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

Electronic Supplementary Information

Continuous Flow Oxidation of Alkynes with $KMnO_4$ for the Synthesis of 1,2-Diketone Derivatives

Viktoria Velichko,[a] Dario Cambiè[b*] and Francesco Secci[a*]

a) Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Complesso Universitario di Monserrato, 09042, Monserrato (Cagliari) Italy, e-mail: fsecci@unica.it

b) Max Planck Institute of Colloids and Interfaces, Biomolecular Systems Department, Am Mühlenberg 1, 14476 Potsdam, Germany, e-mail: dario.cambie@mpikg.mpg.de

Table of contents

1. General remarks

Unless stated otherwise, respectively the synthesis of compounds **2** were performed at room temperature using a continuous flow system ad described in the corresponding procedures. During the set-up studies, a stoichiometric amount of internal standard (1,2,4,5-tetracloro-3-nitrobenzene) was added to the alkyne stock solutions. Moreover, the synthesis of the same compounds were attempted in batch to compare the continuous flow performances. Commercially available alkynes **1** (TCI, Fluorochem and Merck) were used as received unless otherwise noted. Al the organic solvents used in this work have to be considered HPLC grade. $_{1}$H NMR spectra were recorded on Bruker Ascend 400, and Varian 500 MHz spectrometers at 300.15 K using $CDCl_3$ (ref. 7.27 ppm), as a solvent. $_{13}$C NMR were recorded at 126 MHz (ref. $CDCl_3$ 77.00 ppm) at 300.15 K. Chemical shifts (□) are given in ppm. Coupling constant values (*J*) are reported in Hz. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), tt (triplet of triplets). Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers (cm^{-1}). Low Mass Spectra Analysis were recorded on an Agilent-HP GC-MS (E.I. 70eV). High Resolution Mass Spectra (HRMS) were obtained using a Bruker High Resolution Mass Spectrometer in fast atom bombardment (FAB^+) ionization mode. Melting points were determined with a Büchi M-560. Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merk 70-200 mesh silica gel. Yields refer to chromatography and spectroscopically pure materials when indicated or as the result of the continuous flow oxidation process. qNMR yields were calculated using 1,2,4,5-tetracloro-3-nitrobenzene as an internal standard by the integration of the selected peaks. For continuous flow processes syringe pumps Harvard Apparatus Elite11 and HPLC pumps KNAUER, Azura P 4.1S were used.

2. Reaction conditions screening

2.1. 2 mL reactor continuous flow set-up

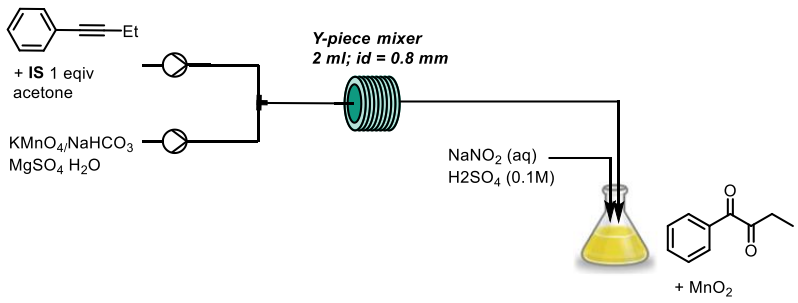


Figure S1. 2 mL continuous flow set-up

10 ml syringes were settled on two syringe pump streams. The first stream contains a solution of 1-phenyl-1-butyne (33.33 mg, 0.25 mmol) and 1,2,4,5-tetracloro-3-nitrobenzene (1 eq) in acetone (10 mL). The second stream contains a water solution (10 mL) of $KMnO_4$ (166 mg, 1.05 mmol), $NaHCO_3$ (12.6 mg, 0.15 mmol), $MgSO_4$ in H_2O (61.4 mg, 0.51 mmol). These streams were mixed via a Y-piece before entering the coil (PTFE) reactor (total Vol: 2mL, *i.d.*: 0.8 mm, length: 400 cm) for indicated times at room temperature

(table S1, Figure S1). To avoid clogging, the coil reactor was placed into a thermoregulated ultrasound bath at 22-24° C. The resulting reaction mixture was collected into an Erlenmeyer flask and kept under stirring. Then a $NaNO_2$ (79.3 mg, 1.1 equiv., 1.15 mmol) and 0.1 M H_2SO_4 (10 mL) water solution was added continuously to abate the excess of $KMnO_4$. Extractions performed with DCM followed by removal of the solvent under reduced pressure provided desired products (Figure S2).

Table S1. screening of reaction conditions

Entry	Residence time [min]	Product [qNMR yield%][a]	Starting material [qNMR yield%][a]
1	60[b]	>99	0
2	45[b]	>99	0
3	30[b]	85	15
4	15	75	25
5	10	66	33
6	5	29	70

[a] Calculated by ^{1}HNMR on the crude reaction mixture
[b] Residence time 30 min, 45 min, 60 min led to major clogging problem despite of ultrasonic bath employment

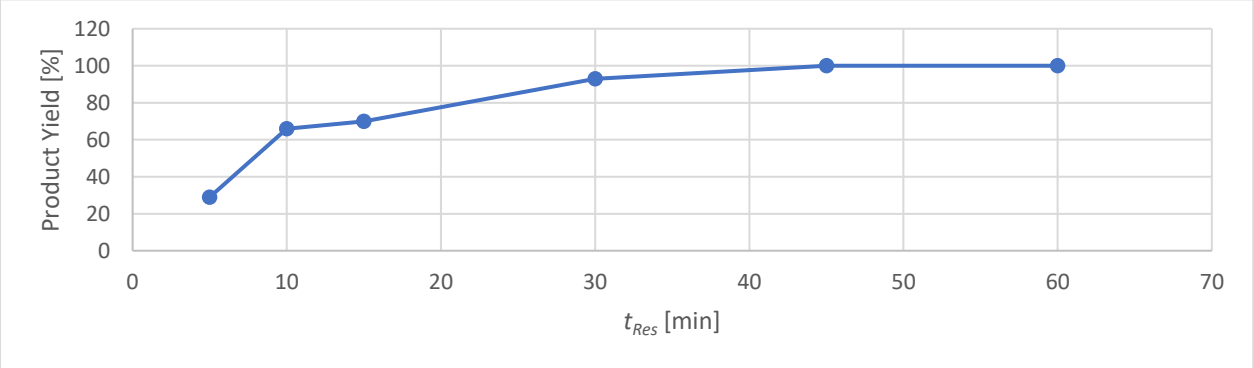


Figure S2. Residence time (t_{Res}) screening

Table S2. Concentration screening

Entry	Molarity of solution [M]	Product [qNMR yield%][a]	Productivity (mmol/h)
1	0.025	78	0.15
2	0.05	70	0.28
3	0.06	70	0.33
4	0.1[b]	70	0.56
5	0.15[b]	70	0.84
6	0.20[b]	50	0.82

[a] Calculated by ^{1}HNMR on the crude reaction mixture
[b] Concentrations 0.102 M, 0.153 M, 0.204 M min led to major clogging problem despite of ultrasonic bath employment

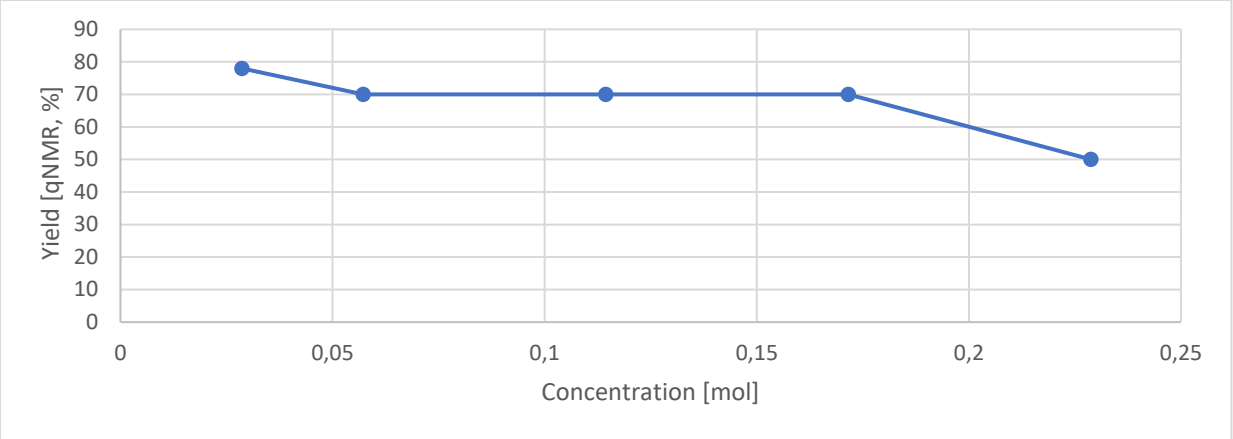


Figure S3. Concentration screening

Calculated productivity:

$$\text{Productivity (mmol/h)} = \left(\frac{moles\ of\ product\ fomed}{residence\ time\ (h)}\right) \times 1000$$

From collecting 2 mL of 0.025 M solution containing 1-phenyl-buta-1.2-dione **2a**, we calculate productivity based on a 78% yield determined by qNMR, as detailed in Table S2, entry 1:
(0.025*0.002L)*0.78=0.000039 moles of product formed (entry 1, Table S2)
Residence time: 15 min/60 min = 0,25 h
Productivity: 0.000039moles/0.25*1000=0.15 mmol/h

Table S3. Reactor parameters (Screening)

Entry	Tubing diameter	Tubing lenght	Reactor volume	Product [qNMR yield%][a]
1	0.8 mm	4 m	2 mL	78%
2	1.5 mm	1.7 m	2 mL	>99%

[a] Calculated by ^{1}HNMR on the crude reaction mixture

Table S4. Reactor parameters (Optimized)

Entry	Tubing diameter	Tubing lenght	Reactor volume
1	1.5 mm	3.4 m	4 mL
2	1.5 mm	4.53 m	8 mL

Table S5. Solvent Screening

Ethyl acetate and dichloromethane were tested as reaction solvents in place of acetone with the idea of working with a biphasic system and facilitating the separation of the reaction product, without modifying the initial set up. However, experiments conducted with these solvents have given poor results. Therefore it was decided to introduce a solvent delivery that would allow the diketone compound to be efficiently extracted from the water/acetone mixtures. Given the availability on the market of specific membranes, to be used in L/L separators, dichloromethane was chosen as the extraction solvent (See General Procedure 3).

Entry	Solvent	Product [qNMR yield%][a]
1	Acetone	>99%
2	Ethyl Acetate	>1%
3	Dichloromethane	>1%

[a] Calculated by ^{1}HNMR on the crude reaction mixture

3. General procedure for the continuous-flow $KMnO_4$ promoted oxidation of alkynes with in-line liquid-liquid extraction

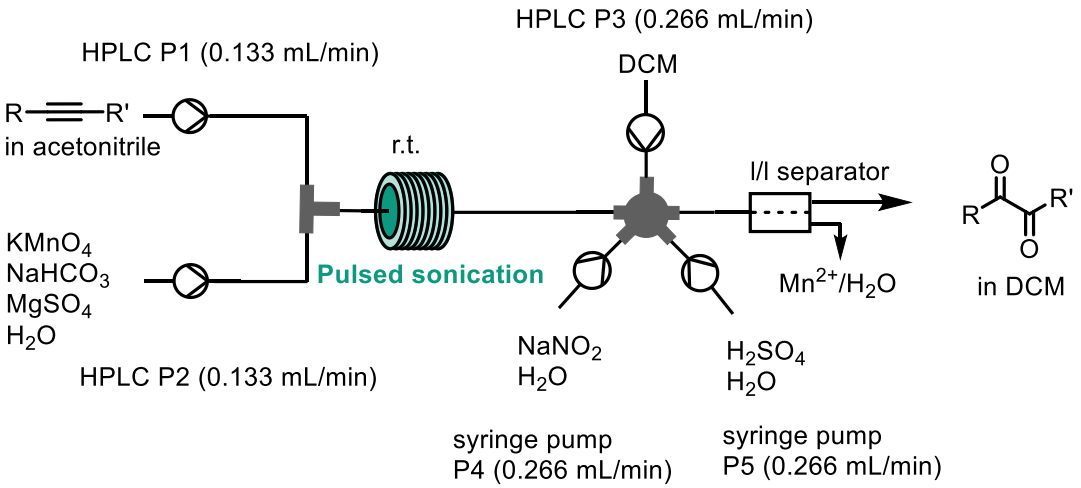


Figure S4. Continuous flow set-up adapted for the synthesis of compounds **2** and **3**

A peek Y-shaped micromixer (inner volume = 0.50 mL), a PTFE microtube reactor (4 mL, diameter = 1.5 mm, length = 2.26 cm), and a multimixer (inner volume = 0.50 mL), were employed (Figure S4 and S5). The 0.05M solution of alkyne (stock solution of 30 mL) (flow rate: 0.13 mL/min) and a 0.2 M solution of $KMnO_4$ (in H_20), 0.03 M $NaHCO_3$, 0.1 M $MgSO_4$ in water (flow rate: 0.13 mL/min), were delivered by the HPLC pumps **P1** and **P2** respectively, into the Y-shaped peek micromixer. The resulting mixture (total flow rate 0.266 mL/min) passed through a coil reactor (4 mL, t_{Res}: 15 min), dipped in a sonication bath and kept at 22-24 °C. A second multimixer was connected with the reactor output to deliver DCM (0.266 mL/min) by the HLPC pump **P3**. A 0.1 M solution of $NaNO_2$ in water (flow rate: 0.266 mL/min) and a 0.1 M solution

of H_2SO_4 (flow rate: 0.266 mL/min) were delivered by two syringe pumps as described in the Figure S4. The resulting solution was then introduced to a Zaiput SEP-10 device equipped with hydrophobic PTFE OB-900 pore size membrane. The resulting aqueous and organic phases were collected separately. At steady-state conditions (two reactor volumes) the organic phase, containing the desired products, was collected for a duration necessary to process the entire volume of reactants but also subsequent quenching, extraction and separation: approximately 225.56 minutes. Removal of organic solvents under reduced pressure provided the desired products **2.**

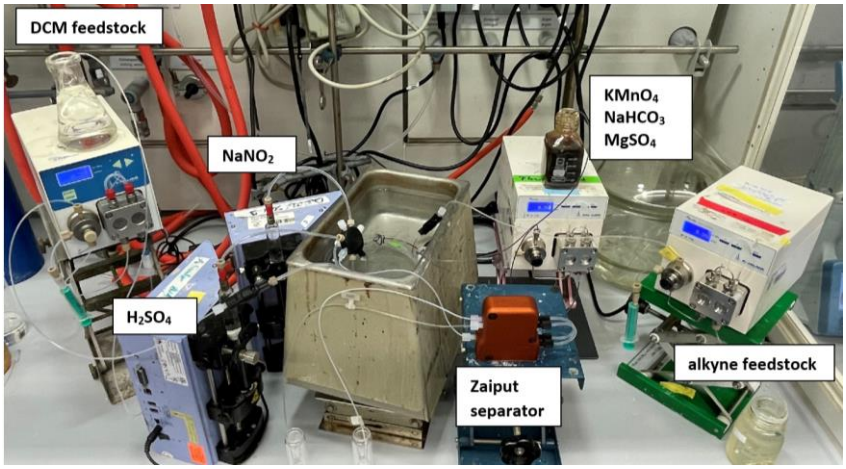


Figure S5. Continuous flow set-up adapted for the synthesis of compounds **2**

3.1. Representative continuous flow synthesis of 2,3-pentanedione 2g

A solution of 2-pentyne **1g** (30 mL, 0.05 M in acetone, 1.53 mmol; flow rate = 0.133 mL/min) and a solution of $KMnO_4$ (4 eq, 6.12 mmol), $NaHCO_3$ (0.6 eq, 0.9 mmol), $MgSO_4$ (2 eq, 3.06 mmol) in water (30 mL, flow rate: 0.133 mL/min), were delivered into a Y-shaped peek micromixer by HPLC pumps. The resulting mixture (total flow rate 0.266 mL/min) was passed through a coil microreactor (4 ml, t_{Res} = 15 min) dipped into a sonication bath kept at 22-24°C. A second multimixer was connected with the reactor output to deliver DCM (0.266 mL/min) by a third HLPC pump. A 0.1 M solution of $NaNO_2$ (flow rate: 0.266 mL/min) and a 0.1 M solution of H_2SO_4 (flow rate: 0.266 mL/min) were delivered by two syringe pumps as described in the Figure S4. The resulting solution was then introduced to a Zaiput SEP-10 device equipped with hydrophobic PTFE OB-900 pore size membrane. The resulting aqueous and organic phases were collected separately. At steady-state conditions (two reactor volumes) the organic phase, containing desired products, was collected for a duration necessary to process the entire volume of reactants but also subsequent quenching, extraction and separation: approximately 225.56 minutes. Removal of organic solvents under reduced pressure provided the desired product **2g** (2,3-pentanedione) in 67% yield (100,5 mg).

3.2. Scale-up continuous flow synthesis of 1-phenylbutane-1,2-dione 2a

A peek Y-shaped micromixer (inner volume= 0.5 mL), a PTFE microtube reactor (8 mL, diameter = 1,5 mm, length = 453 cm), and a multimixer (inner volume= 0.5 mL), were employed.
A 205.8 mL solution of 4-phenyl-1-butyne **1a** (0.05 M in acetone, 10.5 mmol, flow rate: 0.272 mL/min) and a 0.2M solution of $KMnO_4$ (4 eq, 42 mmol) , $NaHCO_3$ (0.6 eq, 6.3 mmol), $MgSO_4$ (2 eq, 27.6 mol) in 205.8 mL of water (flow rate: 0.272 mL/min) , were delivered into a Y-shaped peek micromixer by HPLC pumps. The resulting mixture (total flow rate 0.544 mL/min) was passed through a coil microreactor (t_{Res} = 15 min) , dipped into a ultrasonic bath kept at 22-24°C. A second multimixer was connected with the reactor output to deliver DCM (flow rate: 0.544 mL/min) by a third HLPC pump. A water solution of 0.1 M $NaNO_2$ (flow rate: 0.544 mL/min) and a water solution of 0.1M H_2SO_4 (flow rate: 0.544 mL/min) were delivered by two HPLC pumps as shown in the Figure S6. The resulting solution was then introduced to a Zaiput SEP-10 device equipped with hydrophobic PTFE OB-900 pore size membrane. The resulting aqueous and organic phases were collected separately. After achieving steady-state conditions (two reactor volumes), and continuous 12-hours reaction (collected volume of organic phase after work-up and quenching approximately 587.5 mL), removal of organic solvents under reduced pressure provided the desired product **2a** (1-phenylbutane-1,2-dione) in 90% yield (1.44 g).

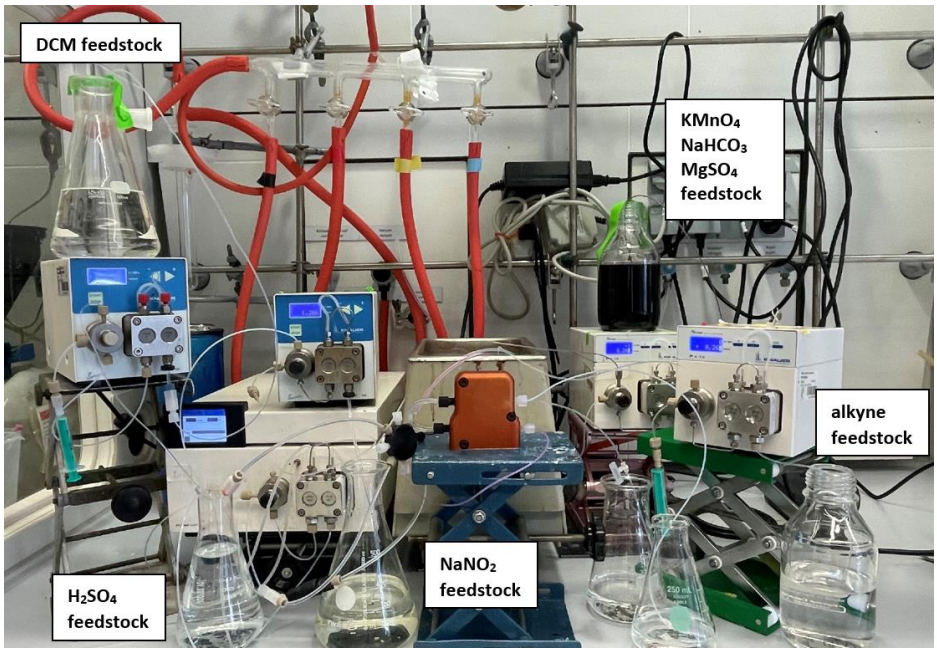
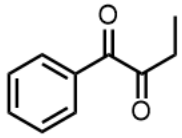
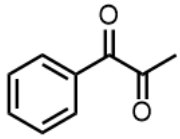


Figure S6. Scale-up continuous flow set-up adapted for the synthesis of compounds **2**

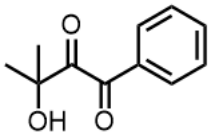
4. ^{1}H and ^{13}C NMR Characterization of compounds 2, 4, 5, 6



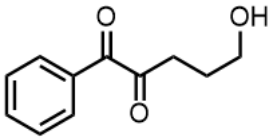
1-phenylbutane-1,2-dione 2a. Yellow oil, 90% yield (208.4 mg) . ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 2.90 (q, J = 7.3 Hz, 2H), 1.18 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 203.8, 192.4, 132.0, 130.0, 128.7, 32.0, 6.8. Spectral data are in agreement with the literature.[1]



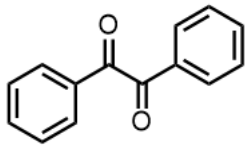
1-phenylpropane-1,2-dione 2b. Yellow oil, 93% yield (206.68 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.07 (m, 2H), 7.55-7.52 (m, 1H), 7.40-7.38 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 200.5, 191.3, 134.5, 131.7, 130.3, 128.8, 26.3. Spectral data are in agreement with the literature.[2]



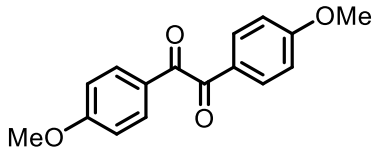
3-hydroxy-3-methyl-1-phenylbutane-1,2-dione 2c. Yellow solid, 92% yield (265.24 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95-7.93 (m, 2H), 7.60-7.56 (m, 1H), 7.45-7.41 (m, 2H), 6.26 (br, s, 1H) 2.46 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ: 200.6, 191.4, 134.6, 131.7, 130.3, 130.2, 128.8, 128.5, 30.9, 26.4. Spectral data are in agreement with the literature.[3]



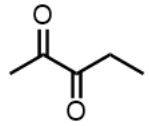
5-hydroxy-1-phenylpentane-1,2-dione 2d. Yellow oil, overall yield 70% (201.82 mg). ^{1}H NMR (400 MHz, CDCl3) δ 8.00-7.98 (d, *J* = 7.5 Hz, 2H) □: 7.67-7.65 (m, 1H), 7.55-7.28 (dd, *J* = 15.7, 7.9 Hz, 2H), 6.10 (br, s, 1H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.73-1.67 (m, 2H), 1.46-1.40 (dt, *J* = 14.6, 7.4 Hz, 2H). ^{13}C NMR (101 MHz, CDCl3) δ: 203.6,192.6, 188.6, 185.2, 171.4, 134.6, 133.8, 131.9, 130.1, 130.1, 129.1, 128.9,128.8, 128.5, 38.5, 33.6, 30.9, 29.2, 28.2, 26.7, 24.9, 22.3, 22.1, 20.7, 13.8, 13.7. HRMS calcd. for C11H12O3: 192,0786; found [M+]: 192,0791. Spectral data were extrapolated by the mixture of the linear product **2d** and the 2-hydroxy-2-phenyldihydro-2H-pyran-3(4H)-one hemiacetals in a ratio 90:10.



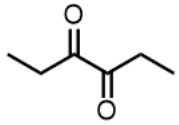
1,2-diphenyl-ethan-1,2-dione 2e. White solid, 95% yield (299.57mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92-7.89 (m, 2H), 7.62-7.58 (m, 1H), 7.48-7.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 194.6, 134.9, 132.9, 131.6, 129.9, 129.0. Spectral data are in agreement with the literature.[2]



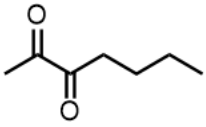
1,2-bis(4-methoxyphenyl)ethane-1,2-dione 2f. Yellow solid, 84% yield (340.55 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (d, J = 9.0 Hz, 4H), 6.97 (d, J = 9.0 Hz, 4H), 3.89 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 193.6, 164.8, 132.4, 126.4, 114.3, 55.6. Spectral data are in agreement with the literature.[8]



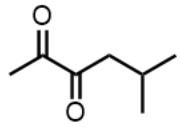
pentane-2,3-dione 2g. Yellow liquid, 67% yield (100.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.82 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.8, 197.5, 29.2, 23.8, 6.9. Spectral data are in agreement with the literature.[4]



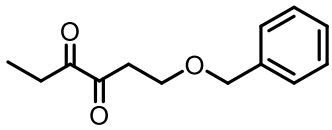
hexane-3,4-dione 2h. Yellow liquid, 84% yield (143.64 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.83-2.77 (q, *J* = 7.2 Hz, 2H), 1.12-1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl^3$) δ: 200.3, 29.6, 6.8. Spectral data are in agreement with the literature.[4]



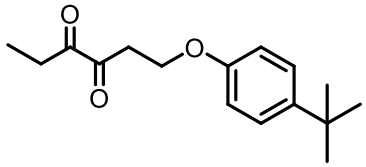
heptane-2,3-dione 2i. Yellow oil, 89% yield (170.88 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.68-2.65 (t, *J* = 7.3 Hz, 2H), 2.26 (s, 3H), 1.51-1.49 (t, 2H), 1.29-1.22 (t, 2H), 0.86-0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 199.5, 197.6, 35.4, 25.1, 23.7, 22.2, 13.7. Spectral data are in agreement with the literature.[4]



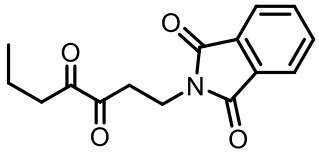
5-methylhexane-2,3-dione 2j. Yellow oil, 50% yield (106.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.56-2.55 (d, *J* = 6.0 Hz, 2H), 2.26 (s, 3H), 0.87-0.86 (t, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 199.2, 197.7, 44.3, 24.2, 23.6, 22.5. Spectral data are in agreement with the literature.[4]



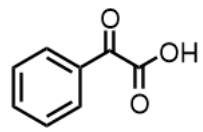
1-(benzyloxy)hexane-3,4-dione 2k. Yellow oil, 87% yield (287.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.56-2.55 (d, *J* = 6.0 Hz, 2H), 2.26 (s, 3H), 0.87-0.86 (t, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 199.2, 197.7, 44.3, 24.2, 23.6, 22.5. Spectral data are in agreement with the literature.[1]



1-(4-(tert-butyl)phenoxy)hexane-3,4-dione 2l . Yellow oil, 88% yield (364.82 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29-7.12 (m, 2H), 6.84-6.61 (m, 2H), 4.19 (t, J = 6.2 Hz, 2H), 3.12 (t, J = 6.2 Hz, 2H), 2.71 (q, J = 7.2 Hz, 2H), 1.21 (s, 9H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.7, 197.3, 156.0, 143.8, 126.2, 114.0, 74.3, 62.4, 36.3, 34.0, 31.4, 29.3. Spectral data are in agreement with the literature.[1]

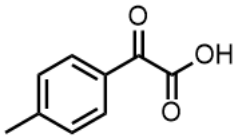


2-(3,4-dioxohexyl)isoindoline-1,3-dione 2m. Yellow oil, 84% yield (362.02 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78-7.70 (m, 2H), 7.70-7.62 (m, 2H), 3.90 (td, J = 6.8, 2.4 Hz, 2H), 3.05 (td, J = 6.8, 1.8 Hz, 2H), 2.67 (td, J = 7.3, 2.4 Hz, 2H), 1.53 (ddd, J = 14.7, 7.3, 2.6 Hz, 2H), 0.93-0.80 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.5, 196.5, 185.7, 168.1, 134.0, 131.5, 123.2, 37.3, 34.9, 32.7, 16.1, 13.3. Spectral data are in agreement with the literature.[1]

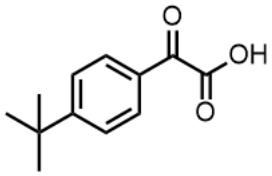


2-oxo-2-phenylacetic acid 2n. White solid, 74% yield (166.64 mg). ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 8.21-8.20 (d, J = 8.0 Hz, 2H), 7.64-7.61 (t, J = 7.6 Hz, 1H), 7.48-7.45 (t, J=7.4 Hz, 2H), 6.90 (br, s, 1H). ^{13}C

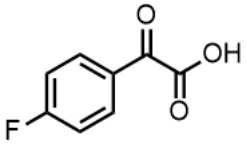
NMR (151 MHz, DMSO-*d6*) δ: 185.0, 162.5, 135.4, 131.9, 131.0, 128.9. Spectral data are in agreement with the literature.[5]



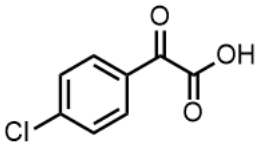
2-oxo-2-(p-tolyl)acetic acid 2o. Yellow solid, 80% yield (196.99 mg). ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 7.77 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 6.93 (br, s, 1H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ: 195.1, 167.7, 143.9, 129.8, 129.7, 129.6, 21.7. Spectral data are in agreement with the literature.[5]



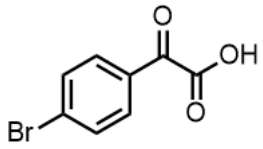
2-(4-(tert-butyl)phenyl)-2-oxoacetic acid 2p. Yellow solid, 63% yield (194.89 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07-8.05 (d, *J* = 8.2 Hz, 2H), 7.53-7.51 (d, *J* = 7.6 Hz, 2H), 7.16 (br, s, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.9, 157.7, 131.1, 130.1, 126.0, 125.5, 35.2, 31.1. Spectral data are in agreement with the literature.[6]



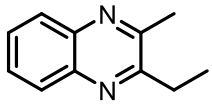
2-(4-fluorophenyl)-2-oxoacetic acid 2q. Beije solid, 81% yield (204.26 mg), ^{1}H NMR (600 MHz, DMSO-*d6*) δ: 8.06-8.02 (m, 2H), 7.46-7.42 (m, 2H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ: 187.0, 166.8 (d, J = 255 Hz), 165.7, 165.17, 132.7 (d, J = 10.1 Hz), 128.7 (d, J = 2.6 Hz), 116.5 (d, J = 22.3 Hz). Spectral data are in agreement with the literature.[5]



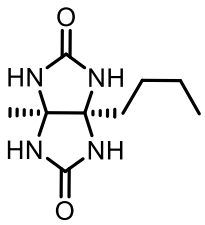
2-(4-chlorophenyl)-2-oxoacetic acid 2r. White solid, 86% yield (238.1 mg), ^{1}H NMR (600 MHz, DMSO-*d6*) δ: 7.97 -7.76 (m, 2H), 7.68-7.49 (m, 2H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ: 194.8, 169.2, 138.1, 133.6, 131.3, 129.1Spectral data are in agreement with the literature.[5]



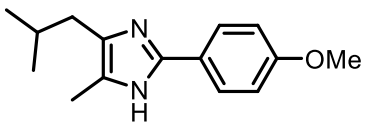
2-(4-bromophenyl)-2-oxoacetic acid 2s. Yellowish solid, 80% yield (274.83 mg). ^{1}H NMR (600 MHz, DMSO-*d6*) δ: 7.89-7.87 (m, 2H), 7.84-7.83 (m, 2H), 3.44 (br. s, 1H).^{13}C NMR (151 MHz, DMSO-*d6*) δ: 187.5, 165.4, 132.4, 131.3, 131.0, 129.4. Spectral data are in agreement with the literature.5



2-ethyl-3-methylquinoxaline 4. To a stirred suspension of **2h** (2.0 mmol, 200 mg) in toluene (10 mL), TsOH (0.1 equiv.) was added and the reaction mixture was stirred at 100°C for 16h. After cooling to room temperature the reaction was diluted with EtOAc (10 mL) and washed once with a 1M solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried with Na_2SO_4 and filterer. After concentration compound **4** was collected as a pale yellow solid in 88% yield (302 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.87 (dd, 2H), 7.52 (d, 2H), 2.87 (dd, 2H), 2.61 (s, 3H), 1.28 (t, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ: 157.3, 152.8, 141.0, 140.6, 128.5, 128.5, 128.3, 128.0, 28.7, 22.4, 11.7. Spectral data are in agreement with the literature.[7]



(3ar,6ar)-3a-butyl-6a-methyltetrahydroimidazo[4,5-d]imidazole-2,5(1H,3H)-dione 5. To a stirred suspension of **2h** (1.56 mmol, 200 mg) in water (20 mL), TFA (3 equiv.) was added dropwise. The resulting suspension was stirred at 50°C for 4h. The resulting reaction mixture was cooled to room temperature and allowed to precipitation at -20°C. The solid was filtered and washed twice with water to afford **5** as a crystalline yellow solid in 92% yield (304 mg). Mp = 188-192 °C with decomposition. ^{1}H NMR (600 MHz, DMSO-*d6*) δ: 7.12 (br, s, 1H), 7.03 (br, s, 1H), 2.08 (s, 3H), 1.61-1.56 (m, 2H), 1.38 -1.33 (m, 2H), 1.28 (dd, J = 14.5, 7.2 Hz, 2H), 0.87 (t, J = 7.3 Hz, 2H), 0.84 (dd, J = 7.6, 1.9 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-*d6*) δ: 159.6, 77.4, 75.5, 35.0, 30.7, 24.7, 22.5, 21.5, 13.8. HRMS calcd. for $C_{10}H_{18}N_4O_2$: 226.1430; found [M+Na]: 249.1328.

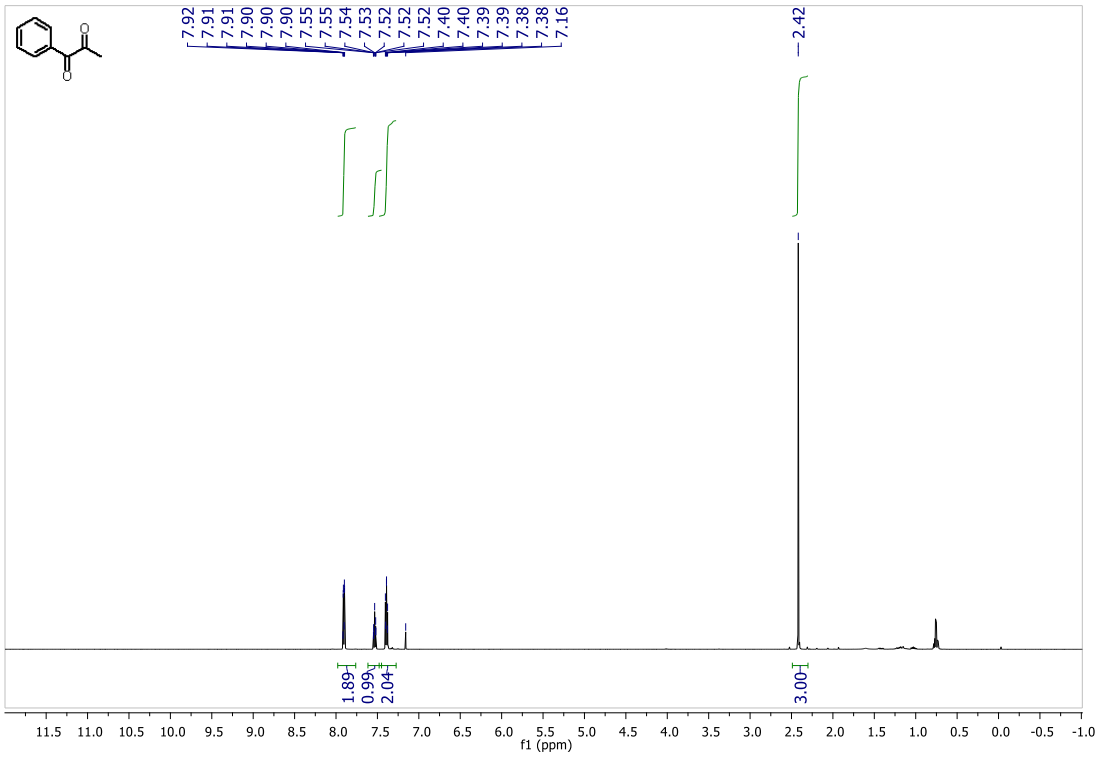


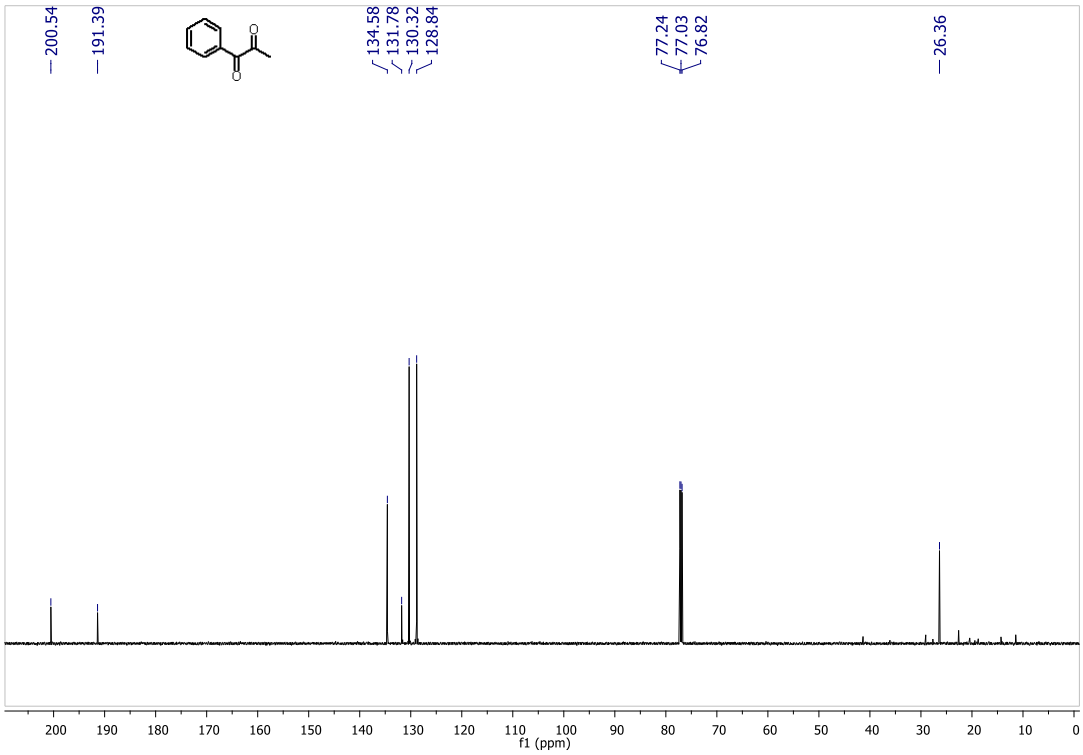
4-isobutyl-2-(4-methoxyphenyl)-5-methyl-1H-imidazole 6. To a stirred solution of AcOH (5 mL) and MeOH (5 mL) of **2i** (1.56 mmol, 200 mg), NH_4OAc (3 equiv.) was added and the resulting suspension was stirred at 100°C for 16h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure, diluted with EtOAc (20 mL) and washed once with a 1M solution of $NaHCO_3$ (20 mL) and Brine (20 mL). The organic phase was dried with Na_2SO_4 and

filterer. After concentration the crude product was purified by flash chromatography (*n*-hexane/EtOAc 5:1) to afford the compound **6** as a brown solid in 76% yield (289 mg). Mp = 50-52 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.80 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 2.34 (d, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.83 (dt, J = 13.6, 6.8 Hz, 1H), 0.84 (d, J = 6.6 Hz, 6H).^{13}C NMR (151 MHz, $CDCl_3$) δ: 159.6, 144.3, 130.3, 129.6, 126.5, 123.4, 114.2, 55.3, 34.5, 29.5, 22.4, 11.3. HRMS calcd. for $C_{15}H_{20}N_2O$: 244.1576; found [M+Na]: 267.1475.

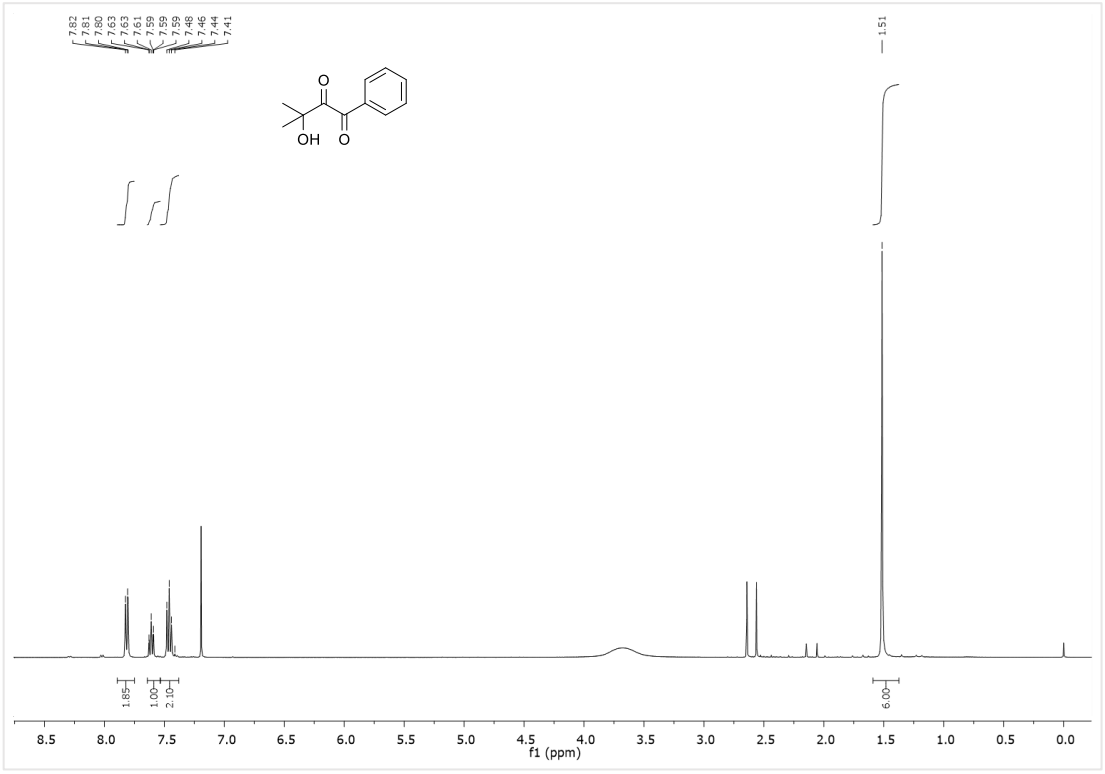
5. Selected ^{1}H and ^{13}C NMR spectra of compounds 2, and 4-6

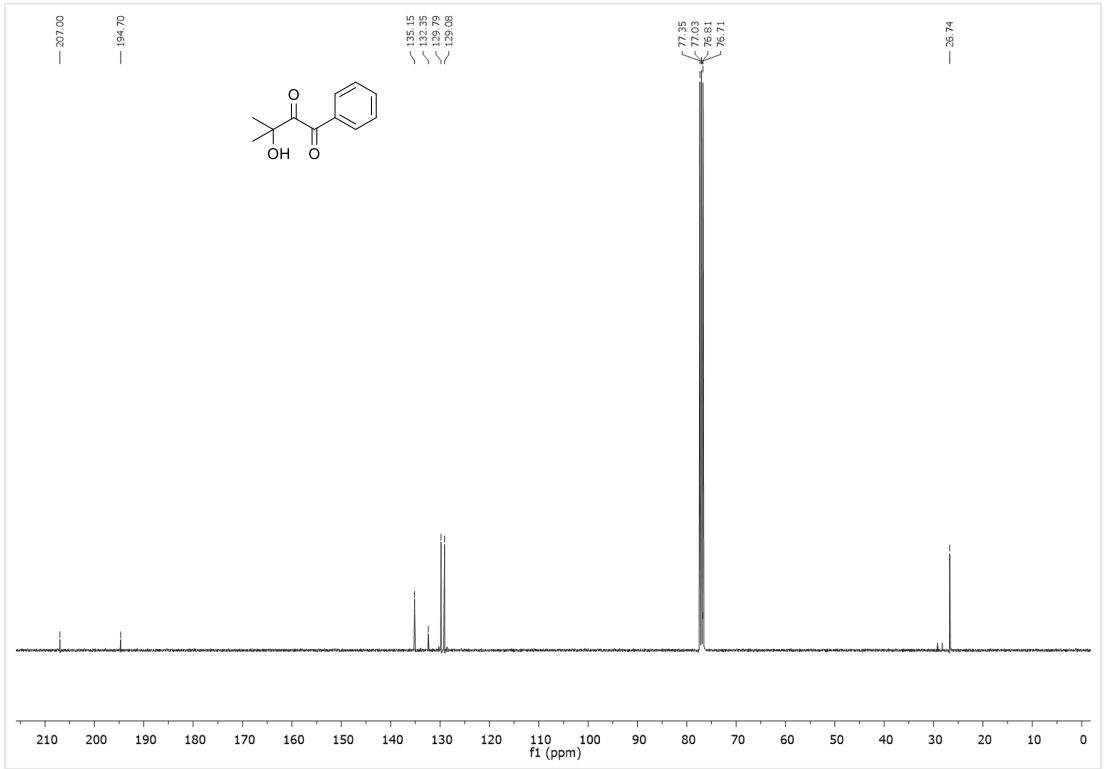
***1-phenylpropane-1,2-dione,* 2b**



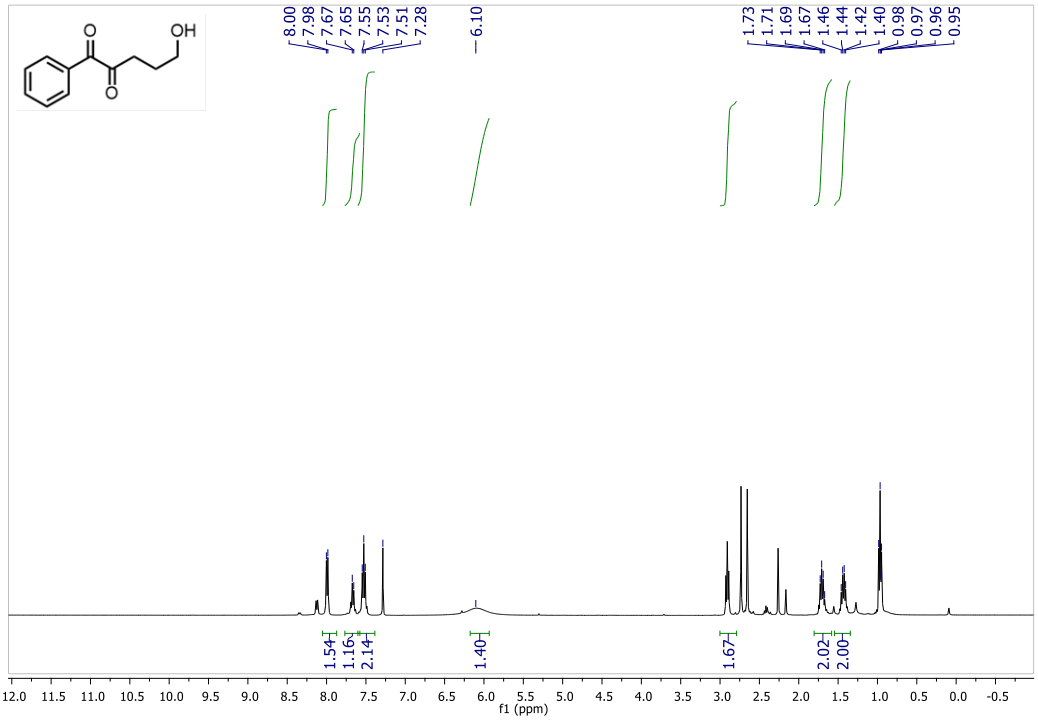


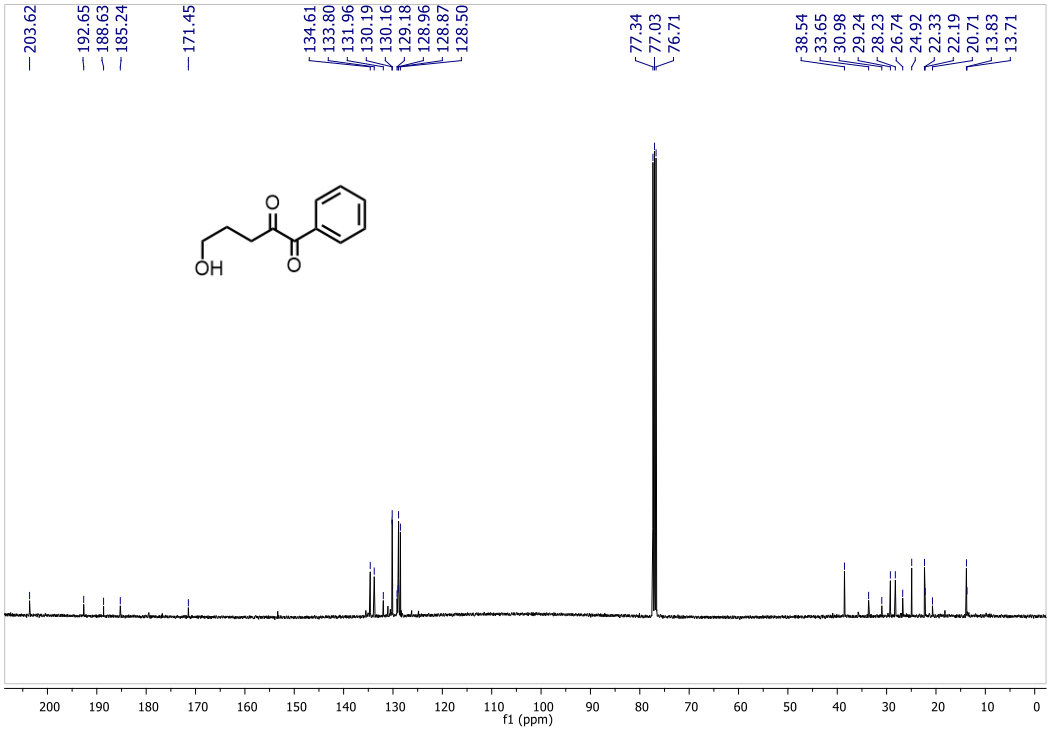
***3-hydroxy-3-methyl-1-phenylbutane-1,2-dione,* 2c**



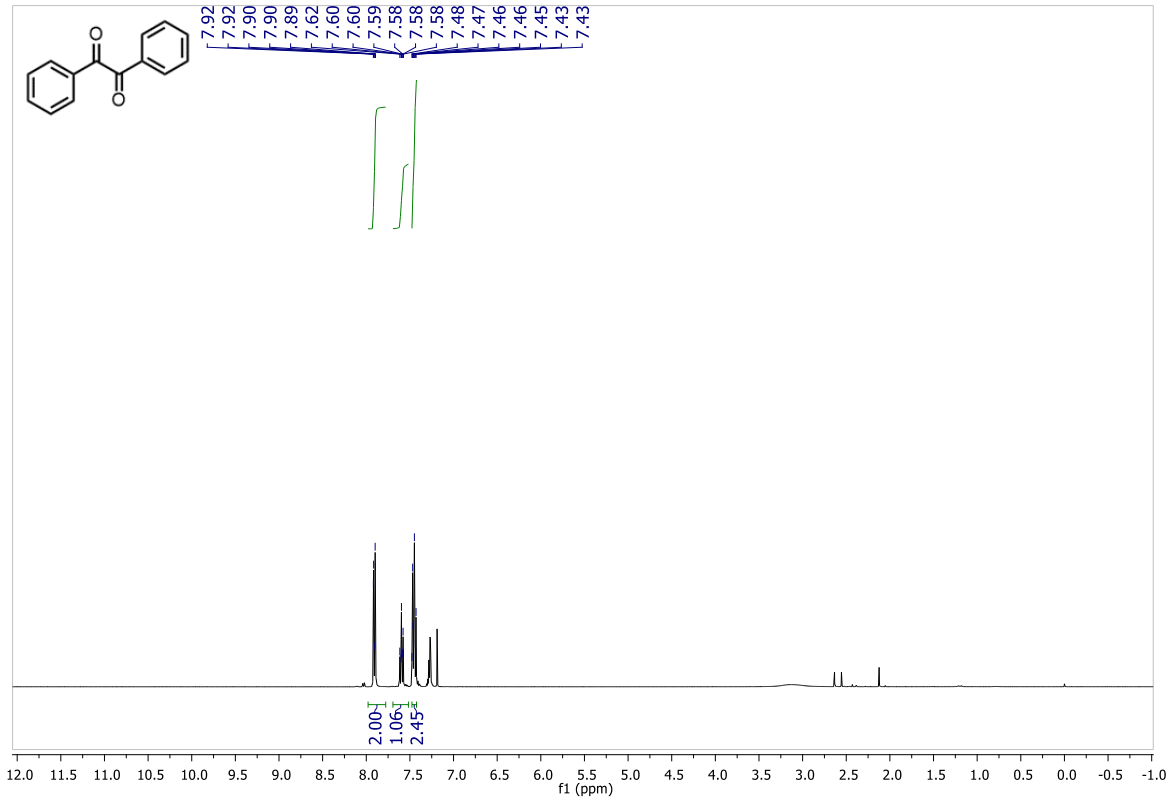


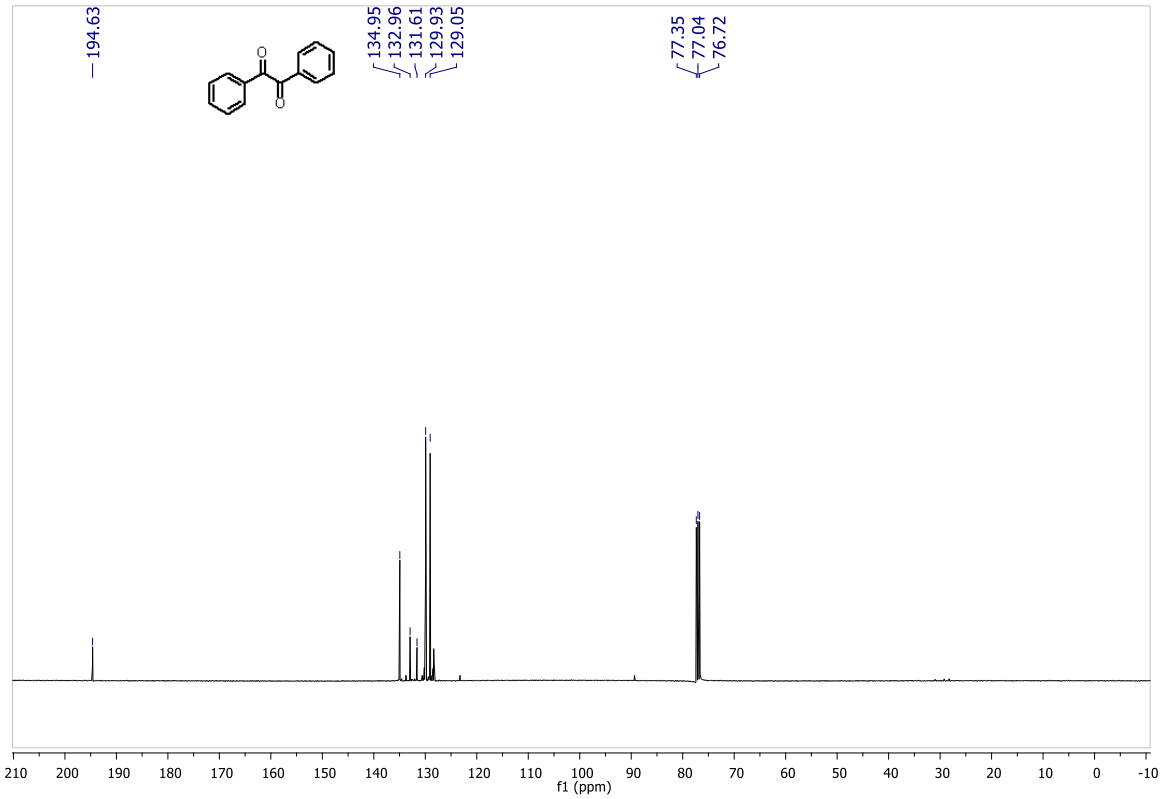
5-hydroxy-1-phenylpentane-1,2-dione, **2d** *(mixture 90:10) of 2d and 2-hydroxy-2-phenyldihydro-2H-pyran-3(4H)-one hemiacetal*



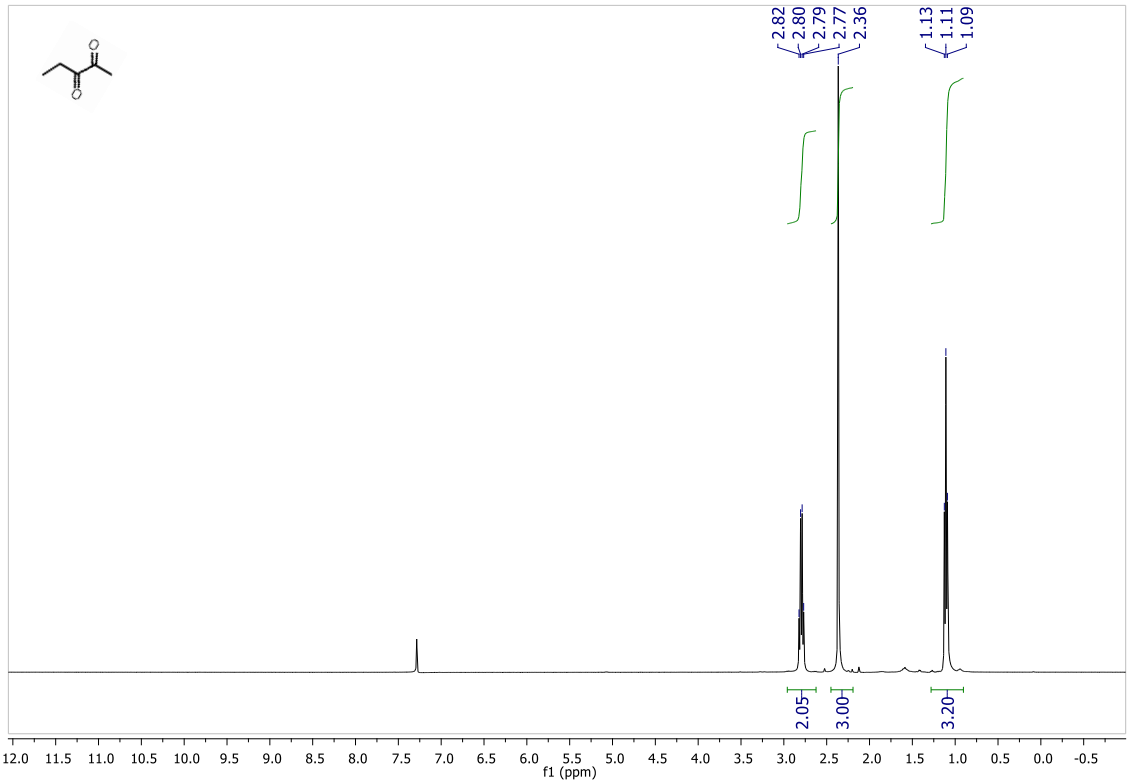


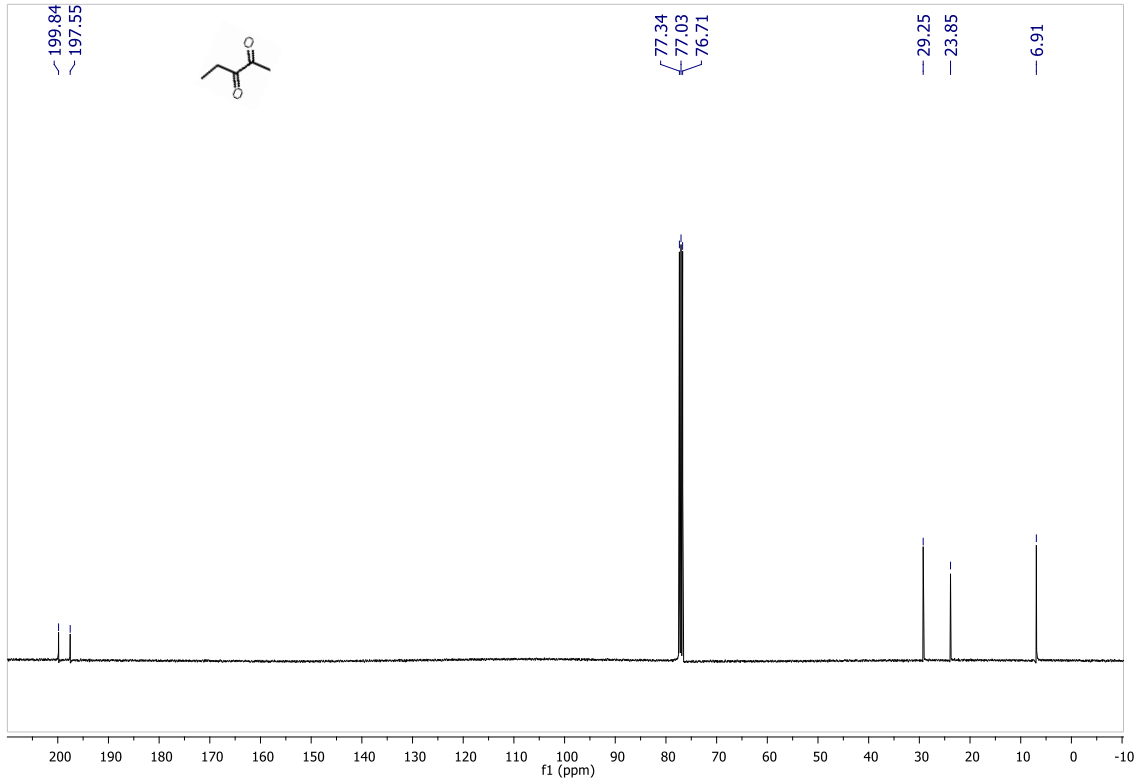
***1,2-diphenyl-1,2-ethandione,* 2e**



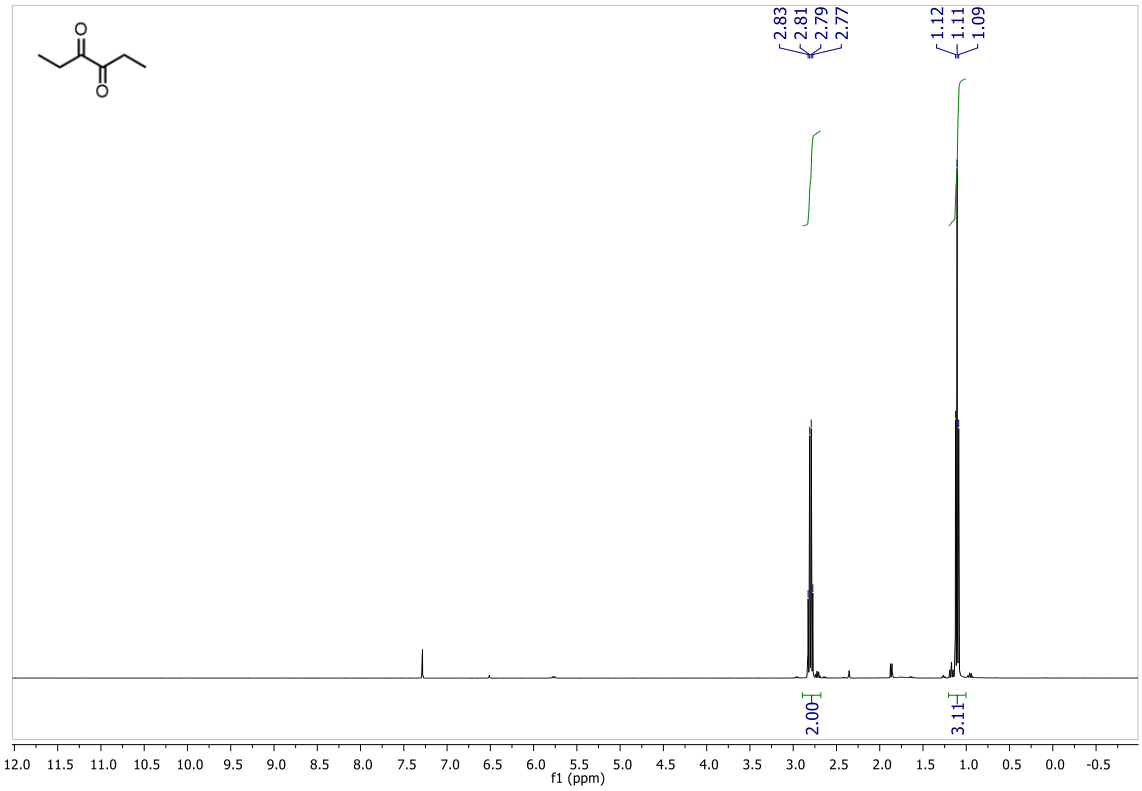


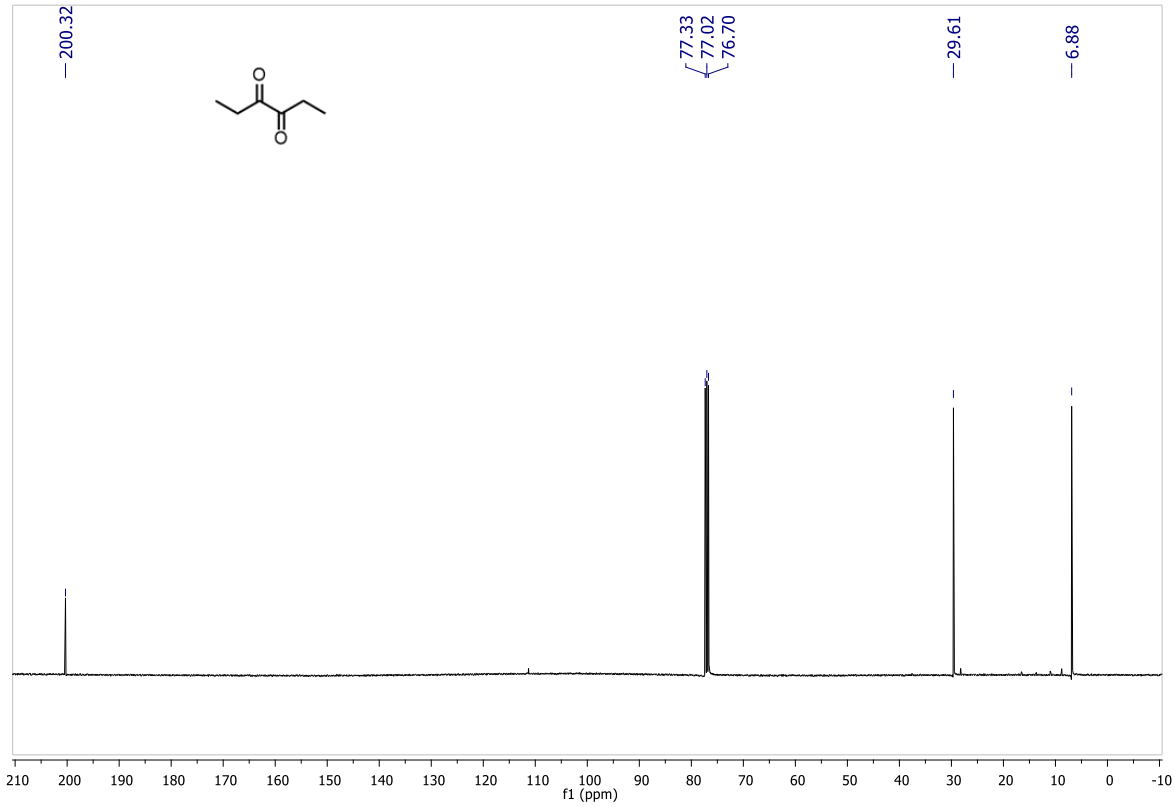
***pentane-2,3-dione*, 2g**



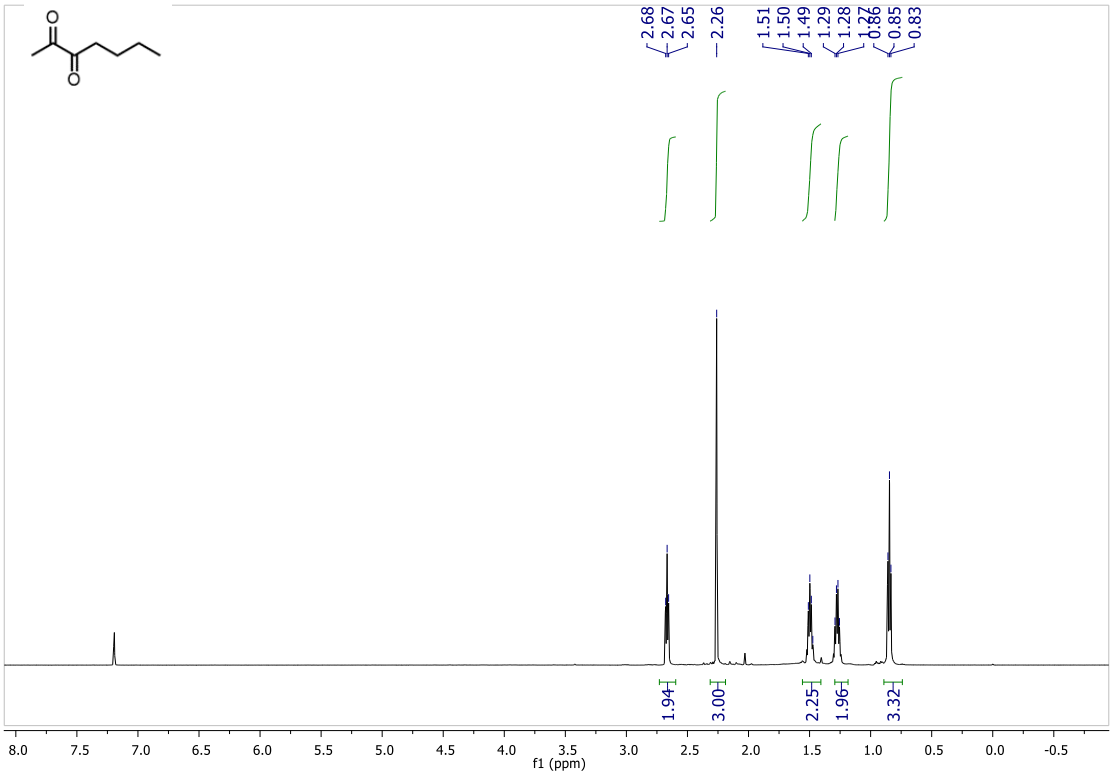


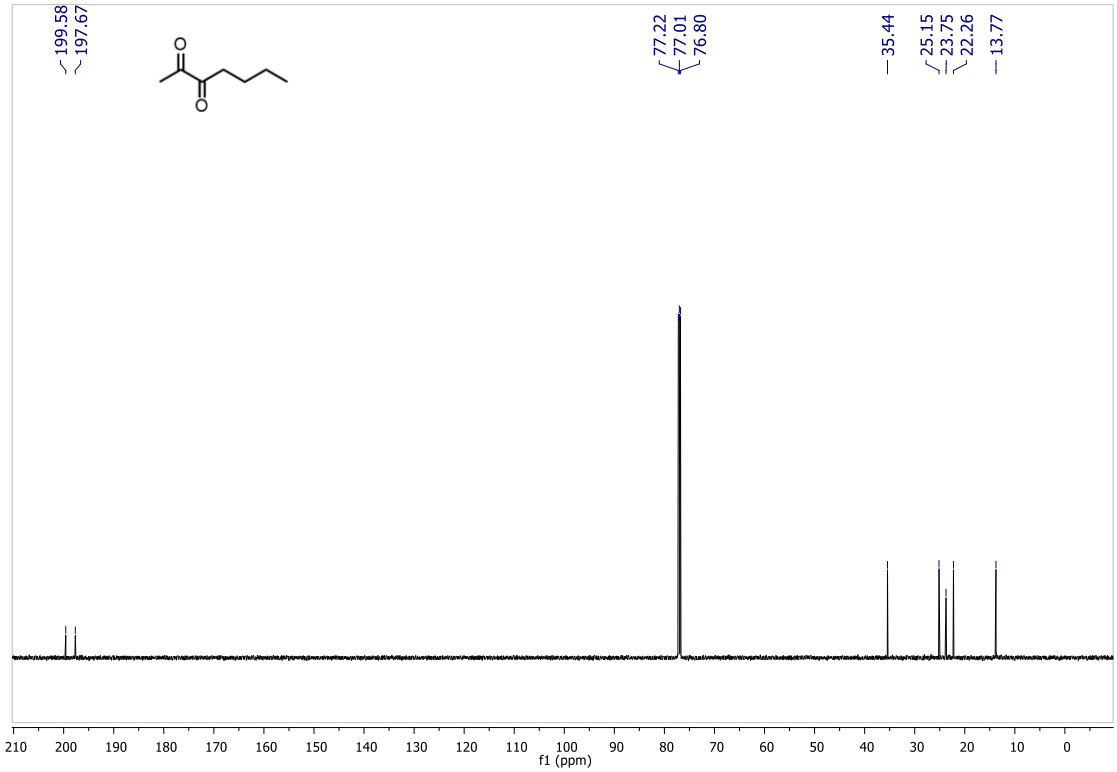
hexane-3,4-dione, **2h**



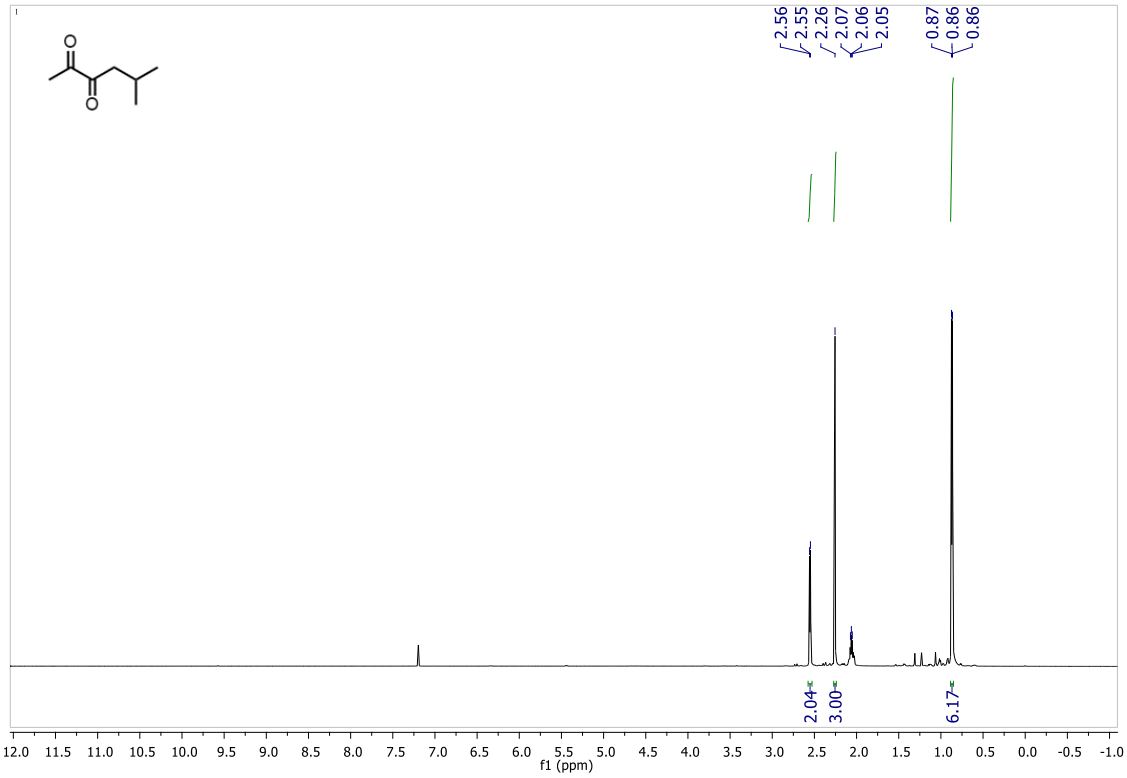


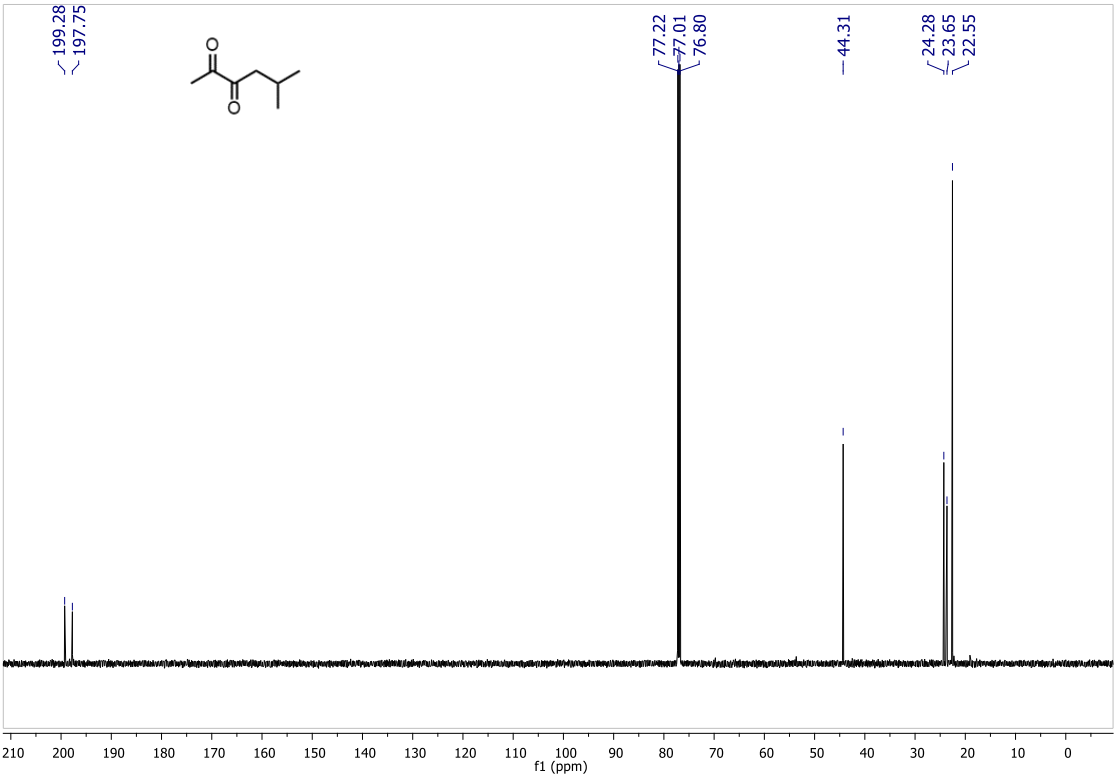
***heptane-2,3-dione,* 2i**



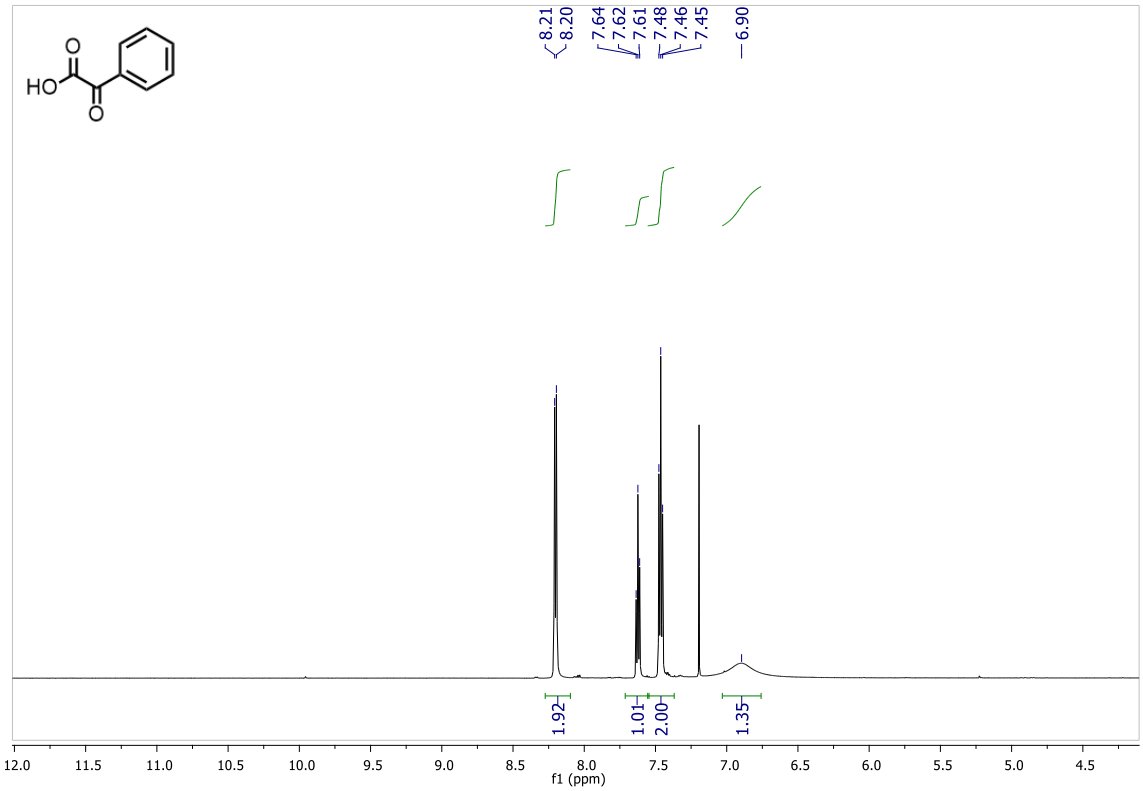


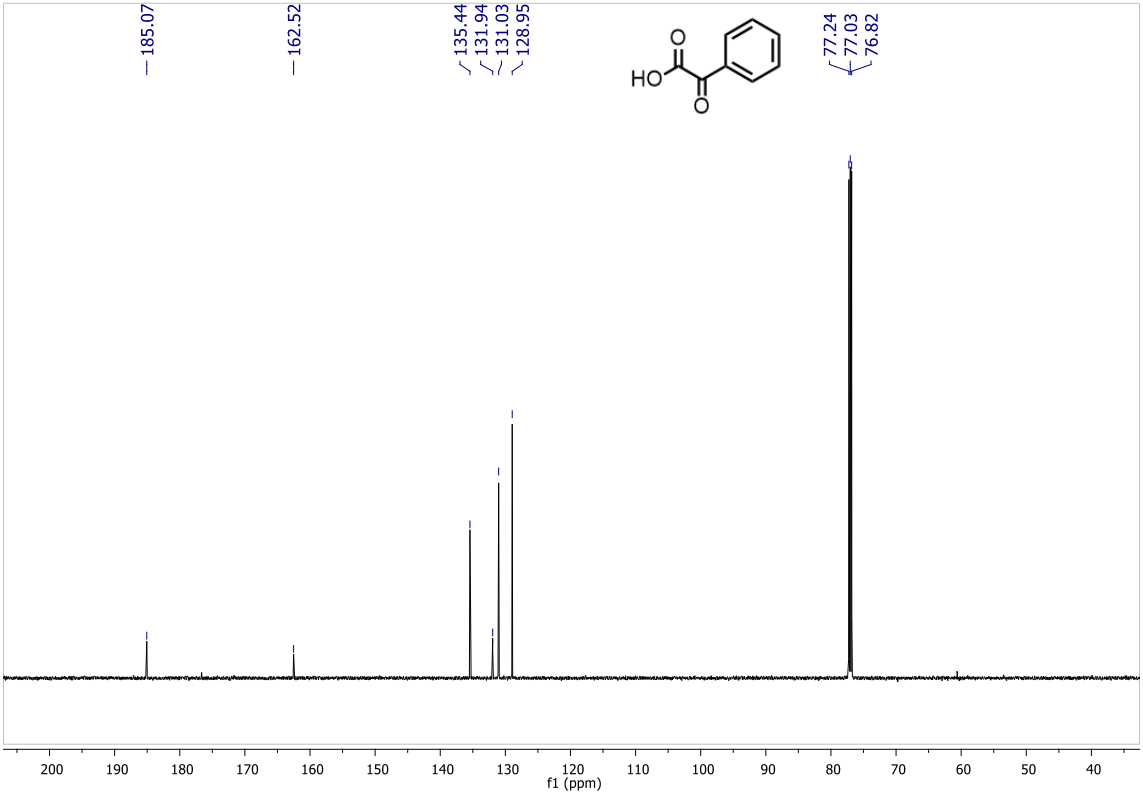
5-methylhexane-2,3-dione, 2j



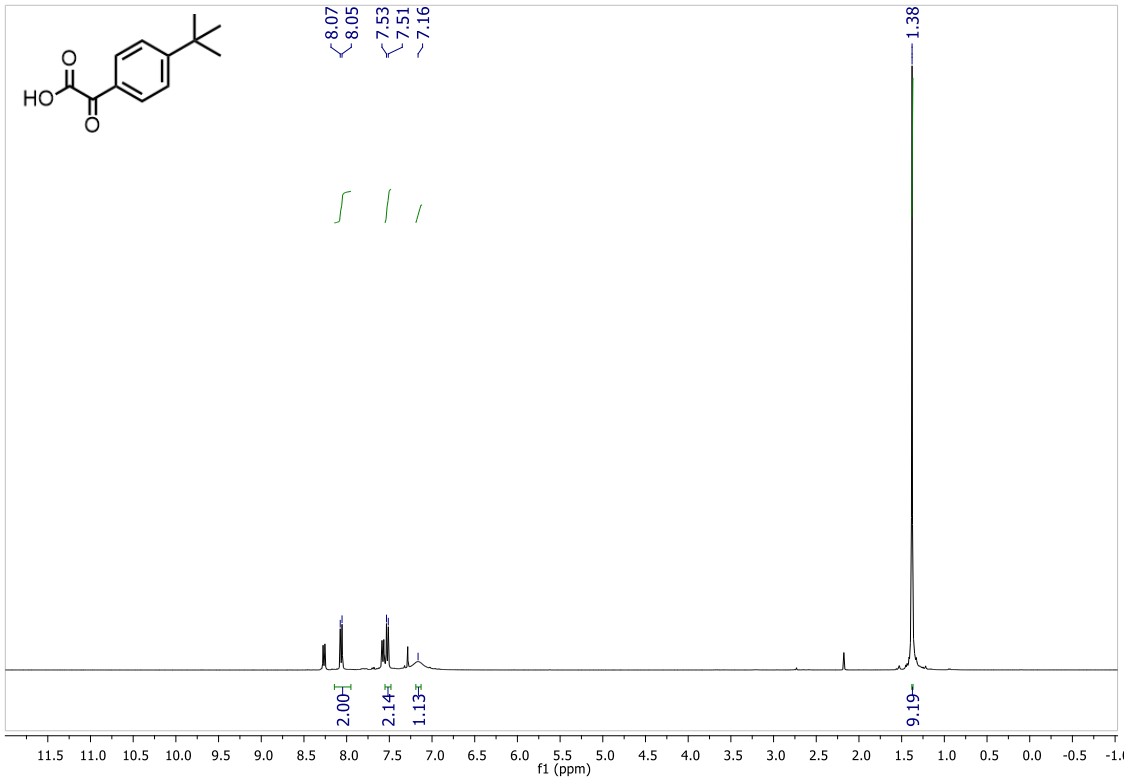


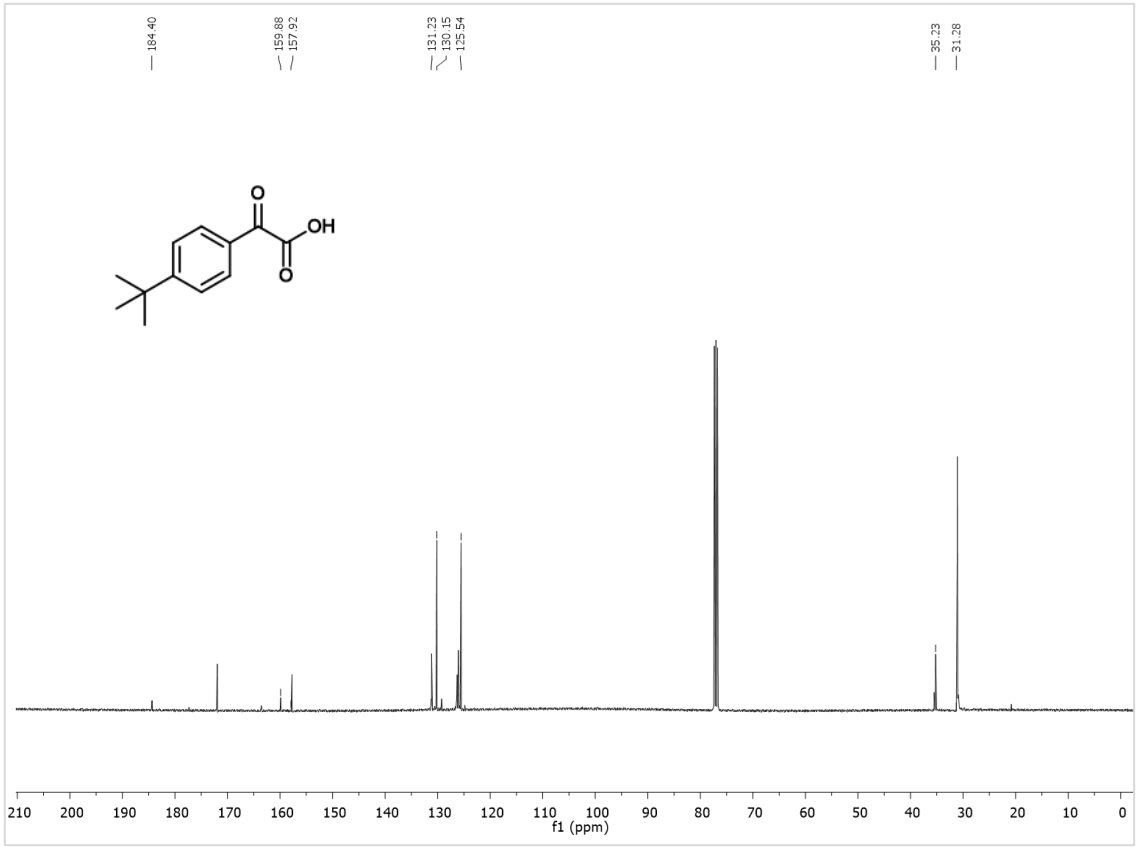
2-oxo-2-phenylacetic acid, 2n



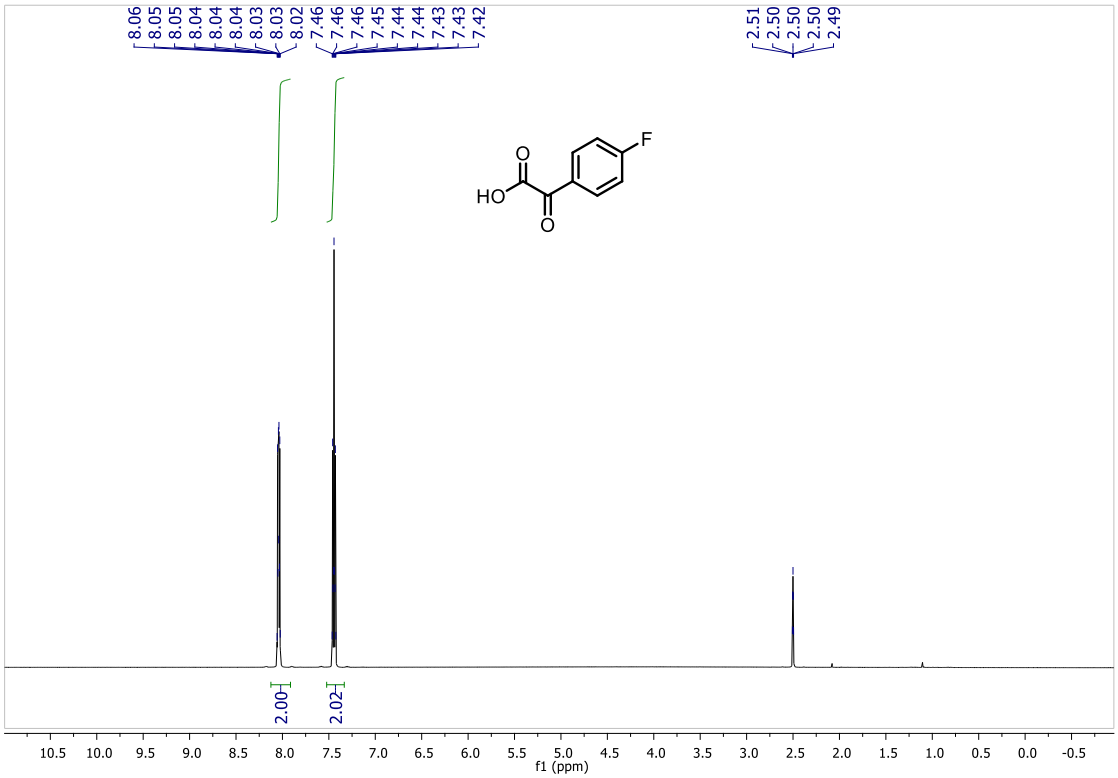


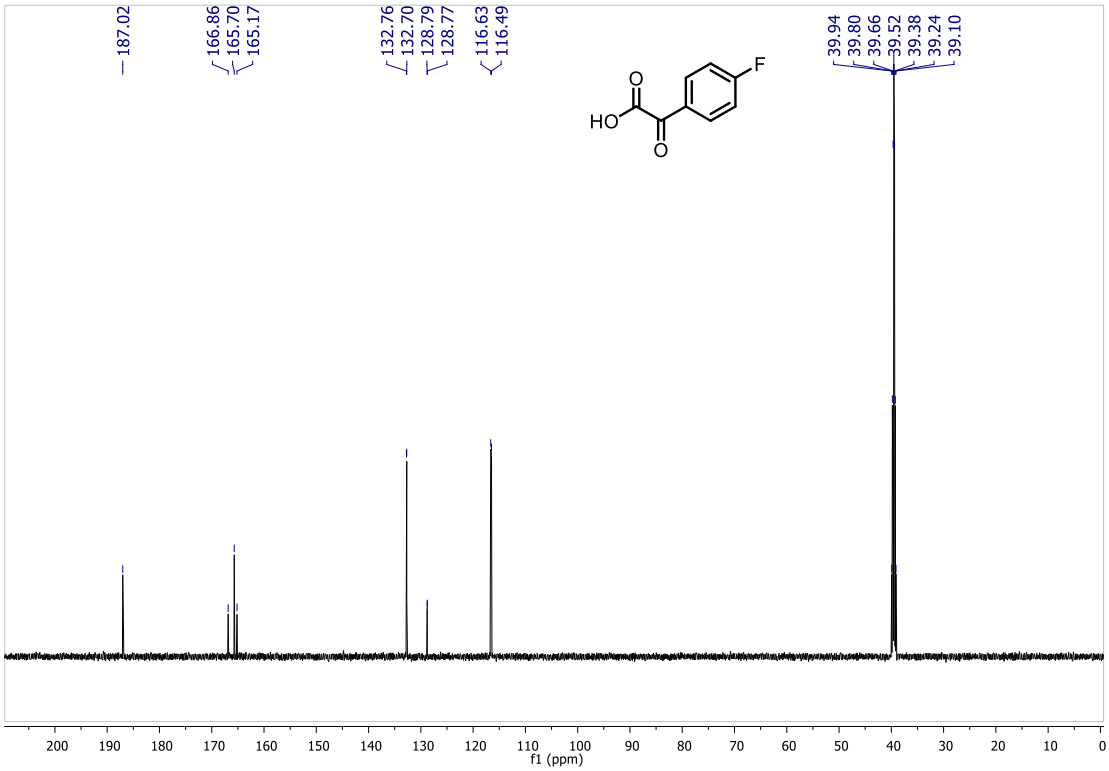
2-(4-(tert-butyl)phenyl)-2-oxoacetic acid, 2p



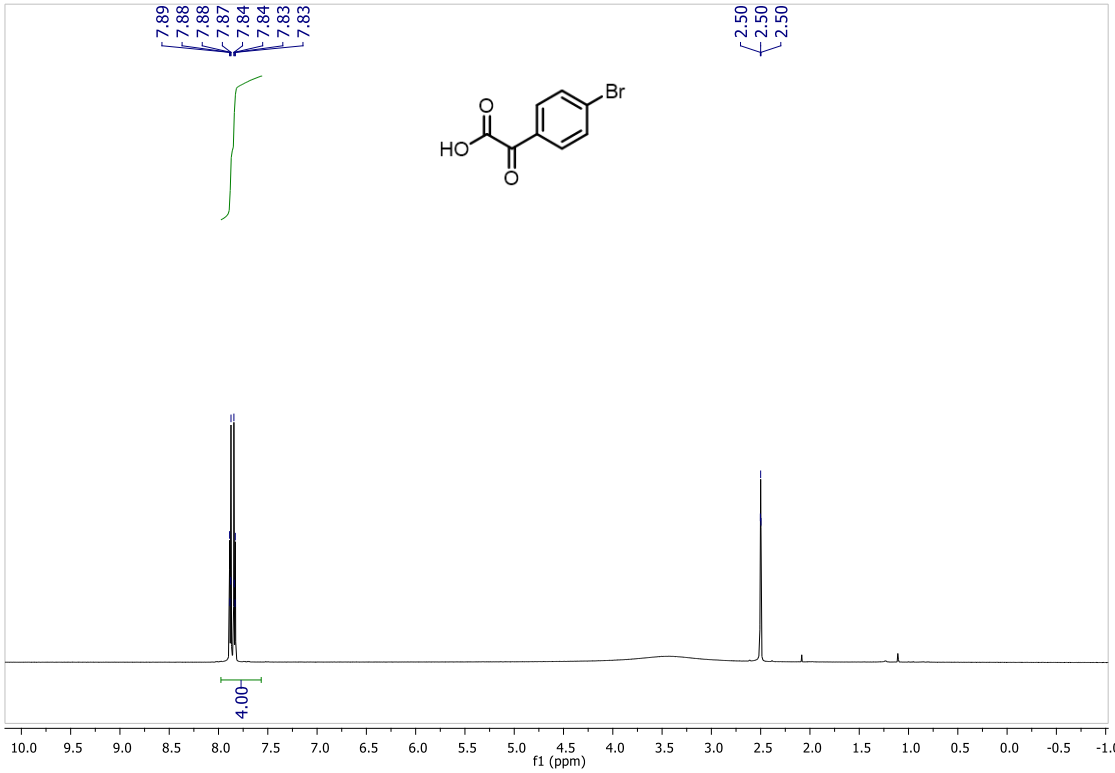


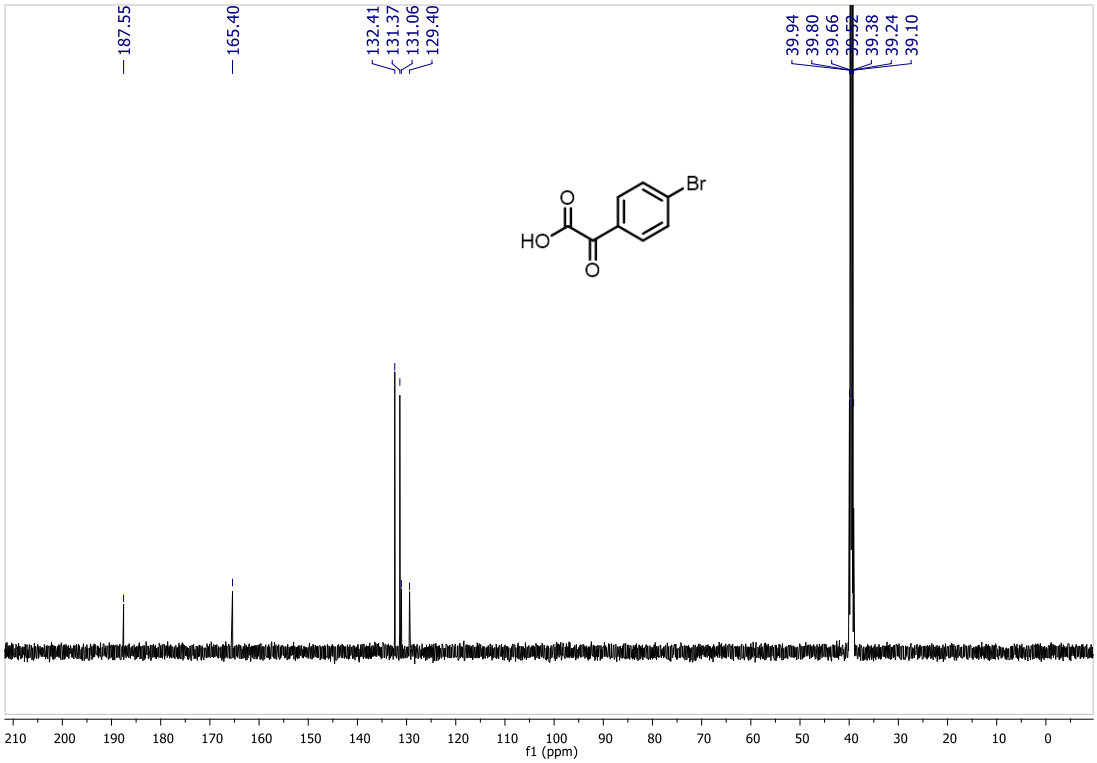
***2-(4-Fluorophenyl)-2-oxoacetic acid*, 2q**



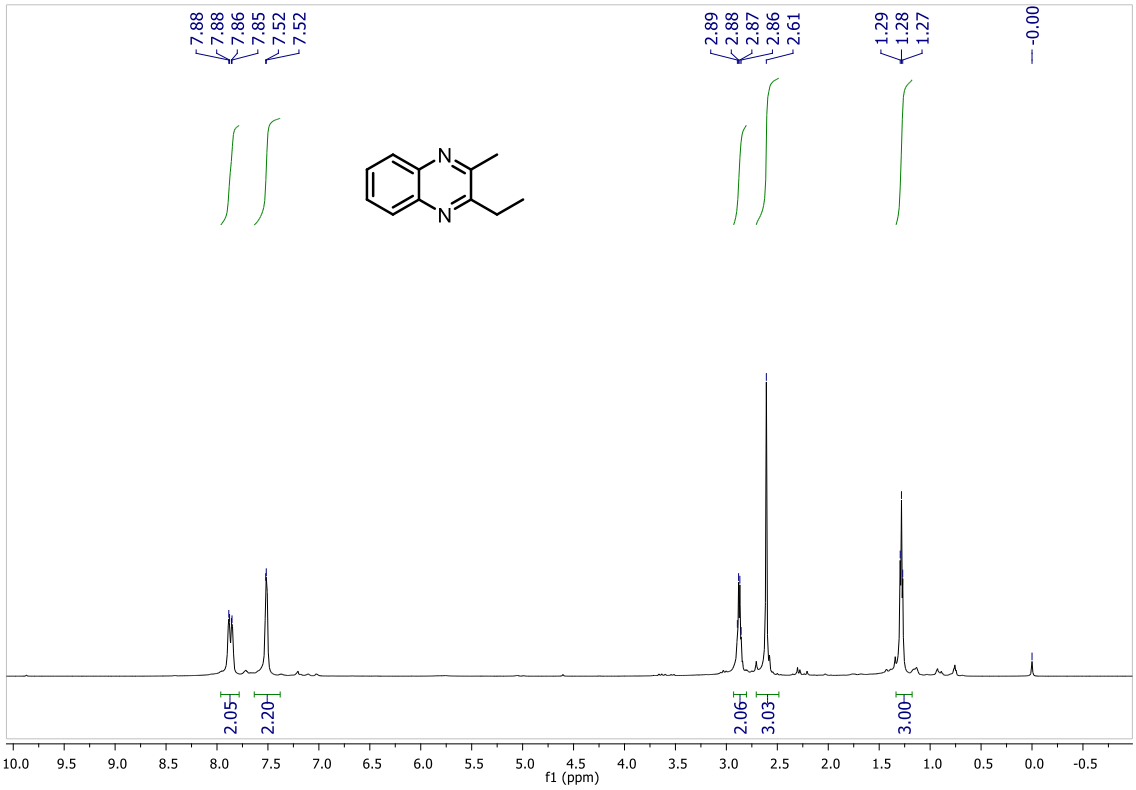


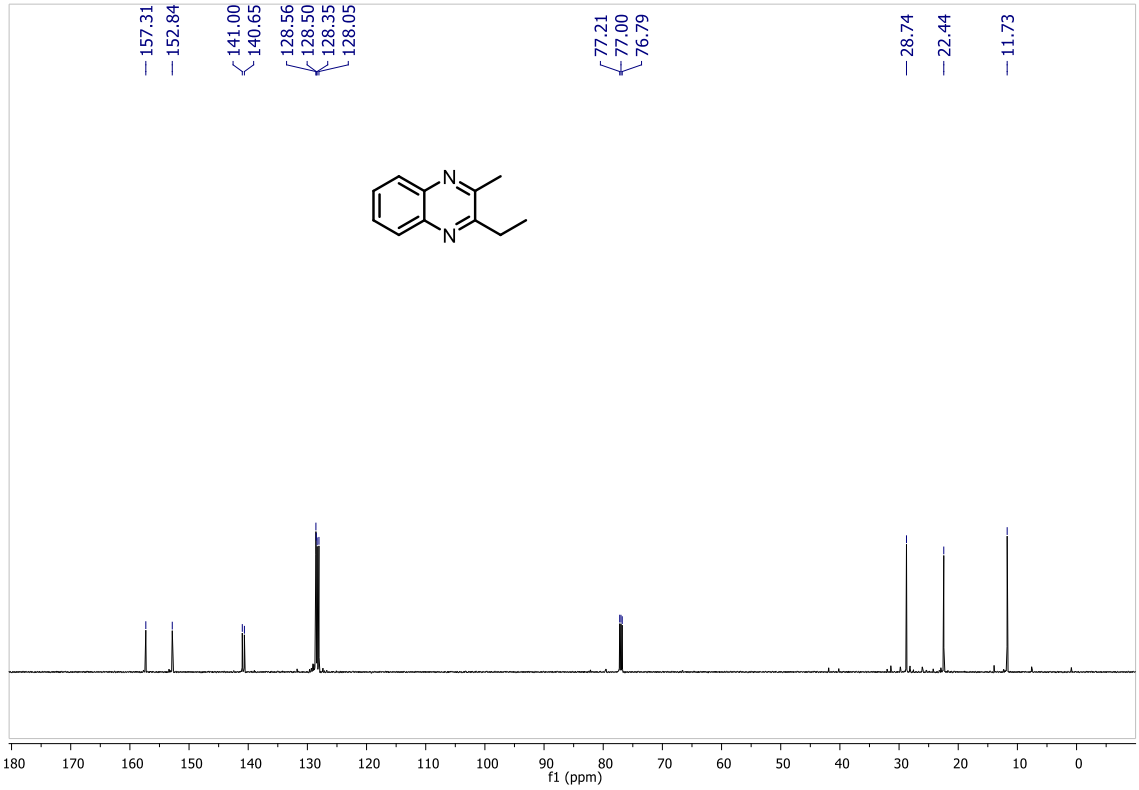
***2-(4-Bromophenyl)-2-oxoacetic acid*, 2s**



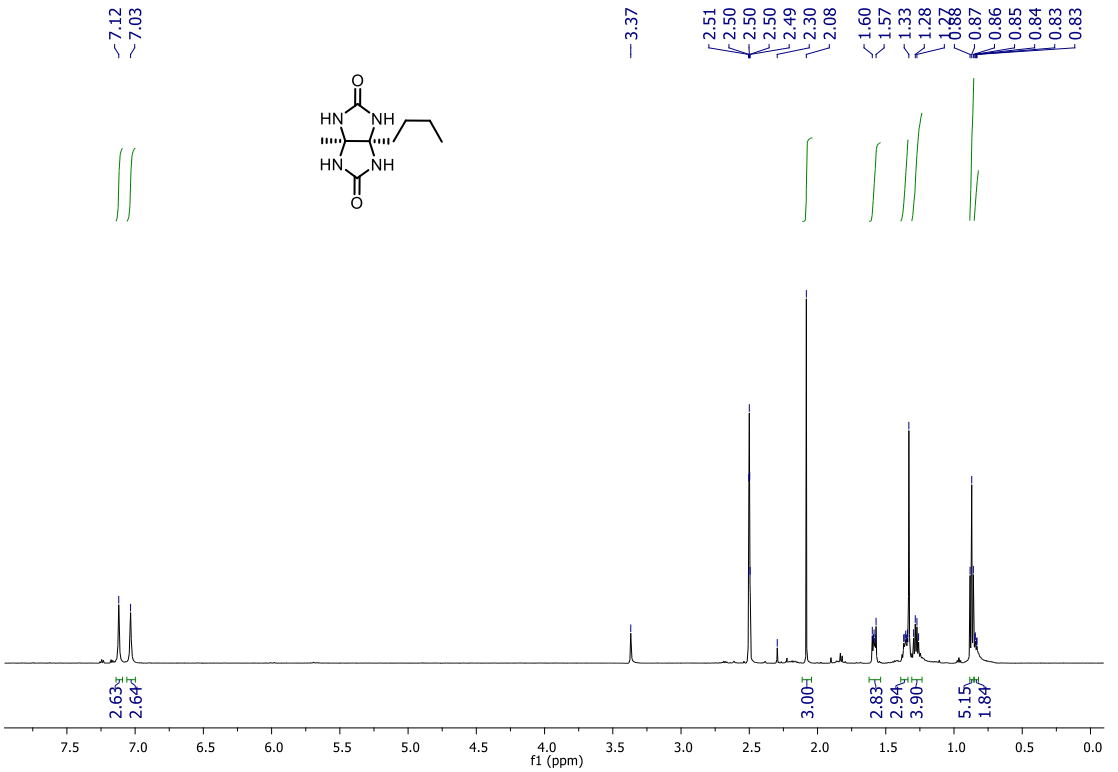


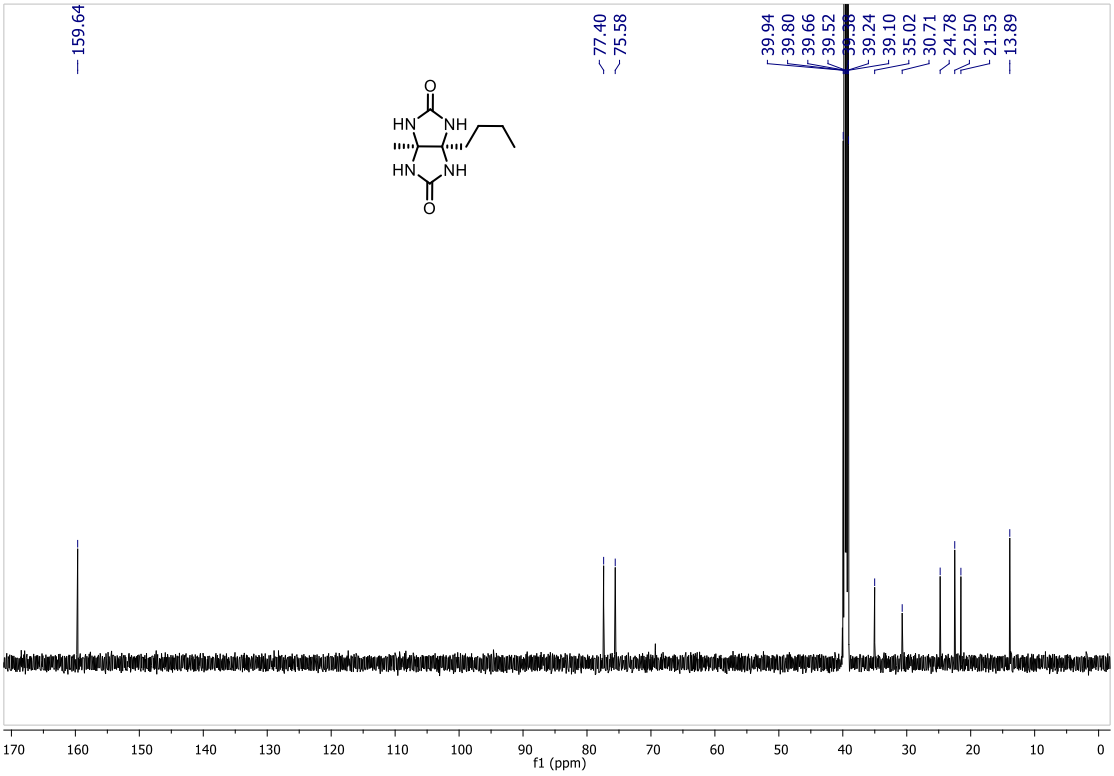
2-ethyl-3-methylquinoxaline, 4



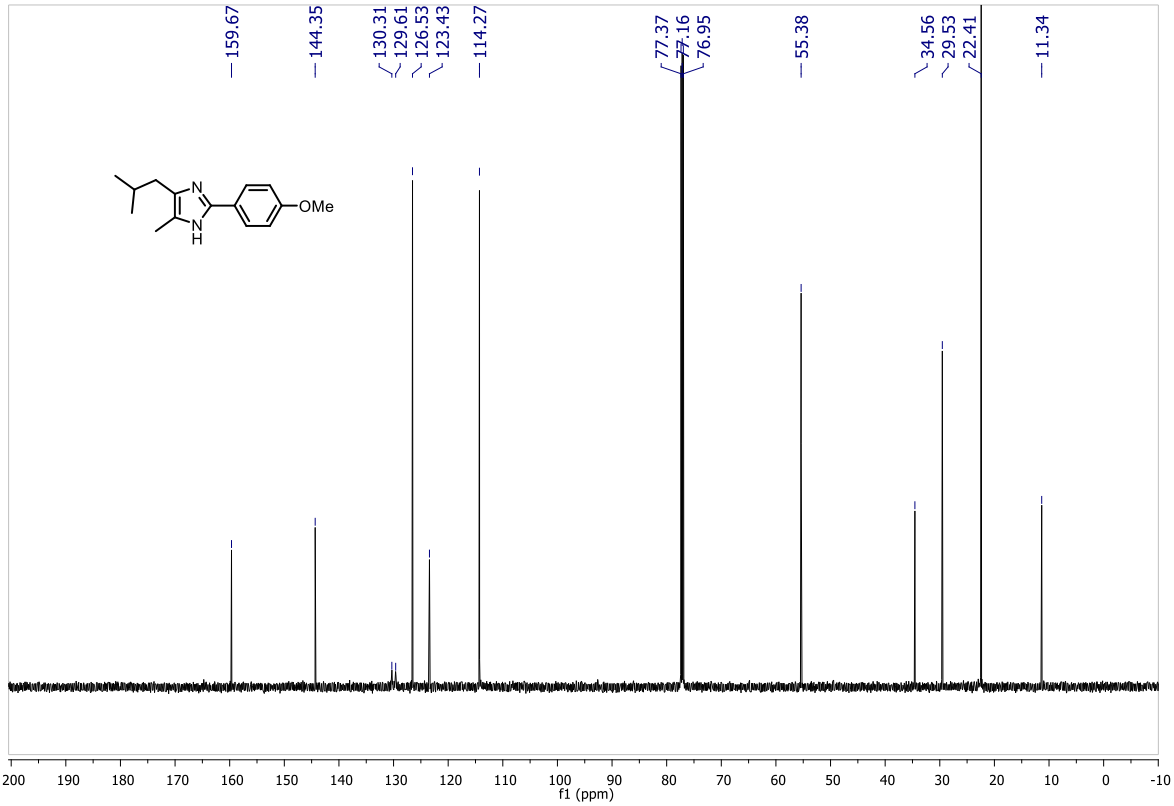


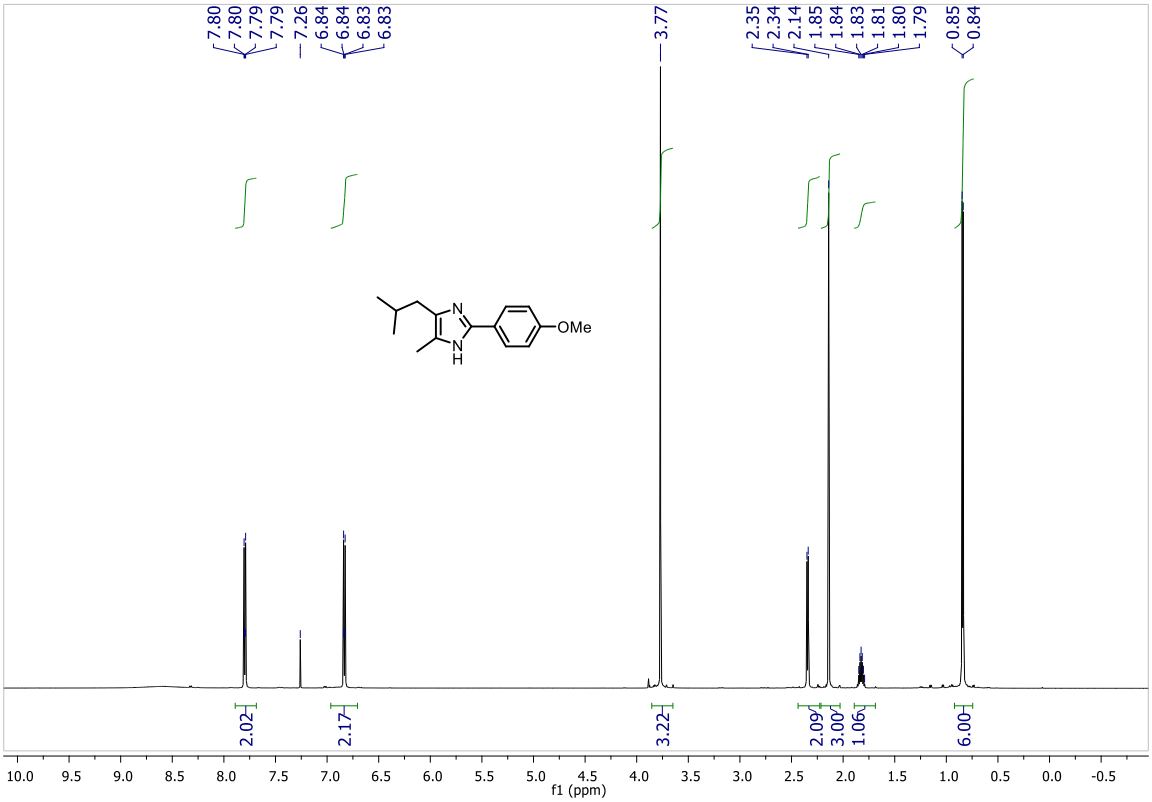
***3a-methyl-6a-pentyltetrahydroimidazo[4,5-d]imidazole-2,5(1H,3H)-dione,* 5**





4-isobutyl-2-(4-methoxyphenyl)-5-methyl-1H-imidazole, 6





6. References and notes

1) F. Secci, S. Porcu, A. Luridiana, A. Frongia, P. C. Ricci, *Org. Biomol. Chem.*, **2020**, 18, 3684-3689.

2) D. Shen, H. Wang, Y. Zheng, X. Zhu, P. Gong, B. Wang, J. You, Y. Zhao, M. Chao, *J. Org. Chem*. **2021**, 86, 7, 5354-5361.

3) S. Guha, I. Kazi, P. Mukherjee, G. Sekar, *Chem. Commun.,* **2017**, 53**,** 10942-10945.

4) All the 1,2-diketones **2g**, **2h**, and **2j** have been compared with the commercially available compounds.

5) Herein we report the $_{1}$H and $_{13}$C NMR spectra of compound **2q** and **2s** in DMSO-d6. However, **2q** and **2s** were already reported in the literature, in $CDCl_3$ by T. Song, Z. Ma, X. Wang, Y. Yang, Org. Lett. 2021, 23, 5917-5921.

6) H. Inada, M. Shibuya, Y. Yamamoto, *J. Org. Chem*. **2020**, 85, 17, 11047-11059.

7) J. Everaert, K. Leus, H. Rijckaert, M. Debruyne, K. Van Hecke, R. Morent, N. De Geyter, V. Van Speybroeck, P. Van Der Voort C. V. Stevens, *Green Chem*., **2023**, 25, 3267-3277.

8) X. Wang , G. Cheng , J. Shen , X. Yang , M.-e Wei , Y. Feng, X. Cui, *Org. Chem. Front*., **2014**, 1, 1001-1004.