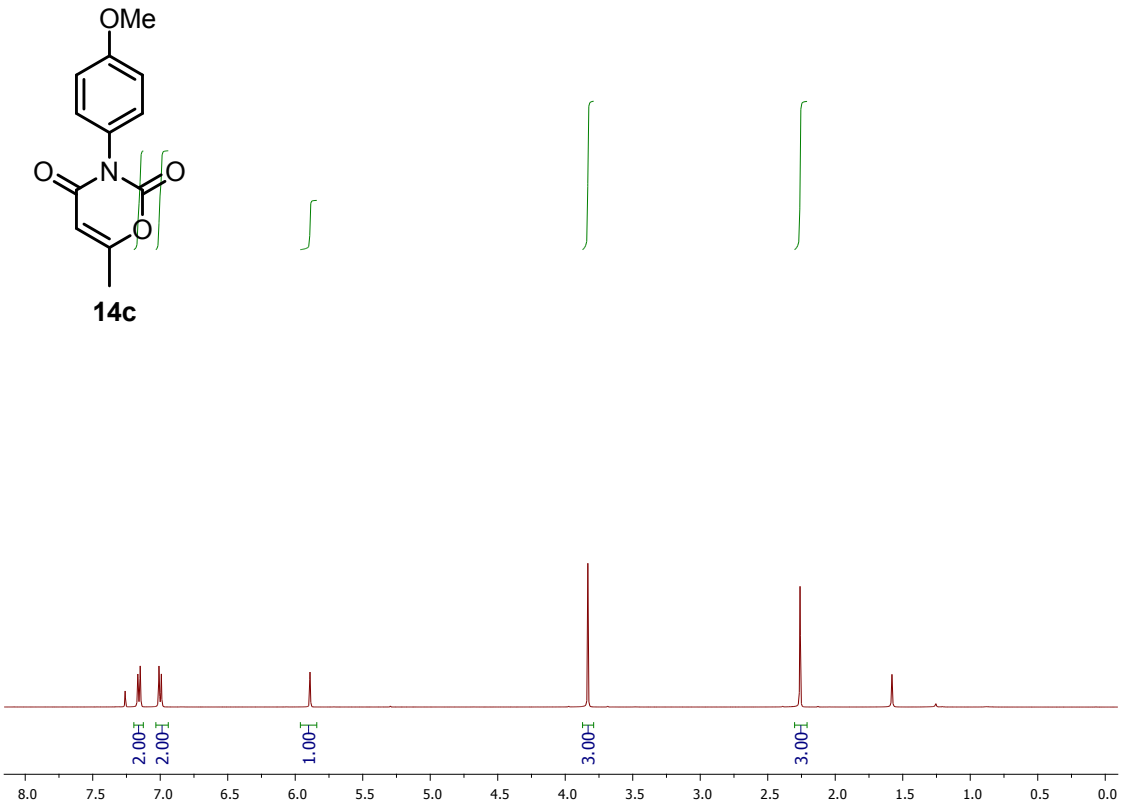


Fig S48. ^{1}H NMR spectrum for 1,3-oxazine-2,4-dione **14c**.

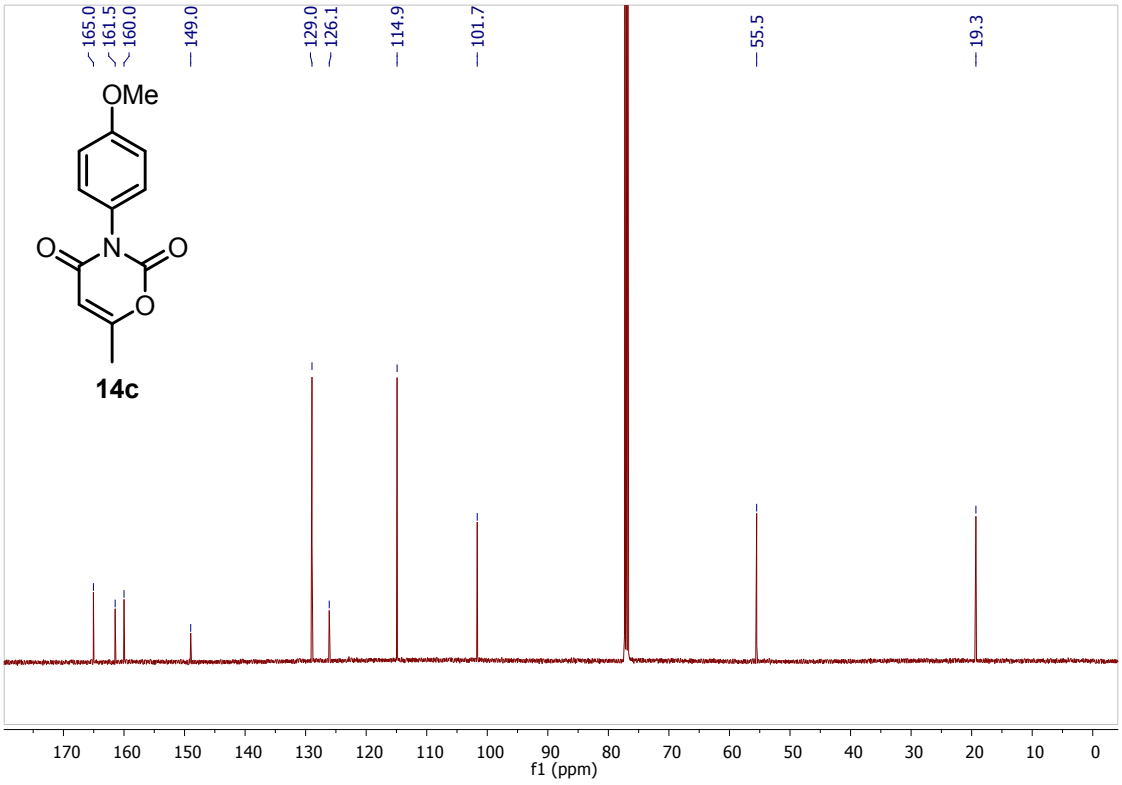


Fig S49. ^{13}C NMR spectrum for 1,3-oxazine-2,4-dione **14c**.

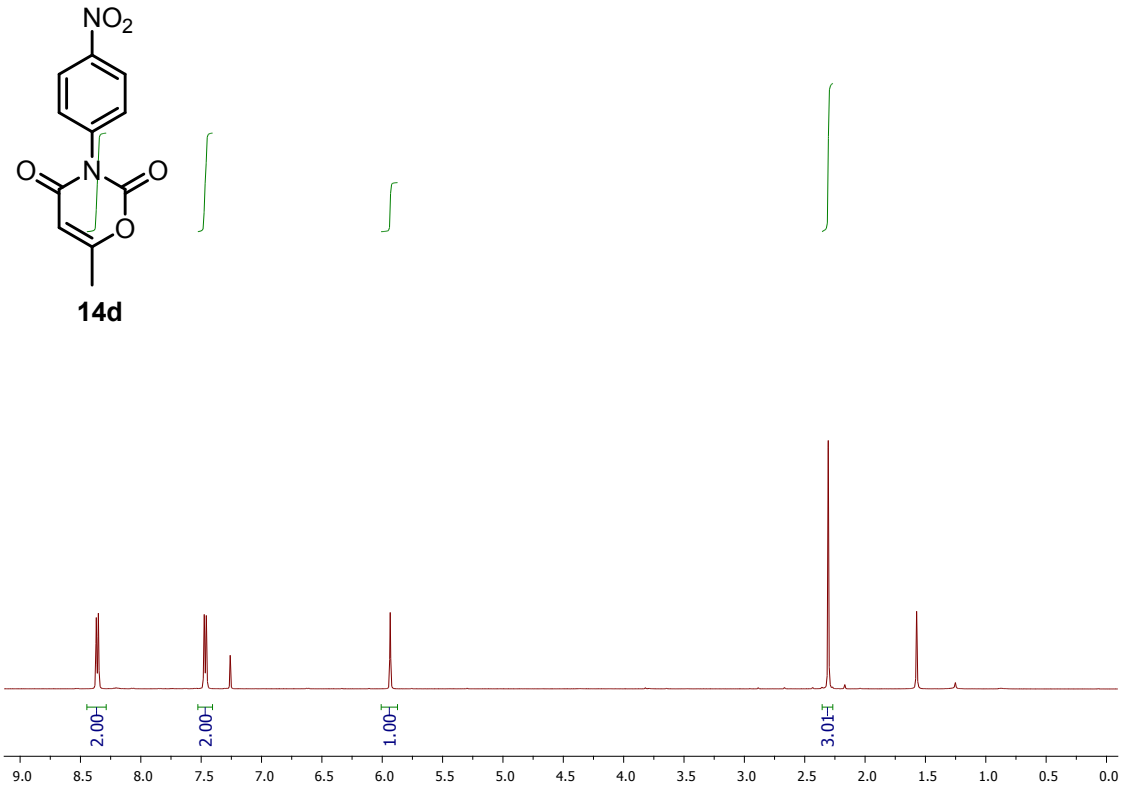


Fig S50. ^{1}H NMR spectrum for 1,3-oxazine-2,4-dione **14d**.

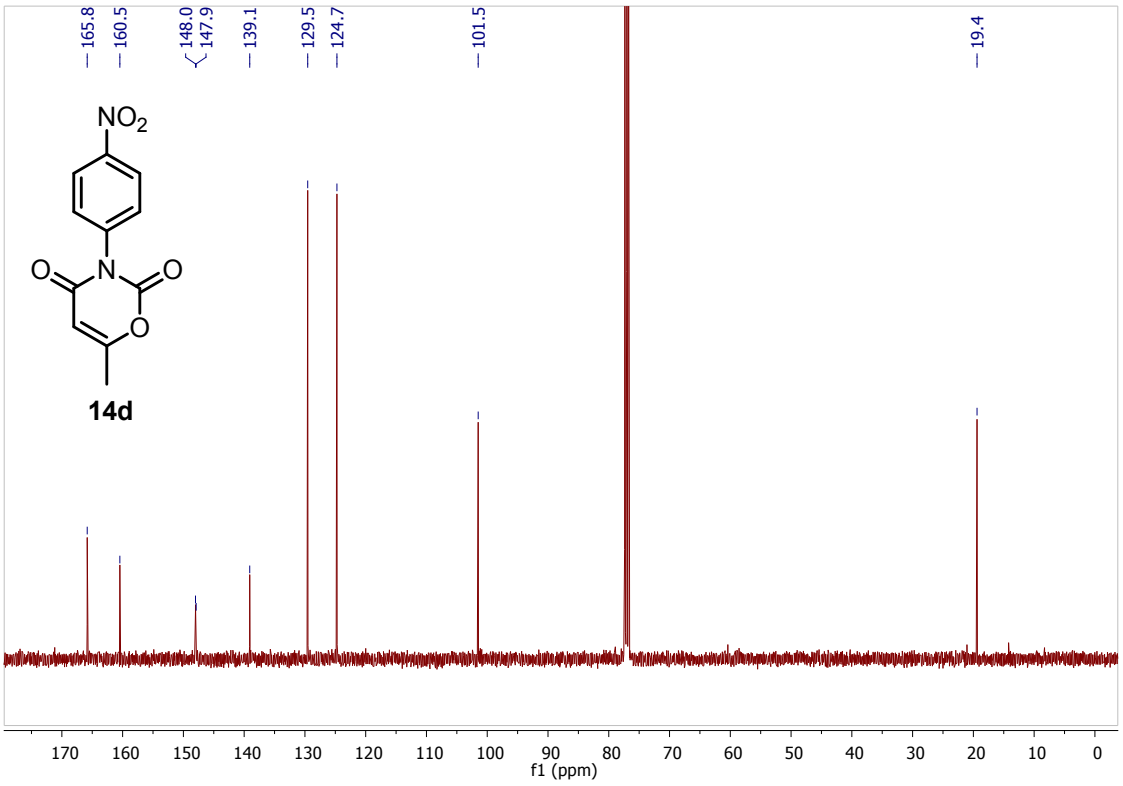


Fig S51. ^{13}C NMR spectrum for 1,3-oxazine-2,4-dione **14d**.

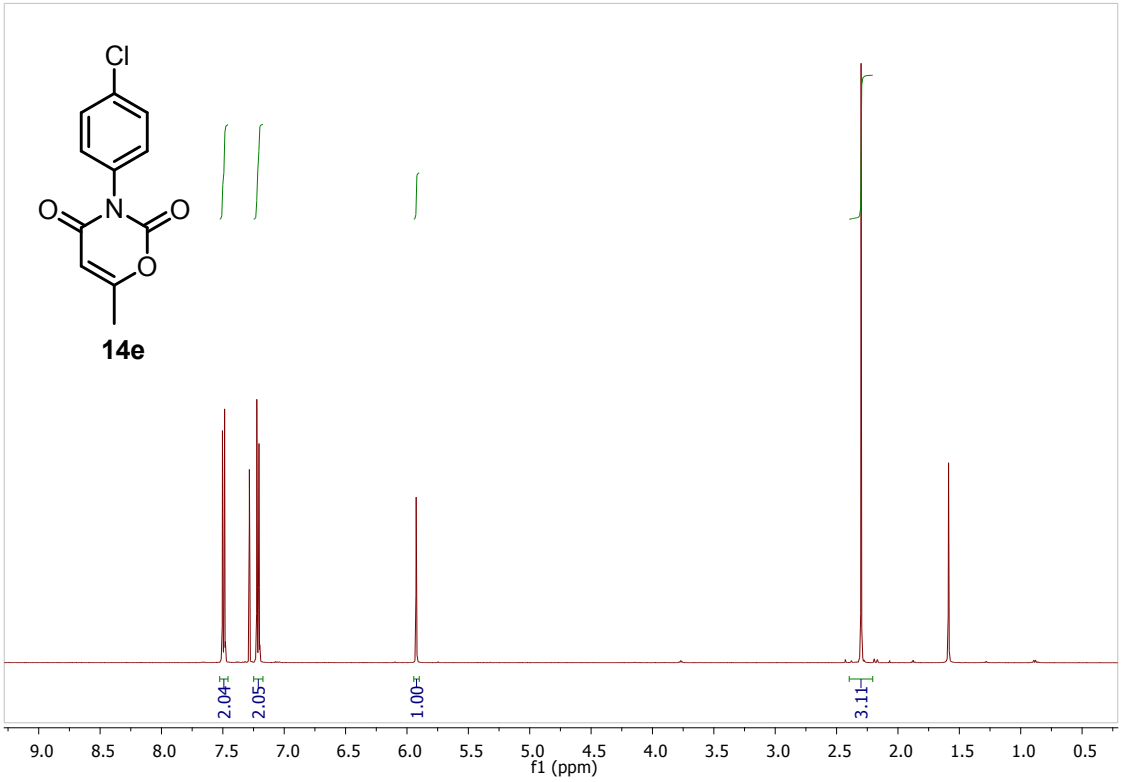


Fig S52. ^{1}H NMR spectrum for 1,3-oxazine-2,4-dione **14e**.

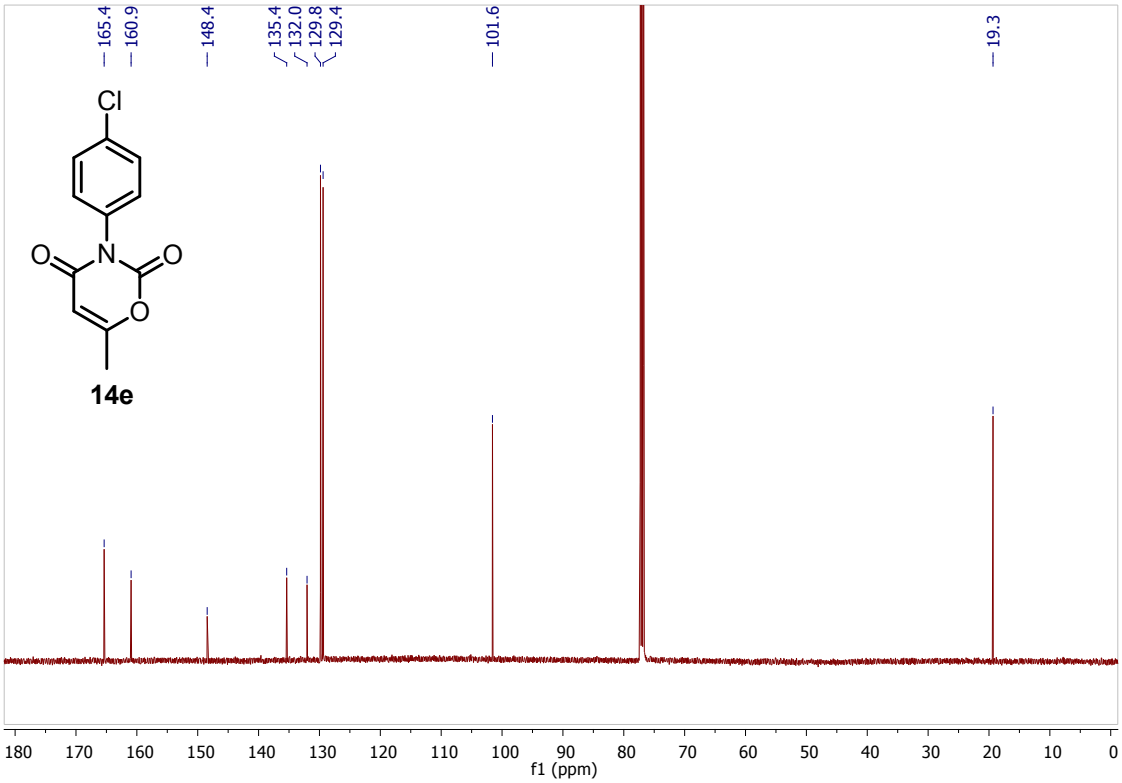


Fig S53. ^{13}C NMR spectrum for 1,3-oxazine-2,4-dione **14e**.

6. References

1. P. Filipponi, A. Gioiello and I. R. Baxendale. *Org. Process Res. Dev*., 2016, **20**, 371.
2. E. V. Dehrnlow and A. R. Shamout. *Liebigs Ann. Chem.* 1982, 1753.
3. M. Alvaro, H. Garcia, S. Miguel and M. J. Primo. Tetrahedron. 1987, **43**, 143.
4. H. Yue, H. Yu, S. Liuab and C. Xu. *RSC Adv*. 2016, **6**, 19041.
5. B. R. Madje, P. T. Patil, S. S. Shindalkar, S. B. Benjamin, M. S. Shingare and M. K. Dongare. *Catal. Commun.* 2004, **5**, 353.
6. J.Christoffers, H. Oertling, P. Fischer and W. Frey. *Tetrahedron,* 2003, **59**, 3769.
7. P. A. Peixoto, A. Boulangé, S. Leleu and X. Franck. *Eur. J. Org. Chem*. 2013, 3316.
8. X. Feng, J-J. Wang, Z. Xun, Z-B. Huang and D-Q Shi. *J. Org. Chem*., 2015, **80**, 1025.
9. N. Döben, H. Yan, M. Kischkewitz, J.Mao and A. Studer. *Org. Lett*., 2018, **20**, 7933.
10. K. Sirisha, G. Achaiah and V. M. Reddy. *Arch. Pharm. Chem. Life Sci*. 2010, **343**, 342.
11. C. S. Morrison, J. B. Lampe, T. C. Kolodziejczyk, R. J. Cavazos and R. A. Petros. *Tetrahedron Lett*. 2014, **55**, 6547.
12. J-I, Sakaki, S. Kobayashi, M. Sato and C. Kaneko. *Chem. Pharm. Bull.* 1989, **37**, 2952
13. Nakazumi, H. and T. Kitao. *Chem. Lett*., 1978, **7**, 929.
14. G. Jager. *Liebigs Ann. Chem*. 1976, 1689.