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

Supporting information

Controlled generation and use of CO in flow

Steffen V. F. Hansen[a,b], Zoe E. Wilson[a], Trond Ulven[b]*, Steven V. Ley[a]*

[a] Department of Chemistry, University of Cambridge Lensfield Road, Cambridge, CB2 1EW, UK.

[b] Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, 5230 Odense M, DK.

Contents

General comments

Unless stated otherwise, reagents and solvents were obtained from commercial sources and used without purification. Toluene was distilled from calcium hydride**,** THF distilled from sodium/benzophenone, methanol distilled from Mg, ethanol was used at 99.8% purity, 1,4-dioxane was stored over activated 3Å sieves, NEt_3 was distilled from CaH_2 and stored over KOH. No efforts were taken to degas the NaOH or oxalyl chloride solutions before use.

Purification by flash chromatography was carried out using silica gel 60 Å (Merck grade 9385) using distilled Et_2O, ethyl acetate and petroleum ether (bp 40-60 °C) as eluent system. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

^{1}H NMR spectra were recorded on either a 400 MHz DPX-400 Dual Spectrometer or a 600 MHz Avance 600 BBI Spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometer with proton decoupling, with the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm.

All pressures are given as pressure relative to ambient atmospheric pressure (psig).

Once the reaction mixture has passed through the tube-in-tube the CO generating pumps are switched to solvent (toluene and water respectively) So that the CO generating reaction is only running while needed.

Reactions were followed using Mettler Toledo Flow-IR, monitoring for the products carbonyl stretch (~1730 cm^{-1} for esters, ~1670 cm^{-1} for the amide) to allow collection of the reaction plug, from which the solvent was removed in vacuo and the product purified by flash chromatography as indicated.

The tube-in-tube reactor used had an outer tube volume of 1.3 mL and an inner tube volume of 0.3 mL.

At the end of each day of use the oxalyl chloride pump was flushed sequentially with THF, water, THF and toluene. If the pump was not properly flushed, residual water could cause gas formation in the pump when oxalyl chloride is next pumped (for the R2+ pump).

CO Safety precautions!

Special precautions must be taken when working with CO as it is a highly toxic and flammable gas. Carbon monoxide is highly toxic. All equipment was set up in a well ventilated fume hood and excess carbon monoxide released was directed into the exhaust. As CO is odorless and tasteless, carbon monoxide monitoring equipment was used inside and outside the fume hood at all times.

Optimization of reaction conditions for the methoxycarbonylation of iodide 3 to ester 4

Optimization of concentration for the methoxycarbonylation of iodide 3 to ester 4

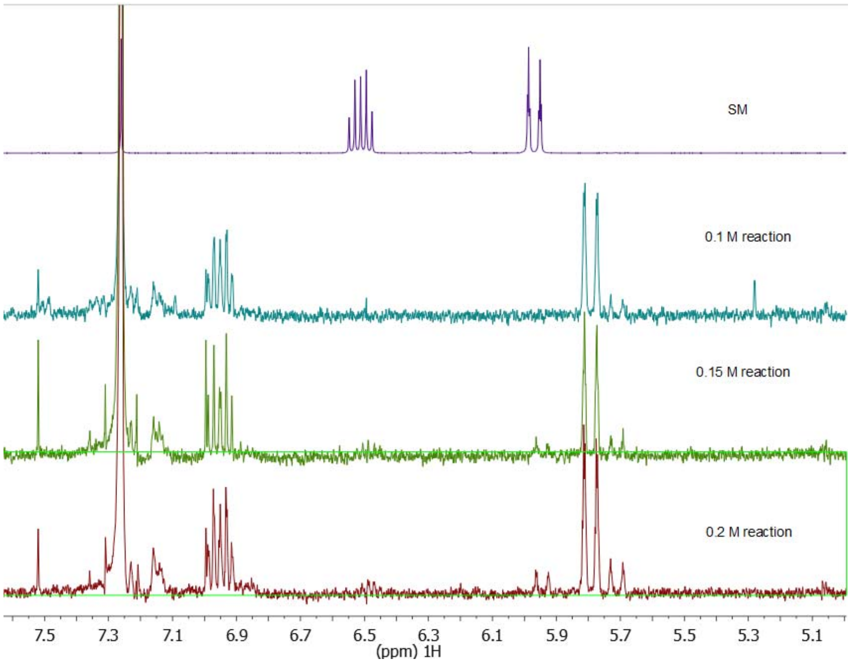


Figure 1. Crude ^{1}H NMR (400 MHz) of reaction mixture for different concentrations of iodide **3**.

Optimization of reaction time for the methoxycarbonylation of iodide 3 to ester 4

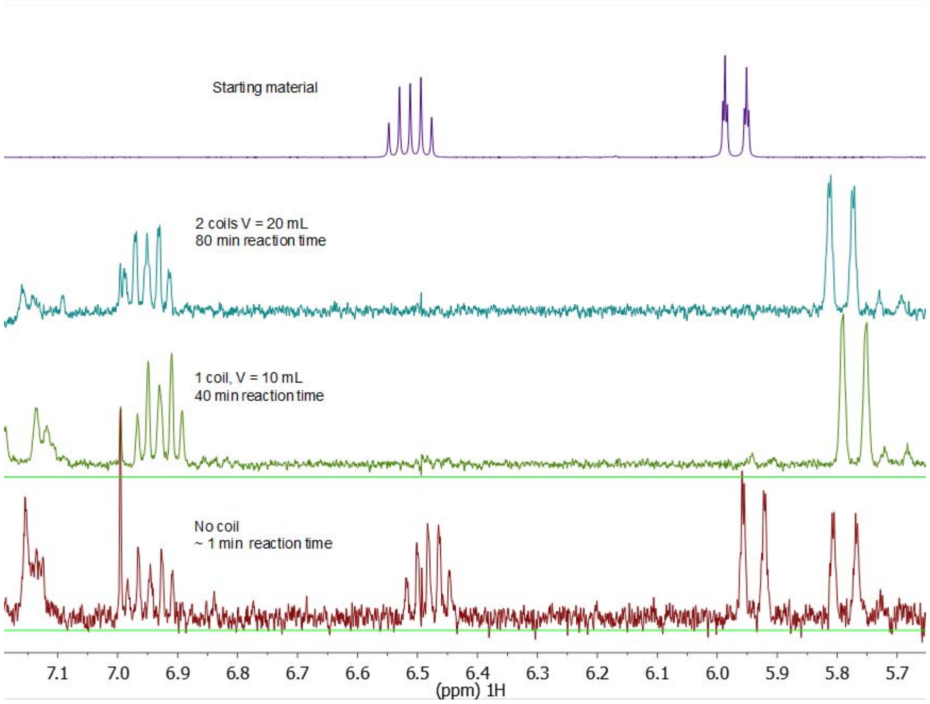
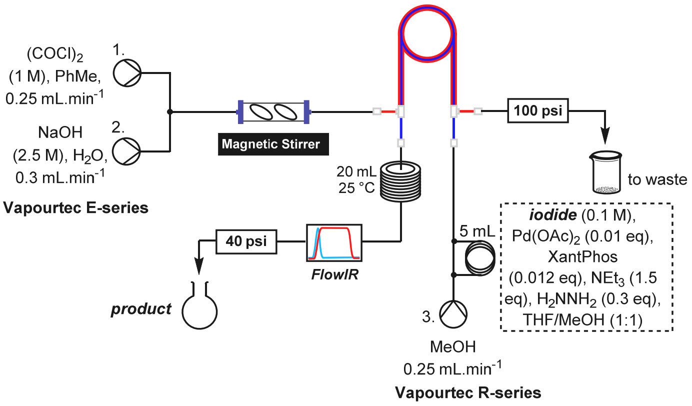


Figure 2. Crude ^{1}H NMR (400 MHz) of reaction mixture for decreasing reaction time.

General Methods

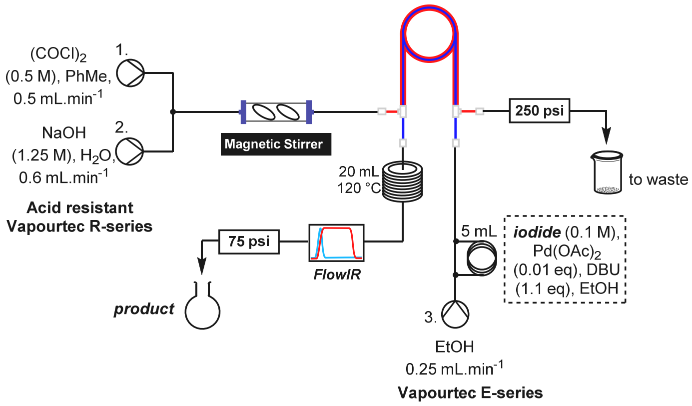
General method A



Scheme 1. Flow set up for General Method A

Flow equipment was set up according to scheme 1. *CO releasing reaction:* A solution of oxalyl chloride (1 M) in toluene was pumped at 0.25 mL.min^{-1} by Pump 1 (Vapourtec E-series, red peristaltic tubing) and a solution of NaOH (2.5 M) was pumped at 0.3 mL.min^{-1} by Pump 2 (Vapourtec E-series, red peristaltic tubing). The two solutions meet at a T-piece and were mixed using an Omnifit column (0.68 mL) with two stirrer bars over a magnetic stirrer. The mixed solution is then passed through a tube-in-tube reactor in the outer tube, which is pressurized by a 100 psi BPR. The outflow was collected and kept in the fume hood for at least a day (to allow diffusion of residual CO) before being discarded. *CO consuming reaction:* Methanol was flowed through the inner tube of the tube-in-tube reactor using Pump 3 (Vapourtec R2+) at 0.25 mL.min^{-1}. Once gas bubbles were observed exiting the tube-in-tube reactor in the inner stream (typically after running the CO generation for a 10-15 minutes) the reaction mixture was injected as a 5 mL sample loop containing a solution of vinyl iodide (0.5 mmol), XantPhos (3.5 mg, 6 μmol), NEt$_3$ (0.1 mL, 0.75 mmol), Pd(OAc)$_2$ (1.2 mg, 5 μmol) and H$_2$NNH$_2$ (1 M in THF, 0.15 mL, 0.15 mmol) in 5 mL MeOH:THF (1:1). The reaction stream passed through the tube-in-tube reactor counter flow to the generation stream, through a 10 mL coil at 25 °C, a Flow-IR and a 40 psi BPR then was collected and purified by flash chromatography.

General method B



Scheme 2. Flow set up for General method B.

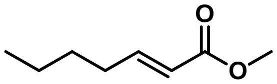
Flow equipment was set up according to Scheme 2, and is shown in figure 3. *CO generating reaction:* A solution of oxalyl chloride (0.5 M) in toluene was pumped at 0.5 mL.min^{-1} by Pump 1 (acid resistant Vapourtec R2+) and a solution of NaOH (1.25 M) was pumped at 0.6 mL.min^{-1} by Pump 2 (acid resistant Vapourtec R2+). The two solutions meet at a T-piece and were mixed using an Omnifit column (0.68 mL) with 2 stir bars over a magnetic stirrer. The mixed solution is then passed through a tube-in-tube reactor in the outer tube, which is pressurized by a 250 psi BPR. The outflow was collected and kept in the fume hood for at least a day (to allow diffusion of any residual CO) before being discarded.

CO consuming reaction: Ethanol was flowed through the inner tube using Pump 3 (Vapourtec E series, red peristaltic tubing) at 0.25 mL.min^{-1}. Once gas bubbles was observed exiting the tube in tube reactor in the inner stream (typically after running the CO generating for a 10-15 minutes) the reaction mixture was injected as a 5 mL sample loop containing an ethanolic solution of aryl iodide (0.5 mmol), $Pd(OAc)_2$ (1.4 mg, 5 µmol) and DBU (0.1 mL, 0.55 mmol). The reaction stream was passed through the tube-in-tube reactor in the opposite direction to the generation stream, through a 20 mL coil at 120 °C, a Flow-IR and a 75 psi BPR, then collected and purified by flash chromatography.

Figure 3. Photograph of set up for general method B. *Note when reactions are conducted the sash of the fume hood is lowered fully, the air flow is set to high and a CO detector is used just outside the hood.* **1** Acid resistant R2+ pumps from Vapourtec, one is used for 1.25 M NaOH (aq) at 600 µL.min^{-1} and the 2nd is used for 0.5 M oxalyl chloride in toluene at 500 µL.min^{-1}). **2** Omnifit column (V = 0.68 mL) with two magnetic stir bars mixes the oxalyl chloride and NaOH. **3** Tube-in-tube T-piece in which the CO generating stream is led to the outer side flowing right, in counter flow to the CO consuming reaction in the inner tube. **4** 250 psi backpressure regulator pressurizes the outer tube. **5** outlet of the outer tube is collected in a flask, and allowed to degas in the fume hood overnight, before being discarded. **6** Peristaltic pump on E-series delivers EtOH at 250 µL.min^{-1}. **7** The EtOH goes through a 5 mL sample loop, containing the reaction. **8**-**9** The reaction enters the tube-in-tube setup and flows counter to the CO generating reaction. **10** After being loaded with CO, the reaction is heated in two 10 mL heating coils at 120 °C. **11** the reaction is analyzed in-line on a Flow-IR using a diamond probe head (computer out of frame). **12** 75 psi backpressure regulator.

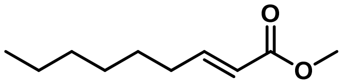
Synthesis and Characterisation

(*E*)-Methyl hept-2-enoate (2)



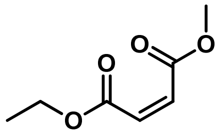
Synthesized according to General method A from **1** (114 mg, 0.49 mmol (90% purity)) and obtained as a colorless oil (48 mg, 69% [corrected for solvent]) after flash chromatography (Pet. Ether:Et_2O, 50:1): ***R_f*** = 0.20 (Pet. Ether:Et_2O, 50:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.4, 7.0 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.72 (s, 3H), 2.23 – 2.17 (m, 2H), 1.47 – 1.41 (m, 2H), 1.38 – 1.31 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.4, 149.9, 121.0, 51.5, 32.1, 30.3, 22.3, 14.0. The spectral data were in agreement with the literature.[1]

(*E*)-Methyl non-2-enoate (4)



Synthesized according to General method A from **3** (130 mg, 0.54 mmol) and obtained as a colorless oil (90 mg, 97%) after flash chromatography (Pet. Ether:Et_2O, 50:1): ***R_f*** = 0.30 (Pet. Ether:Et_2O, 20:1):**^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.81 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.72 (s, 3H), 2.21 – 2.17 (m, 2H), 1.47 – 1.41 (m, 2H), 1.33 – 1.23 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.4, 150.1, 120.9, 51.6, 32.4, 31.7, 29.0, 28.1, 22.7, 14.2. The spectral data were in agreement with the literature.[2]

Ethyl methyl maleate (6)



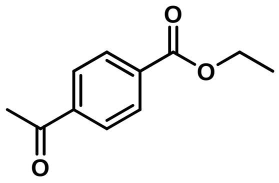
General method A:

Synthesized according to General method A from **5** (116 mg, 0.49 mmol) and obtained as a colorless oil (49 mg, 60%) after flash chromatography (Pet. Ether:Et_2O, 3:1): ***R_f*** = 0.33 (Pet. Ether:Et_2O, 3:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.24 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.9, 165.3, 130.2, 129.6, 61.5, 52.3, 14.2. The spectral data were in agreement with the literature.[3]

General method B:

Synthesized with CO generation according to General method B, but reagents and conditions the same as General method A, from **5** (113 mg, 0.50 mmol) and obtained as a colorless oil (56 mg, 70%) after flash chromatography (Pet. Ether:Et_2O, 3:1): ***R_f*** = 0.33 (Pet. Ether:Et_2O, 3:1). ^{1}H and ^{13}C NMR were in agreement with that obtained using General method A.

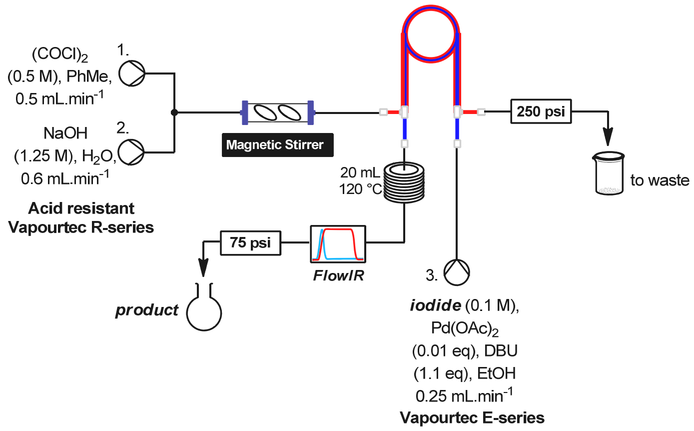
Ethyl 4-acetylbenzoate (9)



Plug flow:

Synthesized according to General method B from **7** (142 mg, 0.50 mmol) and obtained as a white solid (92 mg, 97%**)** after flash chromatography (Pet. Ether:Et_2O, 8:1 → 4:1): ***R**$_f$* = 0.24 (Pet. Ether:Et_2O, 4:1); **mp** = 53.2-54.1 °C, lit[4] 55.5 - 56.5 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.64 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.8, 165.9, 140.2, 134.3, 129.9, 128.3, 61.6, 27.1, 14.4. The spectral data were in agreement with the literature.[4]

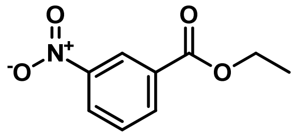
Continuous flow:



Scheme 3. Modification of set up for continuous flow run.

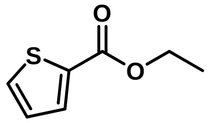
In a modification of General method B, **9** was also synthesised on larger scale using continuous flow, with the flow equipment set up according to Scheme 3. The *CO generation reaction* was unchanged from General method B. The *CO consuming reaction* consisted of an ethanolic solution of aryl iodide (1.97 g, 8.0 mmol), Pd(OAc)$_2$ (18 mg, 0.08 mmol) and DBU (1.30 mL, 8.7 mmol). The mixture was pumped continuously, rather than being injected using a sample loop, but the setup was otherwise unchanged. The title compound was obtained as a white solid (1.47 g, 96%**)** after flash chromatography (Pet. Ether:EtOAc, 4:1): ***R**$_f$* = 0.24 (Pet. Ether:Et_2O, 4:1);. ^{1}H and ^{13}C NMR were in agreement with that obtained using plug flow General method B.

Ethyl 3-nitrobenzoate (10)



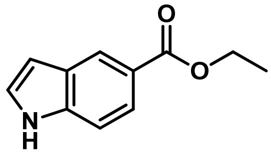
Synthesized according to General method B from **8** (151 mg, 0.50 mmol) and obtained as a white solid (98 mg, 99%) after flash chromatography (Pet. Ether:Et_2O, 8:1): ***R**$_f$* = 0.45 (Pet. Ether:Et_2O, 4:1); **mp** = 40.1-41.5 °C, lit[5] 36 - 38 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.86 – 8.84 (m, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.37 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.6, 148.4, 135.4, 132.4, 129.7, 127.4, 124.7, 62.1, 14.4. The spectral data were in agreement with the literature.[5]

Ethyl thiophene-2-carboxylate (15)



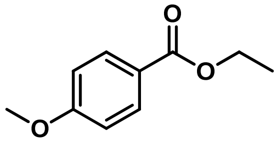
Synthesized according to General method B from **11** (108 mg, 0.52 mmol) and obtained as a colorless oil (58 mg, 74%) after by flash chromatography (Pet. Ether:Et_2O, 95:5): ***R_f*** = 0.61 (Pet. Ether:Et_2O, 8:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.80 (d, J = 3.7 Hz, 1H), 7.54 (d, J = 5.0 Hz, 1H), 7.10 (t, J = 4.3 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.4, 134.2, 133.4, 132.3, 127.8, 61.3, 14.5. The spectral data were in agreement with the literature.[6]

Ethyl 1H-indole-5-carboxylate (16)



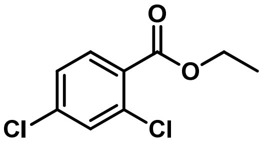
Synthesized according to General method B from **12** (146 mg, 0.50 mmol) and obtained as a pinkish solid (74 mg, 78%) after flash chromatography (Pet. Ether:Et_2O, 4:1→2:1):): ***R_f*** = 0.23 (Pet. Ether:Et_2O, 1.4); **mp** = 92.7 -96.3 °C, lit[7] 96.5 - 97.5 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 8.43 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.27 (t, J = 2.7 Hz, 1H), 6.66 – 6.64 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.93 138.5, 127.6, 125.6, 123.8, 123.5, 122.4, 110.8, 104.1, 60.7, 14.6. The spectral data were in agreement with the literature.[7]

Ethyl 4-methoxybenzoate (17)



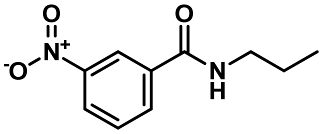
Synthesized according to General method B from **13** (117 mg, 0.50 mmol) and obtained as a colorless oil (76 mg, 78%) after flash chromatography (Pet. Ether:Et_2O, 8:1): ***R_f*** = 0.54 (Pet. Ether:Et_2O, 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.5, 163.4, 131.7, 123.1, 113.7, 60.8, 55.6, 14.5. The spectral data were in agreement with the literature.[8]

Ethyl 2,4-dichlorobenzoate (18)



Synthesized according to General method B from **14** (164 mg, 0.50 mmol) and obtained as a colorless oil (86 mg, 79%) after flash chromatography (Pet. Ether:Et_2O, 99:1): ***R*$_f$** = 0.08 (Pet. Ether); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.0, 138.3, 135.0, 132.6, 131.1, 128.7, 127.1, 61.9, 14.3. The spectral data were in agreement with the literature.[9]

3-Nitro-N-propylbenzamide (19)

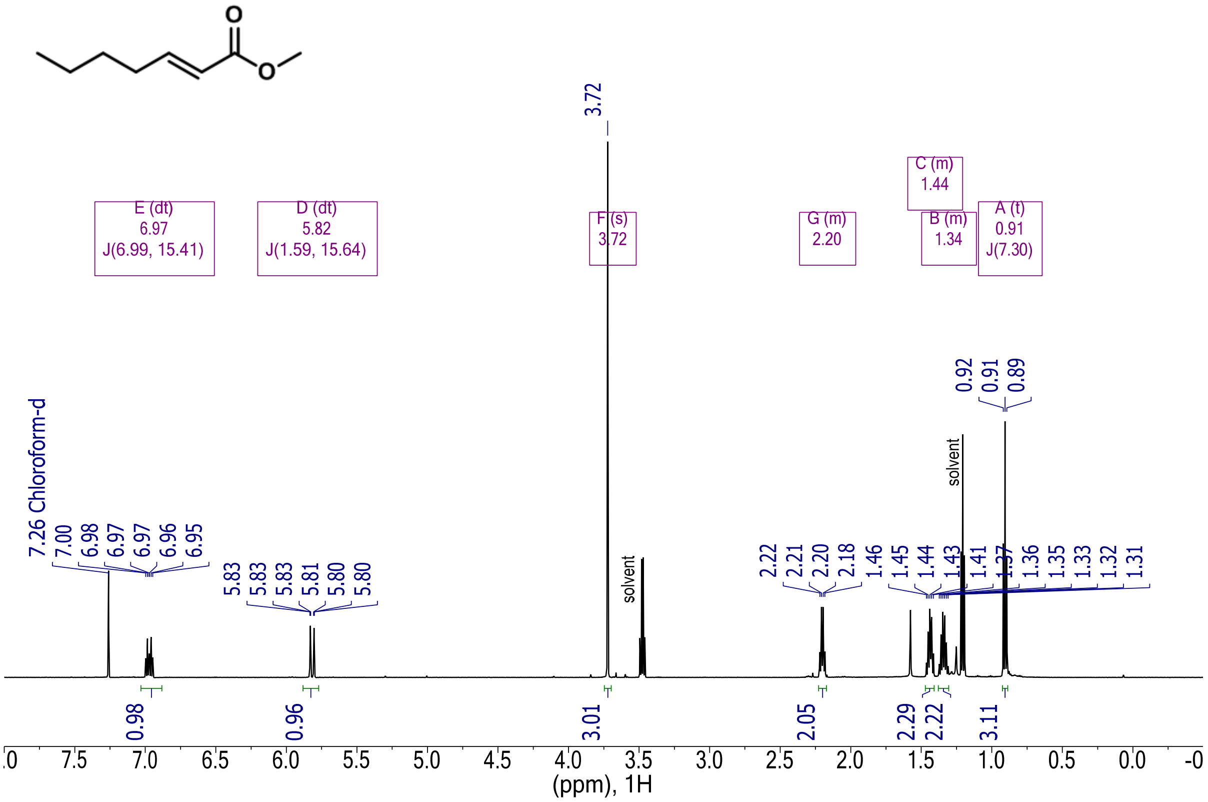


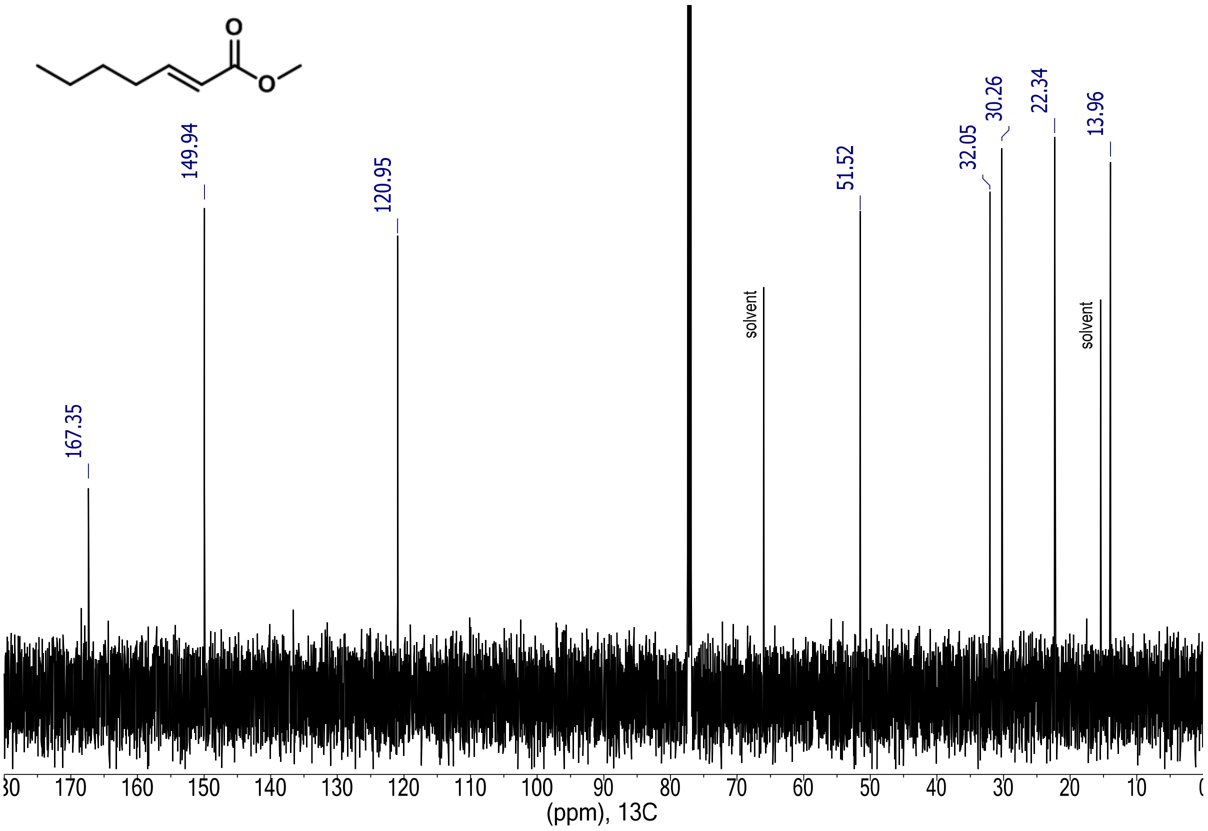
Synthesized according to General method B, with the following two changes: EtOH was replaced by 1,4-dioxane, and 3 equivalents of *n*-propylamine was added the reaction. Starting from **7** (127 mg, 0.51 mmol) **19** was obtained as a pale yellow solid (78 mg, 74%) after flash chromatography (Pet. Ether:Et_2O, 2:1 → 1:1): ***R*$_f$** = 0.17 (Pet. Ether:Et_2O, 1:1); **mp** = 73.2-74.6 °C, lit.[10] 72 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.33 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 6.53 (s, 1H), 3.47 – 3.42 (m, 2H), 1.70 – 1.63 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.3, 148.3, 136.6, 133.4, 129.9, 126.0, 121.8, 42.2, 22.9, 11.6. The spectral data were in agreement with the literature.[10]

NMR Spectra

(E)-Methyl hept-2-enoate (2)

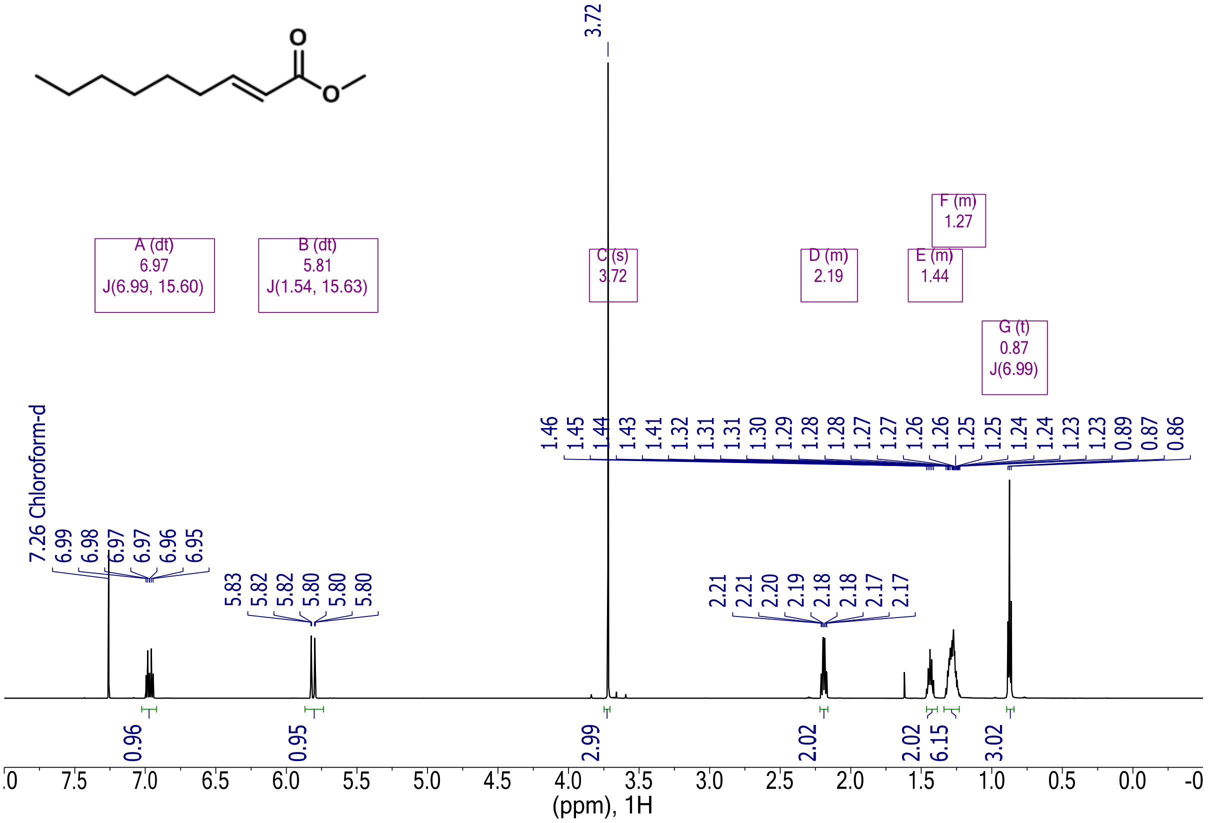
600 MHz/151 MHz

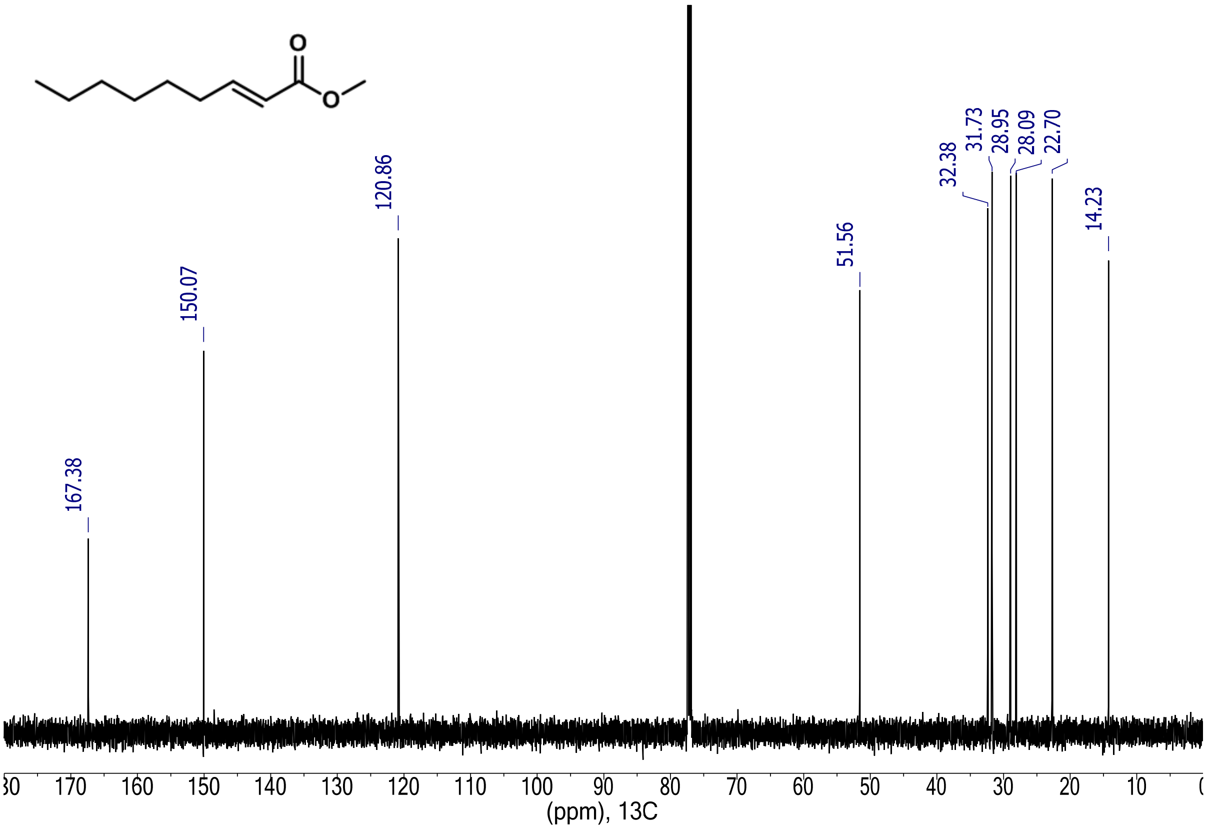




(E)-Methyl non-2-enoate (4)

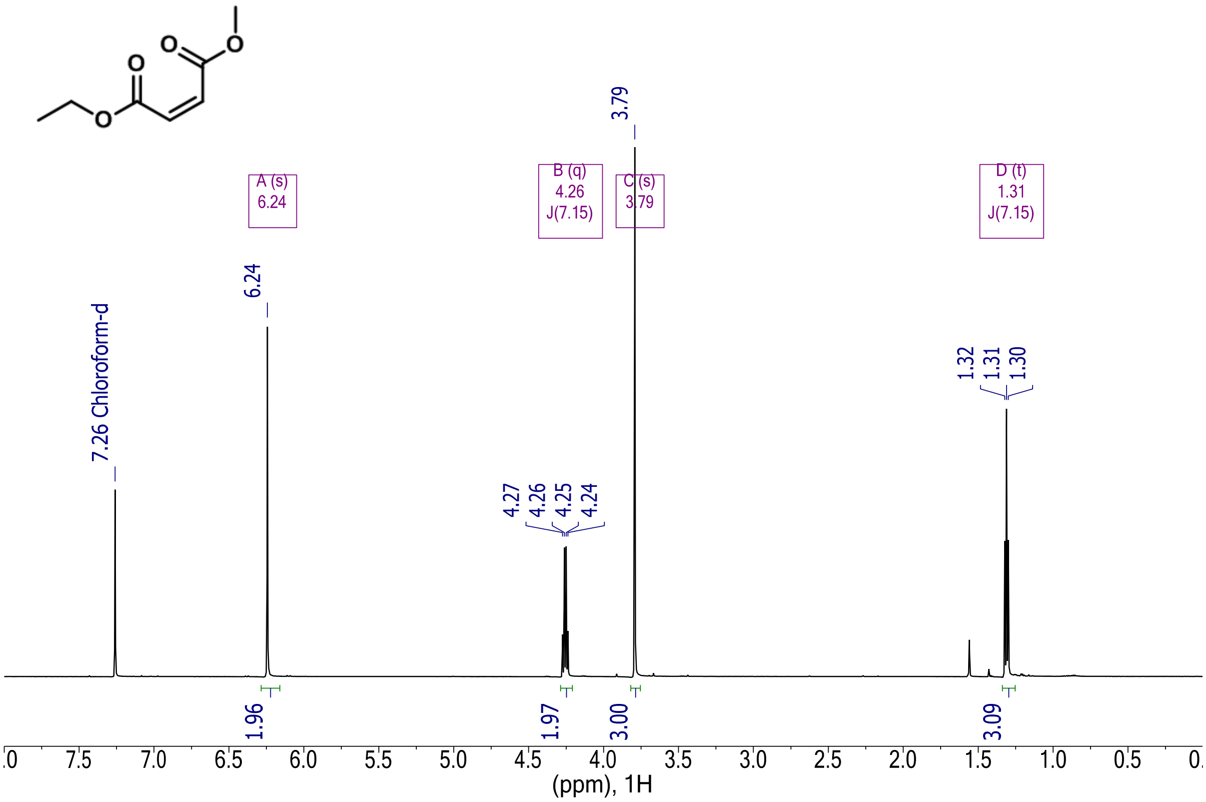
600 MHz/151 MHz

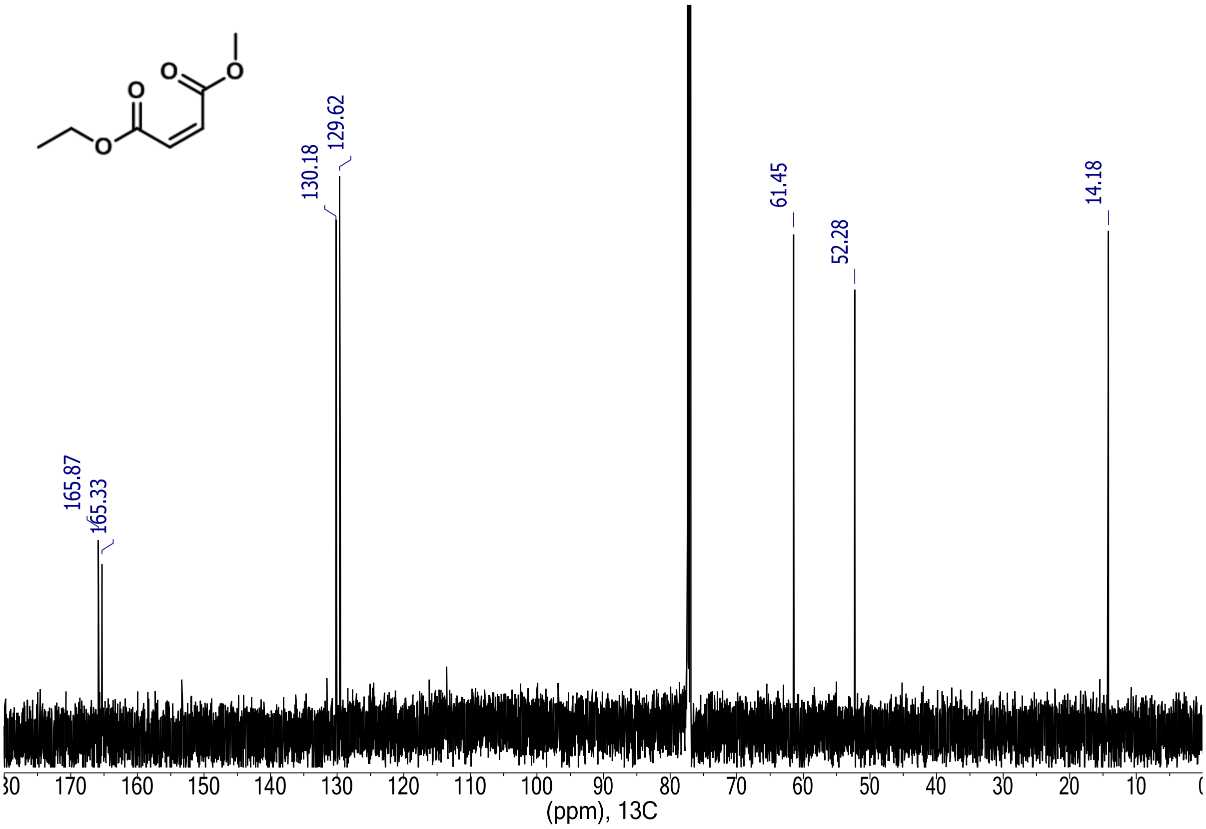




Ethyl methyl maleate (6)

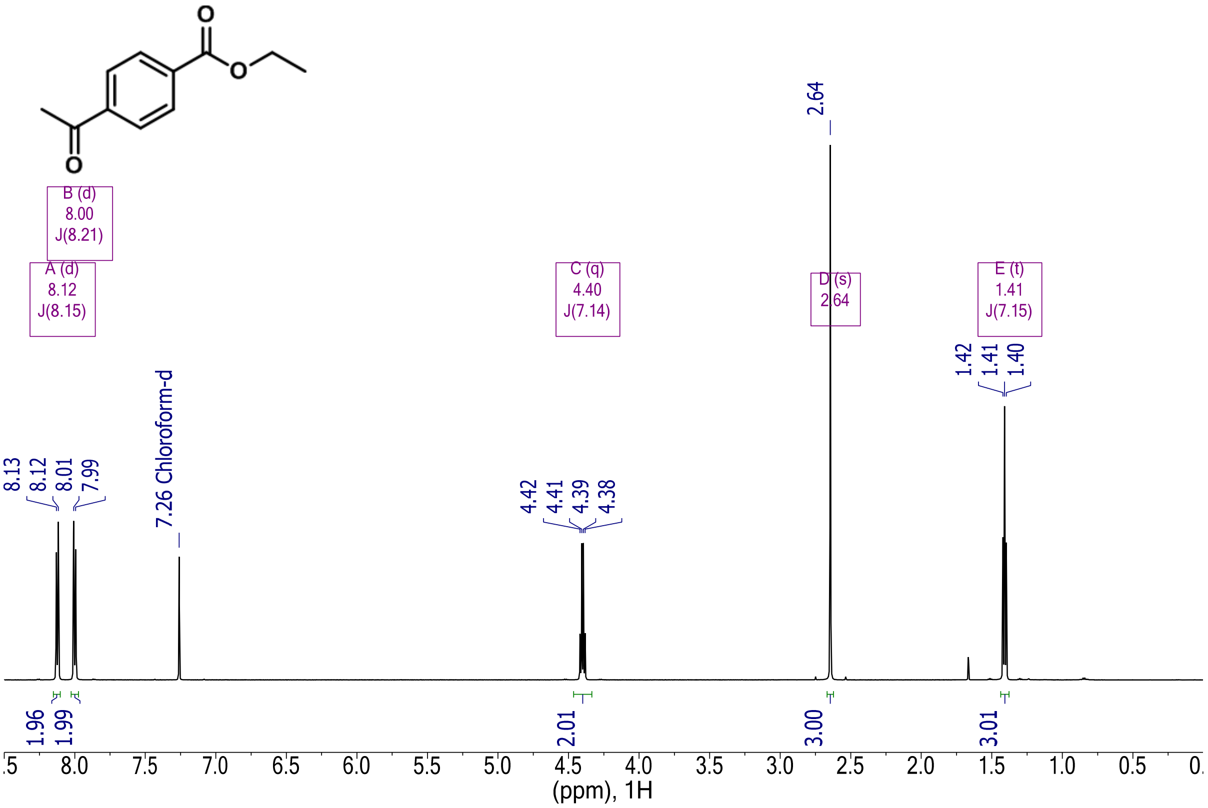
600 MHz/151 MHz

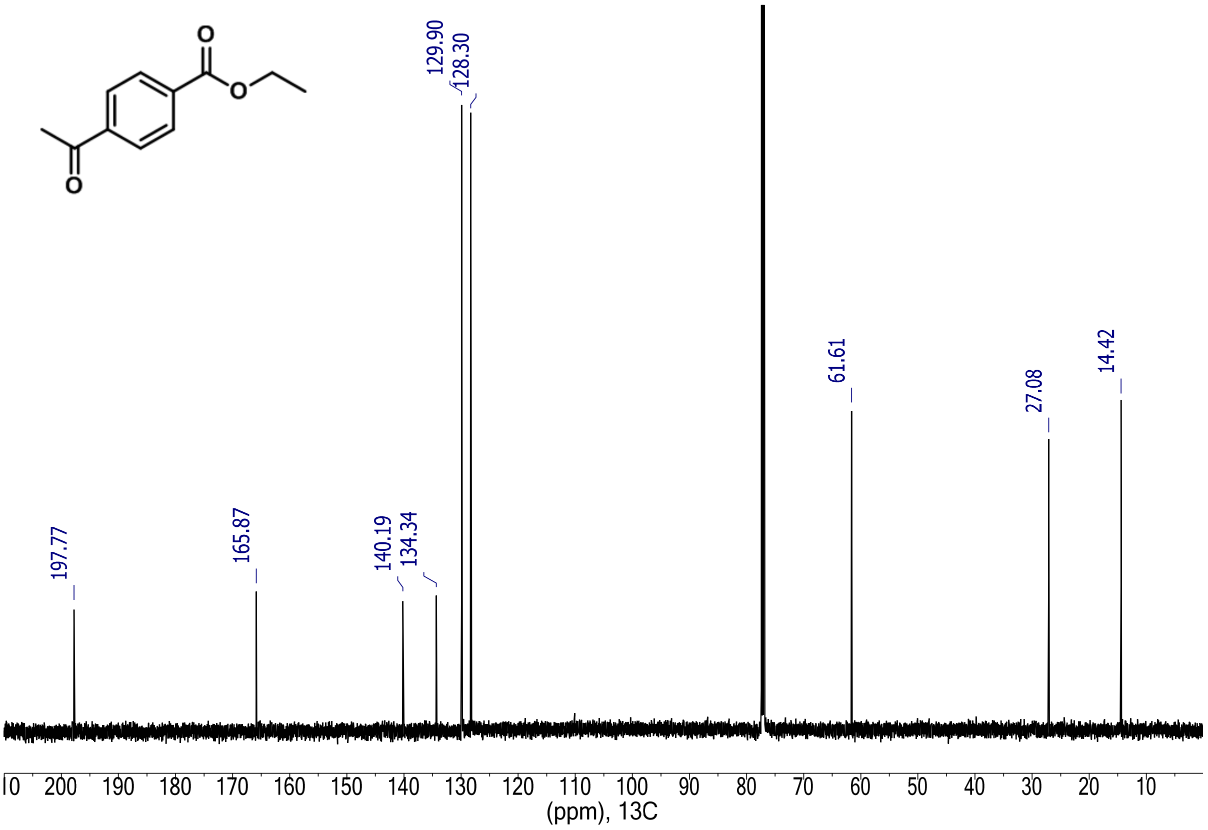




Ethyl 4-acetylbenzoate (9)

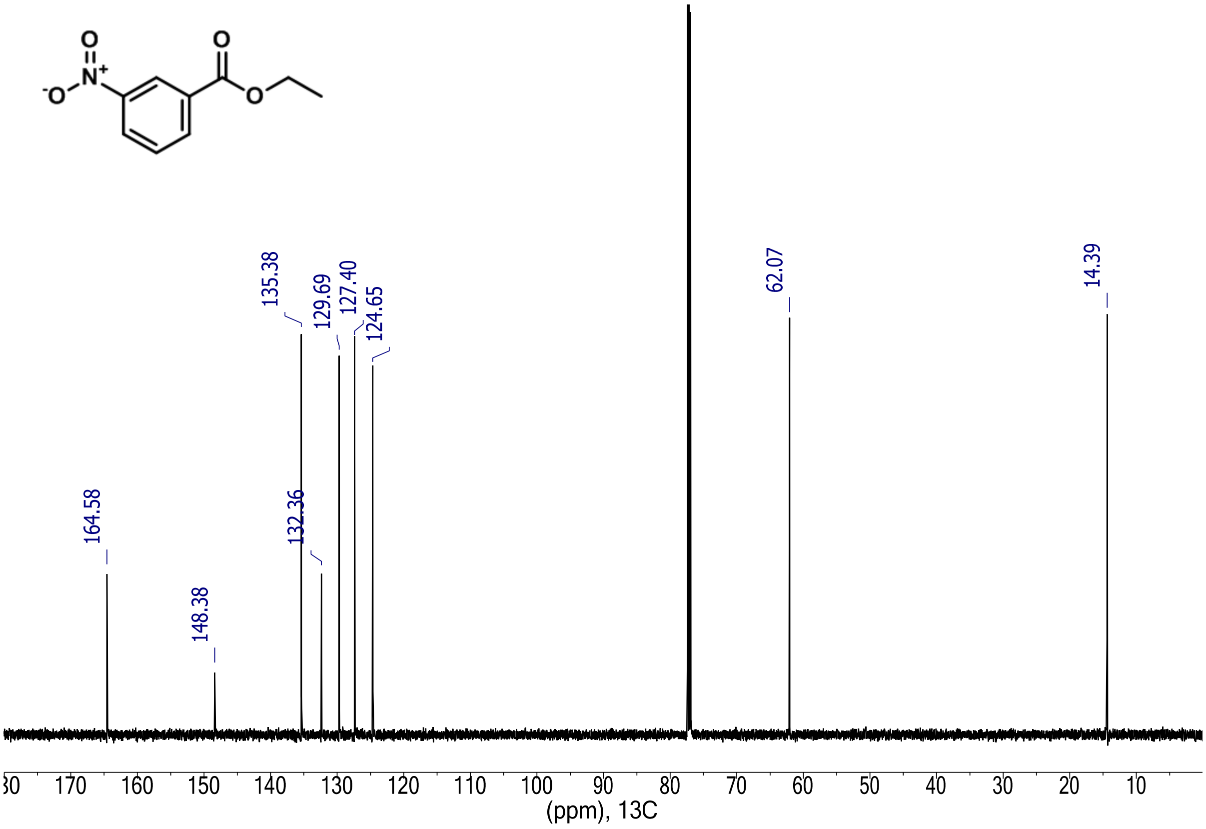
600 MHz/151 MHz





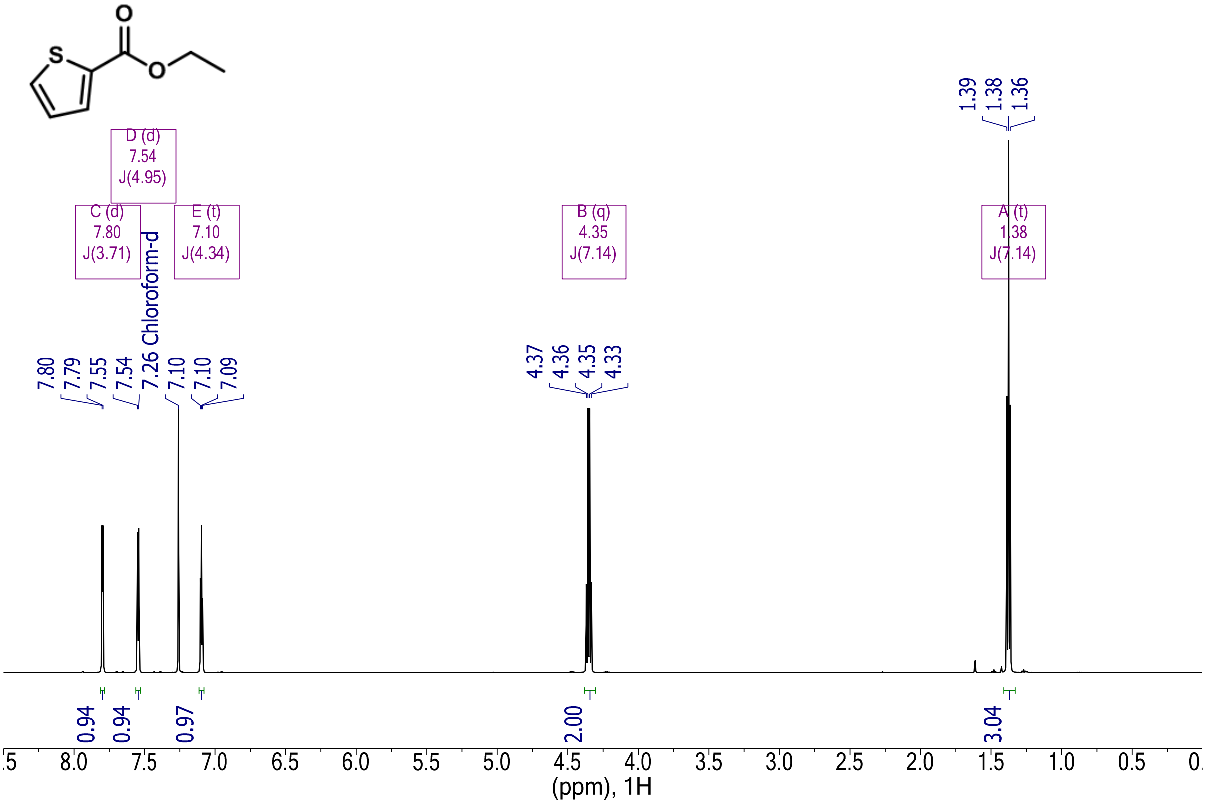
Ethyl 3-nitrobenzoate (10)

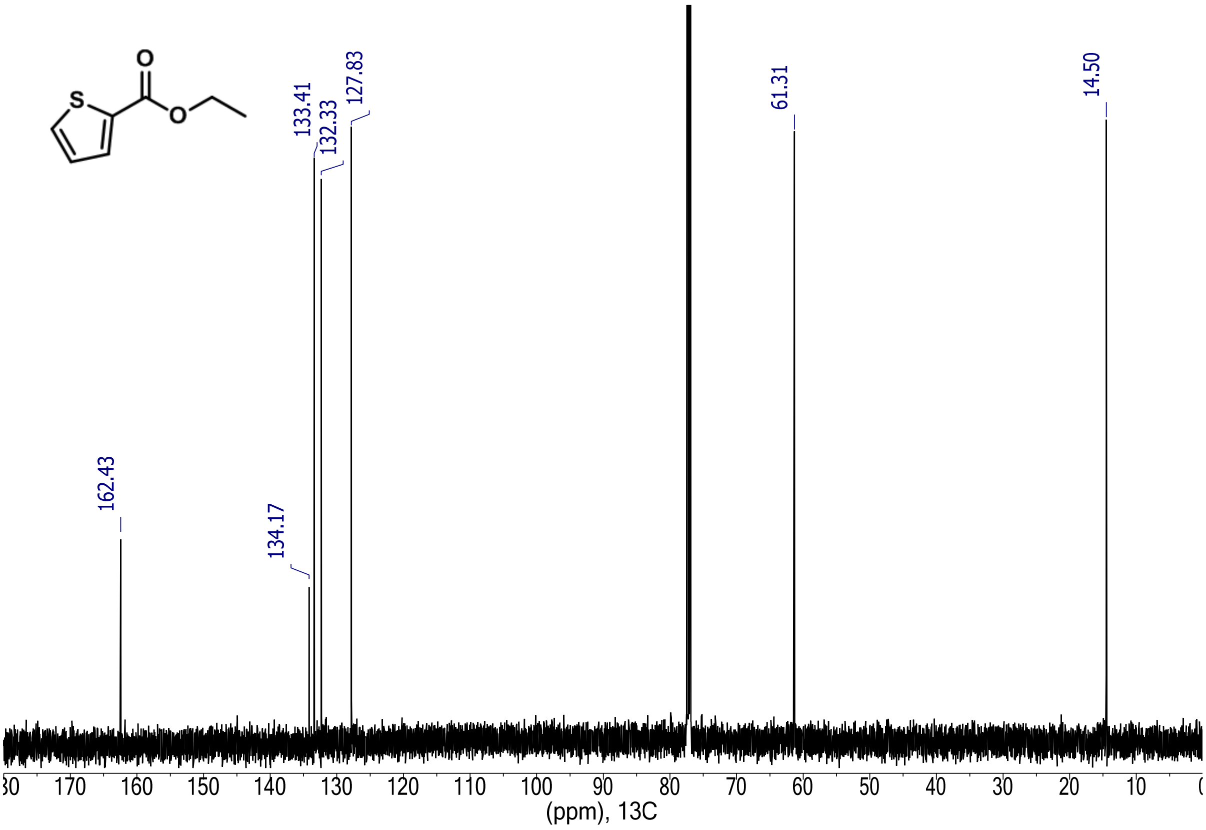
600 MHz/151 MHz



Ethyl thiophene-2-carboxylate (15)

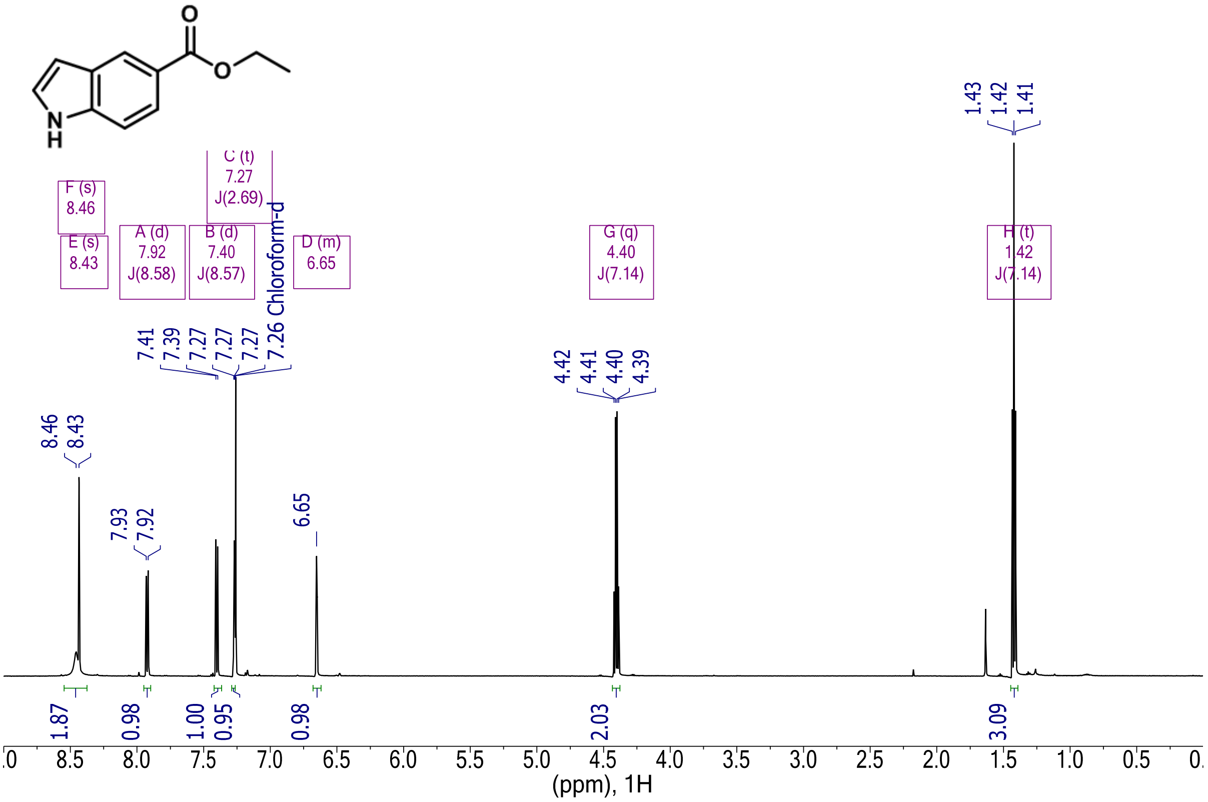
600 MHz/151 MHz

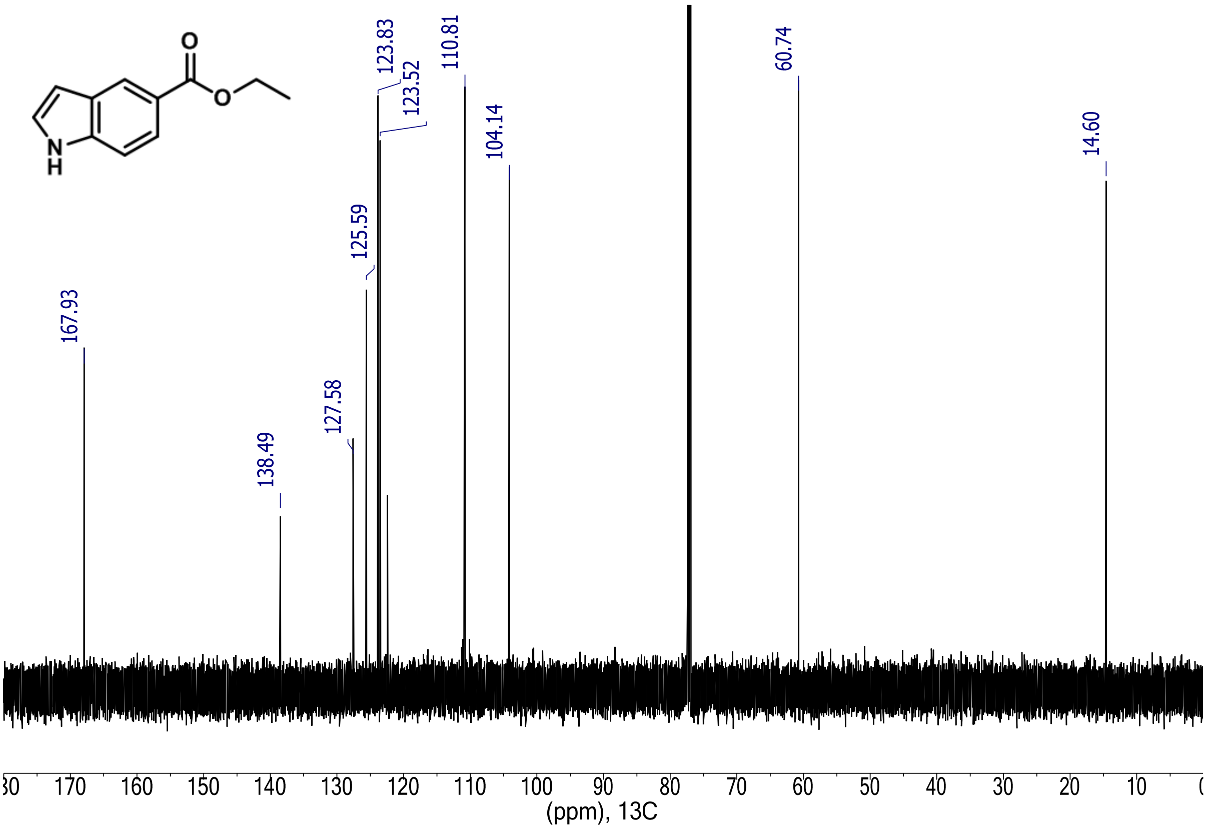




Ethyl 1H-indole-5-carboxylate (16)

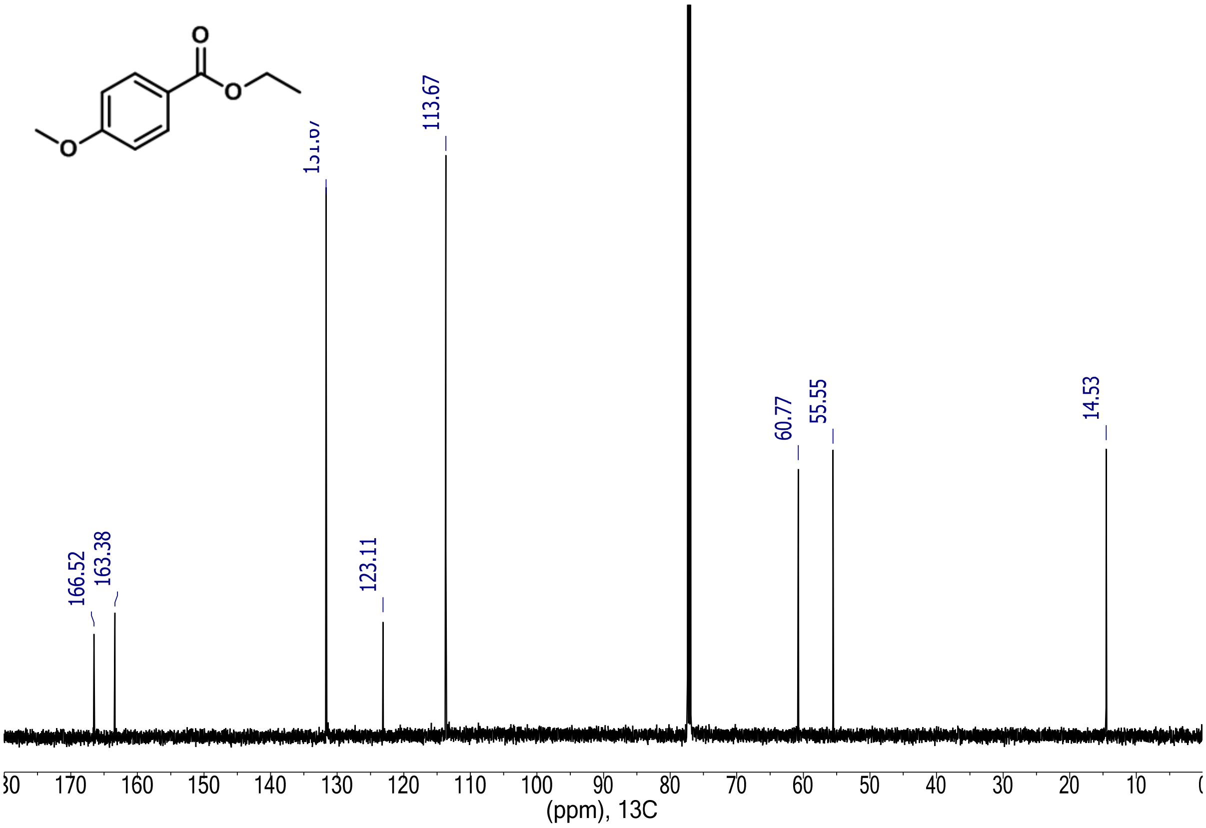
600 MHz/151 MHz





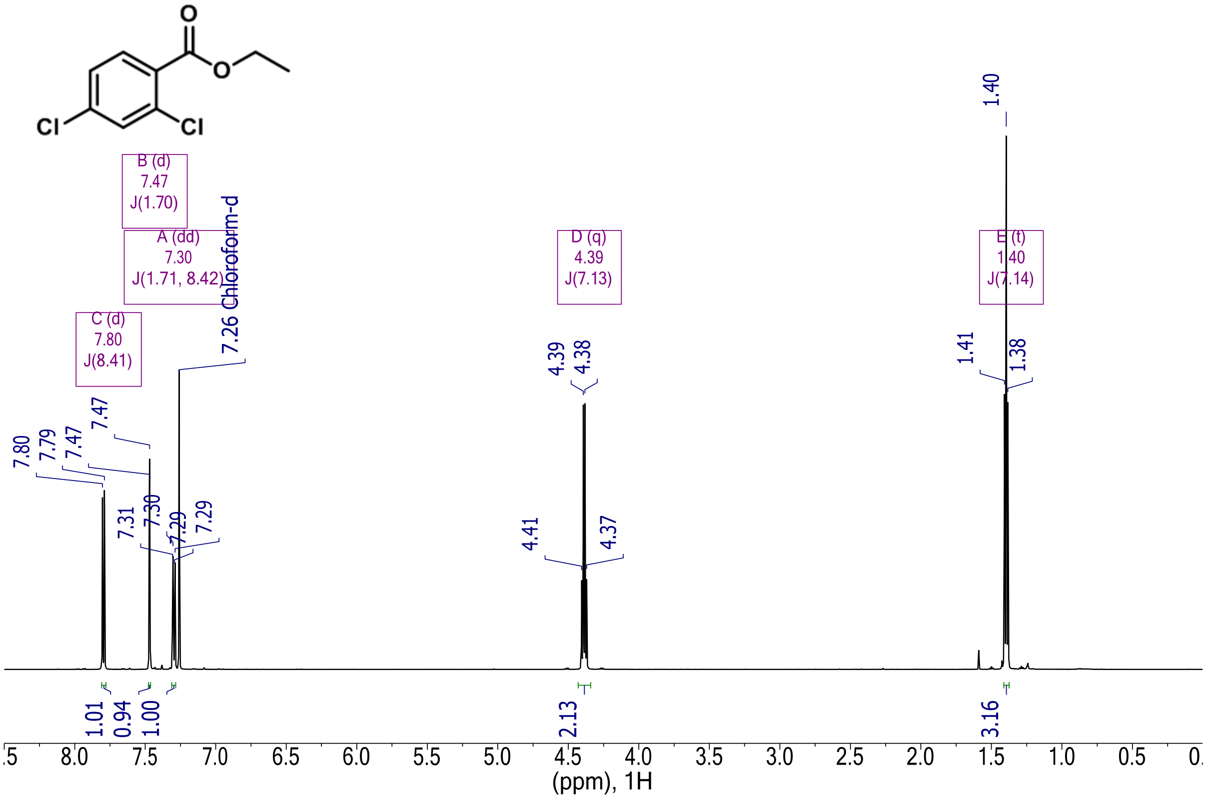
Ethyl 4-methoxybenzoate (17)

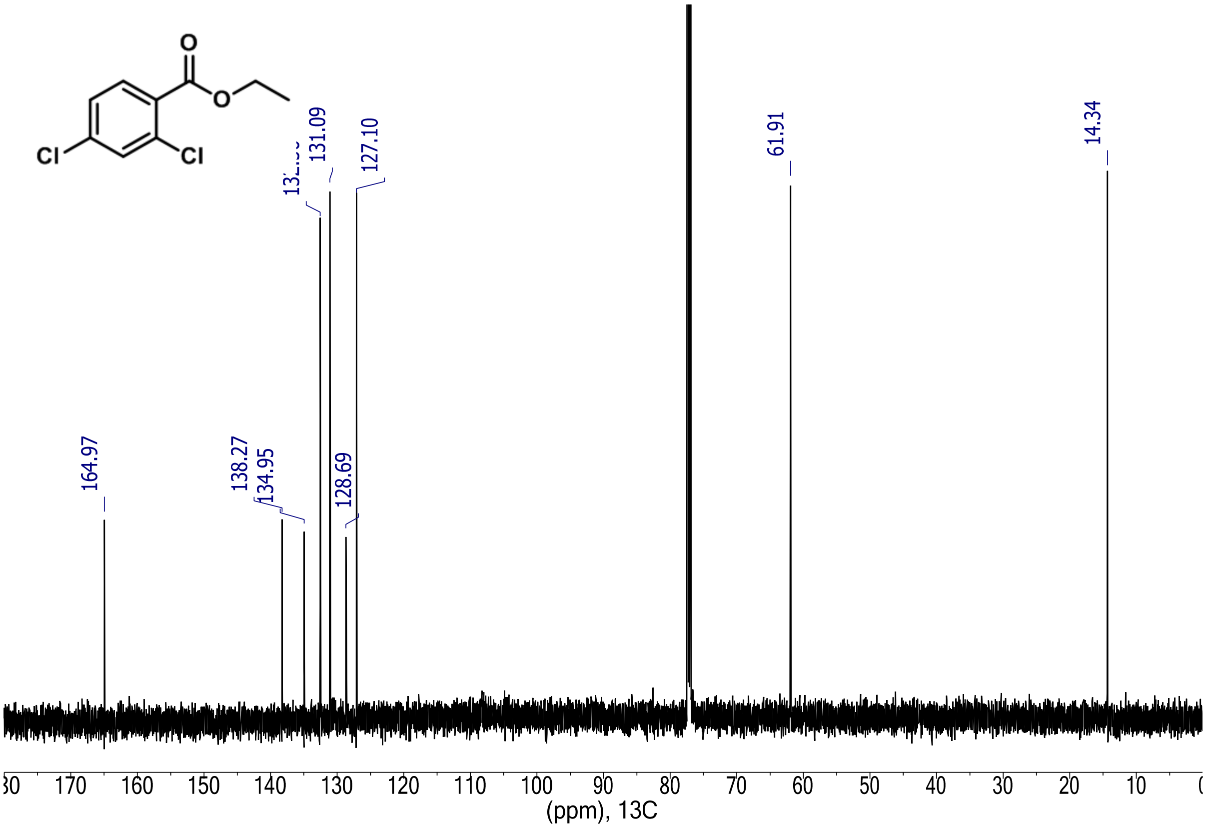
600 MHz/151 MHz



Ethyl 2,4-dichlorobenzoate (18)

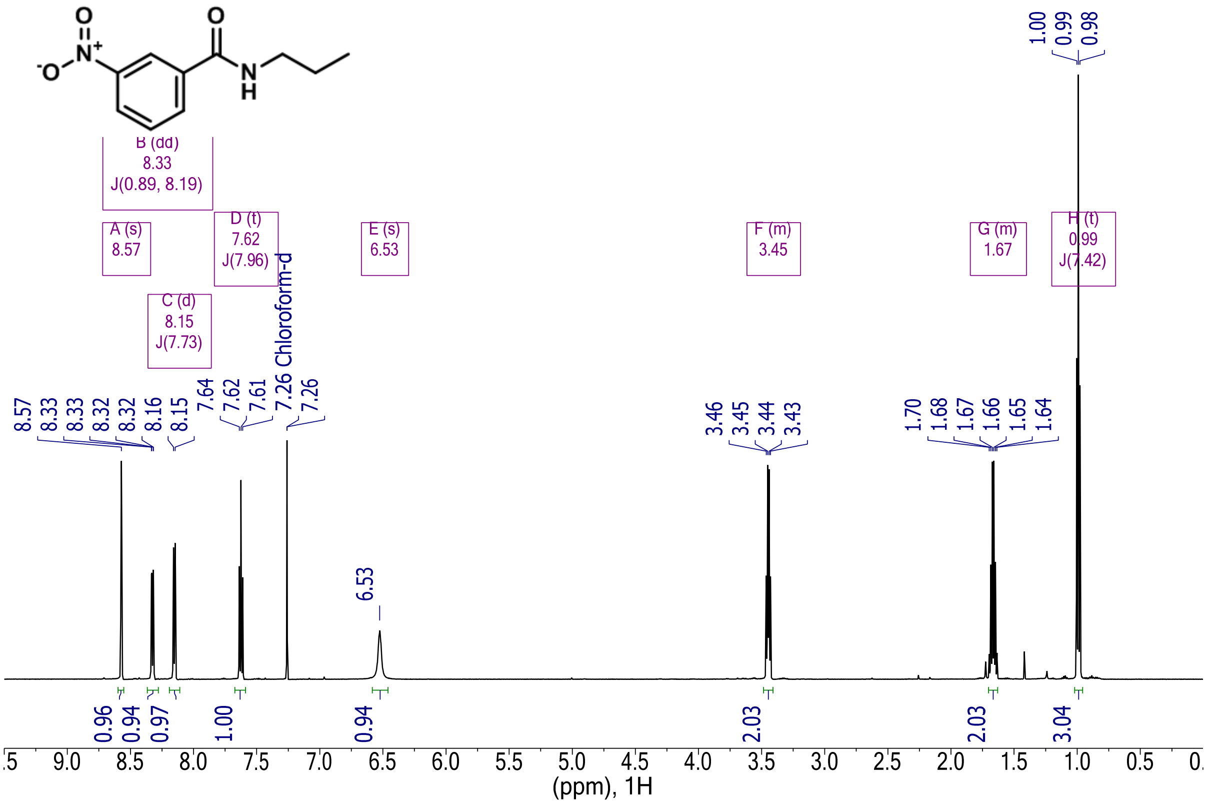
600 MHz/151 MHz

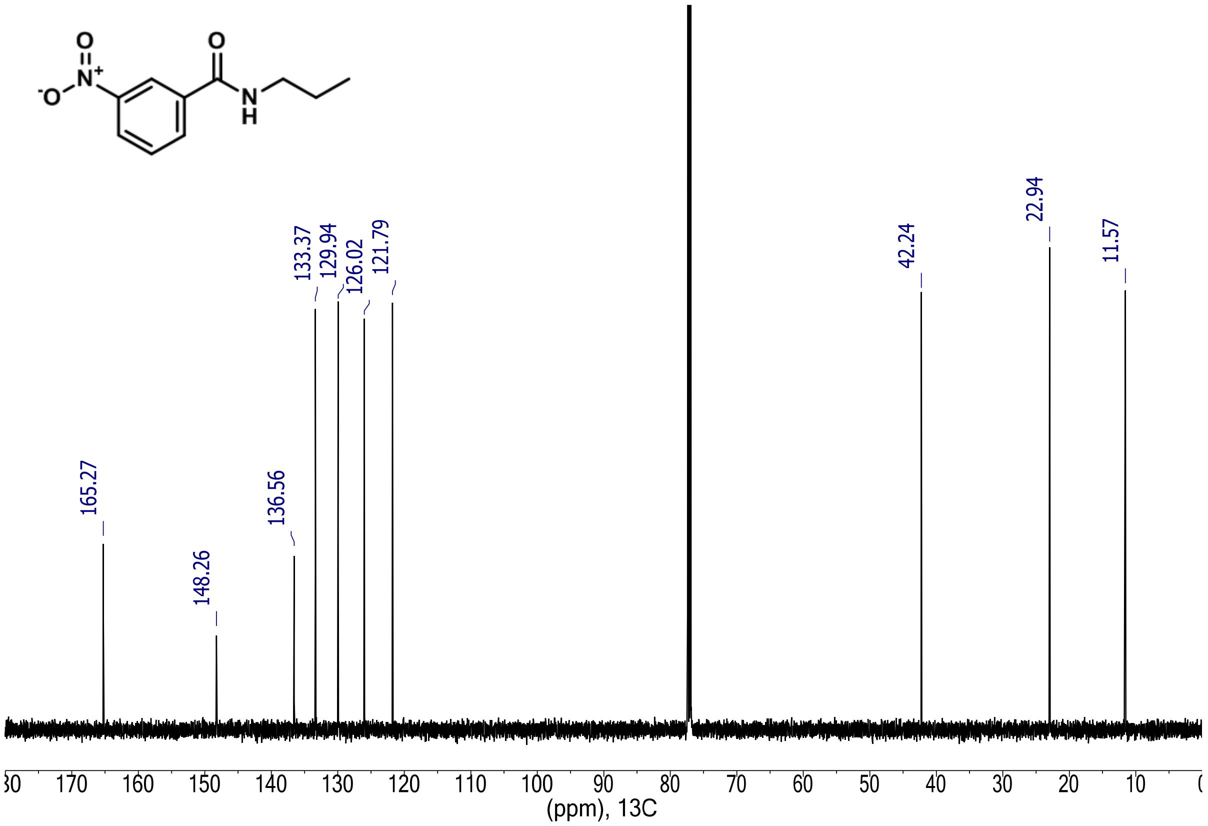




3-Nitro-N-propylbenzamide (19)

600 MHz/151 MHz





References

1. A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.*, 2007, **72**, 5244-5259.
2. G. Deng, B. Xu and C. Liu, *Tetrahedron*, 2005, **61**, 5818-5821.
3. S. Hashimoto, I. Furukawa and T. Kuroda, *Tetrahedron Lett.*, 1980, **21**, 2857-2860.
4. Y. Kubota, S. Nakada and Y. Sugi, *Synlett*, 1998, **1998**, 183-185.
5. E. Moreau, S. Fortin, J. Lacroix, A. Patenaude, J. L. Rousseau and C. G. R, *Bioorg. Med. Chem.*, 2008, **16**, 1206-1217.
6. A. S.-Y. Lee, C.-C. Wu, L.-S. Lin and H.-F. Hsu, *Synthesis*, 2004, 568-572.
7. B. M. Trost and A. McClory, *Angew. Chem., Int. Ed.*, 2007, **46**, 2074-2077.
8. R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754-2755.
9. A. Schmidt, T. Habeck, B. Snovydovych and W. Eisfeld, *Org. Lett.*, 2007, **9**, 3515-3518.
10. W. Bao, W. Qian and C. Fang, *Synlett*, 2008, **2008**, 2529-2531.