

Oxidation of Primary Alcohols to Methyl Esters by Hydrogen Transfer

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General Methods: Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen or argon. In all cases, solvents were distilled and degassed prior to use, apparatus was oven dried or flame dried under vacuum. Toluene and methanol were stored in sealed Young's ampoules.

TLC using polythene, aluminium or glass backed plates precoated with Macherey-Nagel Sil G/UV_{254nm} neutral silica were used to monitor reactions where appropriate. Visualisation of these plates was by 254nm UV light and/or KMnO₄ or 2,4-DNP dips followed by gentle warming. TLC data quoted for specific compounds indicate the most suitable method of visualisation. Organic layers were routinely concentrated using a Büchi rotary evaporator. Where necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60Å silica gel (35-70 micron) purchased from Fluorochem.

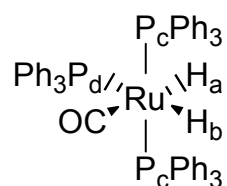
NMR spectra were run in CDCl₃, d⁸-PhMe, d⁶-DMSO, C₆D₆ or d⁴-MeOH on either a Bruker Avance 250 (250 MHz) or Bruker Avance 300 (300 MHz) instrument and recorded at the following frequencies: proton (¹H – 250/300 MHz), carbon (¹³C – 75.4 MHz). Chemical shifts are reported relative to the residual solvent peak where possible or alternatively to SiMe₄ (δ = 0.00 ppm) as internal standard. Coupling constants (*J*) are given in Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent), septet (sep), unresolved multiplet (m) or broad (br.). General assignments are classified as (Ph) phenyl, (Ar) aromatic, (C) quaternary carbon, (CH) methyne carbon, (CH₂) methylene carbon and (CH₃) methyl carbon. All structural assignments of both protons and carbons were achieved with the aid of COSY and PENDANT experiments wherever possible and with comparisons from analogous literature compounds. Protons that possess chemical but not magnetic equivalence (AA'BB' systems) as in the case of 1,4-disubstituted aromatics are reported as multiplets or doublets, depending on their appearance in spectra.

Melting points were carried out on a Gallenkamp MF-370 hot stage melting point apparatus and are uncorrected.

Unless preparative details are provided, all reagents were commercially available and purchased from either Acros Organics, Sigma-Aldrich, Alfa Aesar, Avocado, Fluka, Lancaster, Maybridge or Strem chemical companies.

Experimental Methods:

Preparation of carbonyl(dihydrido)tris(triphenylphosphine)ruthenium (II)^[1]; Ru(PPh₃)₃(CO)H₂



To a nitrogen purged, 3-necked round bottomed flask charged with triphenylphosphine (6.28 g, 23.9 mmol) was added degassed anhydrous methanol (200 cm³). The mixture was heated at reflux for 10 minutes, forming a solution. In quick succession, ruthenium trichloride hydrate (1.04 g, 4.0 mmol) in methanol (40 cm³), aqueous formaldehyde (37% w/w) (40 cm³) and potassium hydroxide (1.20 g, 21.4 mmol) in methanol (40 cm³) were added. The resulting solution was heated for 30 minutes at reflux and then cooled in an ice bath with stirring for a further 30 minutes. The grey precipitate was collected by vacuum filtration and washed with absolute ethanol (50 cm³), water (50 cm³), absolute ethanol (50 cm³) and finally hexane (50 cm³). The crude product was dissolved in toluene and filtered through a column of neutral alumina and washed through thoroughly with toluene. The toluene solution was concentrated *in vacuo* to approximately 20 cm³ and layered with anhydrous methanol producing a precipitate which was collected by vacuum filtration as a white solid (Ru(PPh₃)₃(CO)H₂). Yield 2.50 g, (68%). ¹H NMR (300MHz, C₆D₆, 25 °C); δ = -6.53 (1H, ddt, Ru-H_a, J_{Pc-Ha} = 30.5 Hz, J_{Pd-Ha} = 15.3 Hz, J_{Ha-Hb} = 6.1 Hz), -8.29 (1H, ddt, Ru-H_b, J_{Pd-Hb} = 74.5 Hz, J_{Pc-Hb} = 28.1 Hz, J_{Ha-Hb} = 6.1 Hz). ³¹P{¹H}: δ = 58.2 (d, J_{Pc-Pd} = 16.8 Hz, 46.1 (t, J_{Pd-Pc} = 16.8 Hz). IR (nujol mull, cm⁻¹): 1960 (ν_{CO}).

Representative procedure for the oxidation of benzyl alcohol to benzaldehyde: To an oven-dried, argon purged Schlenk tube containing Ru(PPh₃)₃(CO)H₂ (23 mg, 0.025 mmol, 5 mol %) and Xantphos (14.5 mg, 0.025 mmol, 5 mol %) was added degassed anhydrous toluene (0.5 cm³) and the mixture heated at reflux for 1 hour then allowed to cool to room temperature. To the resultant deep-red solution was added benzyl alcohol (54 mg, 0.5 mmol), alkene (0.75 mmol), and the mixture heated at 110 °C for 2 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo*. The conversion was determined by ¹H NMR spectroscopy.

Representative procedure for the oxidation of primary alcohols to methyl esters: To an oven-dried, argon purged Schlenk tube containing Ru(PPh₃)₃(CO)H₂ (92 mg, 0.1 mmol, 5 mol %) and Xantphos (56 mg, 0.1 mmol, 5 mol %) was added degassed anhydrous toluene (2 cm³) and the mixture heated at reflux for 1 hour then allowed to cool to room temperature. To the resultant deep-red solution was added alcohol (2 mmol), crotononitrile (403 mg, 489 μL, 6 mmol), degassed anhydrous methanol (2 cm³), water (36 μL, 2 eq.) and the resultant yellow solution heated at 110 °C for 24 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (diethyl ether:hexane as eluent), furnishing the corresponding methyl esters.

Methyl phenylacetate^[2]: According to the representative procedure, using 2-phenylethanol (244 mg, 240 μL, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless liquid (250 mg, 83%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.65 (3H, s, CH₃), 3.71 (2H, s, CH₂), 7.29 (5H, m, Ph). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 41.6, 52.4, 127.5, 129.0, 129.6, 134.4, 172.4.

Methyl indole-3-acetate^[3]: According to the representative procedure, using 3-(2-hydroxyethyl)indole (322 mg, 2 mmol), the title compound was obtained and purified by column chromatography (50% diethyl ether:hexane) affording title compound as a colourless solid (277 mg, 79%). m.p. 45-46 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.72 (3H, s, CH₃), 3.81 (2H, s, CH₂), 7.13-7.25 (3H, m), 7.34 (1H, d, *J* = 8.0 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 8.14 (1H, br. s, NH). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 31.6, 40.7, 52.4, 108.8, 111.6, 119.2, 120.1, 122.6, 123.5, 127.6, 136.5, 173.1 .

Methyl (4-hydroxyphenyl)acetate^[4]: According to the representative procedure, using 2-(4-hydroxyphenyl) ethanol (276 mg, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless solid. m.p. 54-56 °C; (255 mg, 84%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.57 (2H, s, CH₂), 3.70 (3H, s, CH₃), 6.77 (2H, d, *J* = 8.4 Hz), 7.14 (2H, d, *J* = 8.4 Hz). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 40.7, 52.5, 115.9, 126.4, 130.9, 155.2, 173.1.

Methyl [2-(4-dimethylamino)phenyl]acetate^[5]: According to the representative procedure, using [2-(4-dimethylamino)phenyl]ethanol (330 mg, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless liquid (313 mg, 87%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 2.94 (6H, s, CH₃), 3.54 (2H, s, CH₂), 3.69 (3H, s, CH₃), 6.72 (2H, d, *J* = 8.4 Hz, Ar-H), 7.16 (2H, d, *J* = 8.4 Hz, Ar-H). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 40.6, 41.1, 52.3, 113.2, 130.3, 173.1.

Methyl 4-nitrobenzoate^[6]: According to the representative procedure, using 4-nitrobenzyl alcohol (306 mg, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a pale yellow solid (249 mg, 74%). m.p. 91-93 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.98 (3H, s, CH₃), 8.22 (2H, d, *J* = 8.8 Hz), 8.29 (2H, d, *J* = 8.8 Hz). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 165.5, 150.8, 135.7, 130.9, 132.7, 53.0.

Methyl cinnamate^[7]: According to the representative procedure, using 4-nitrobenzyl alcohol (306 mg, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless oil which crystallized on standing (249 mg, 74%). m.p. 37-39 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.82 (3H, s, CH₃), 6.46 (1H, d, *J* = 16.0 Hz), 7.39-7.41 (2H, m), 7.52-1.54 (3H, m), 7.71 (1H, d, *J* = 16.0 Hz). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 167.8, 145.3, 134.8, 130.7, 129.3, 128.9, 128.7, 118.2, 52.0, 36.1.

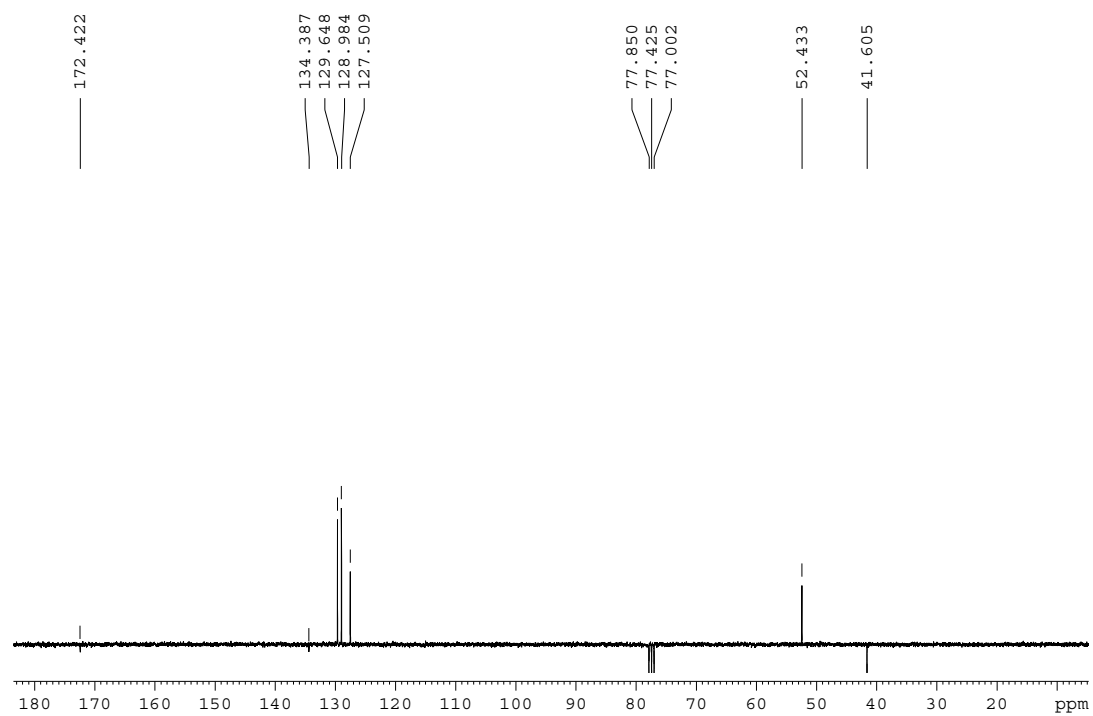
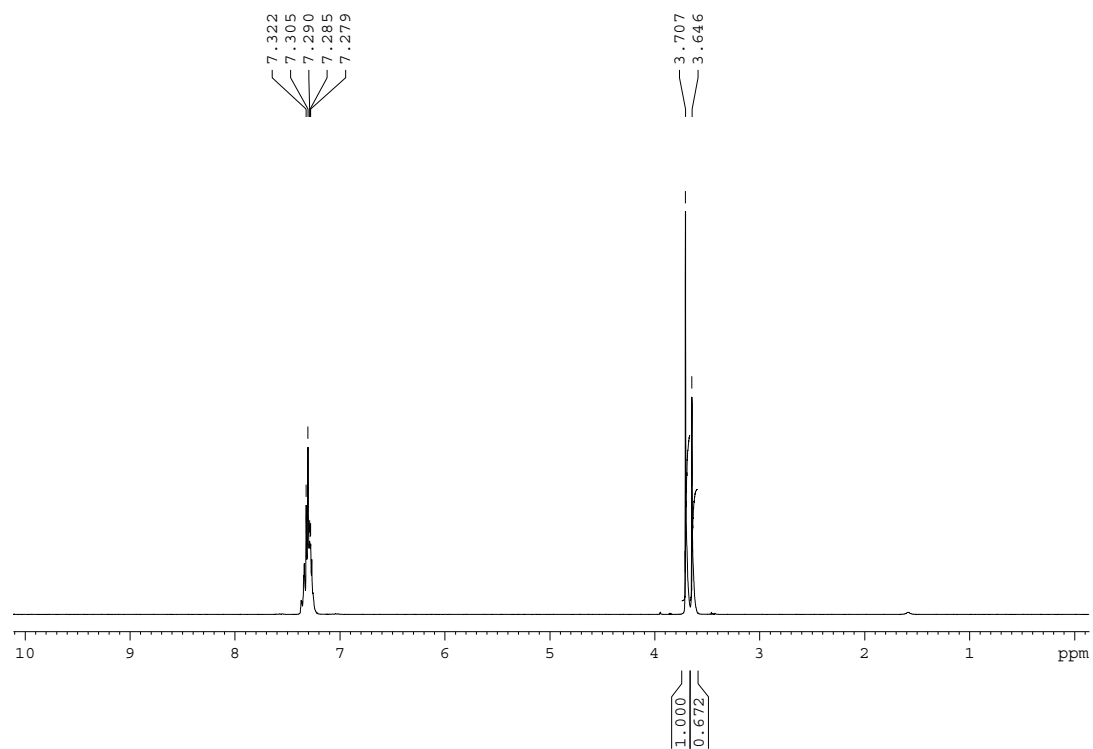
Methyl octanoate^[8]: According to the representative procedure, using 1-octanol (260 mg, 318 μL, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless liquid (248 mg, 86%). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.88 (3H, t, *J* = 6.6 Hz, CH₃), 1.30 (8H, m, CH₂), 1.62 (2H, m, CH₂), 2.31 (2H, t, *J* = 7.8 Hz), 3.67 (3H, s, CH₃). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 14.4, 23.0, 25.4, 29.3, 29.5, 32.0, 34.5, 51.8, 174.8

Methyl hexadecanoate^[9]: According to the representative procedure, using 1-hexadecanol (484 mg, 2 mmol), the title compound was obtained and purified by column chromatography (20% diethyl ether:hexane) affording title compound as a colourless oil which crystallized on standing (248 mg, 86%). m.p. 30-31 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.88 (3H, t, *J* = 6.8 Hz, CH₃), 1.20-1.27 (26H, m, CH₂), 2.24 (2H, t, *J* = 7.4 Hz, CH₂), 3.60 (3H, s, CH₃). ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 22.7, 25.0, 29.1, 29.4, 29.5, 29.7, 32.0, 34.0, 34.2, 51.4, 174.2.

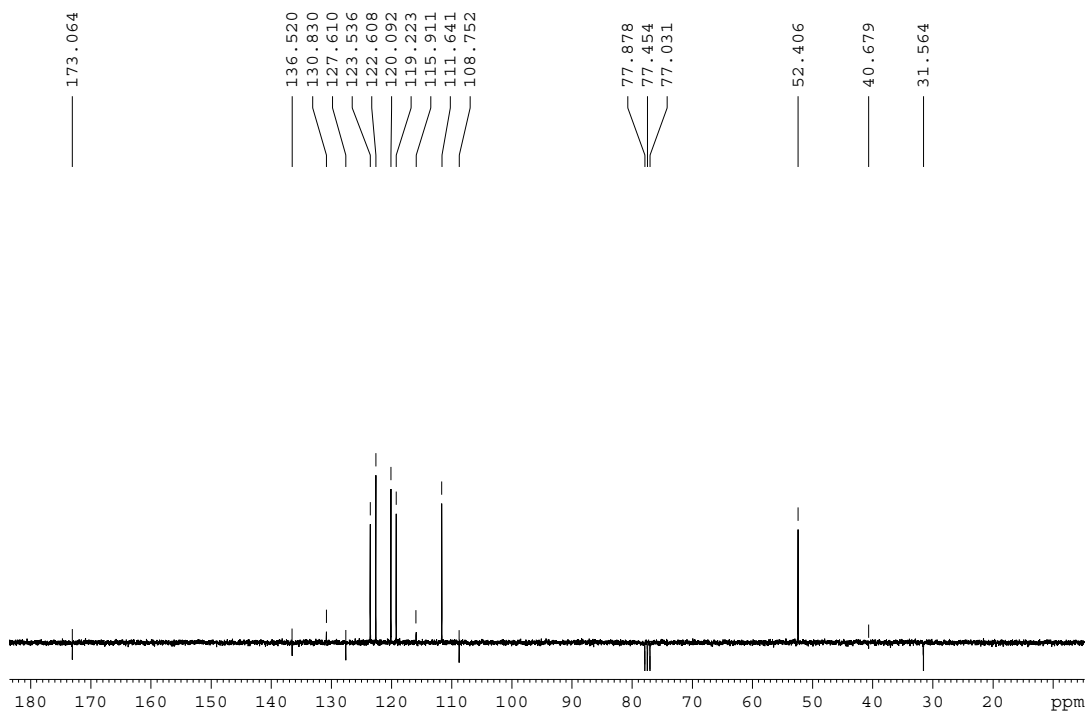
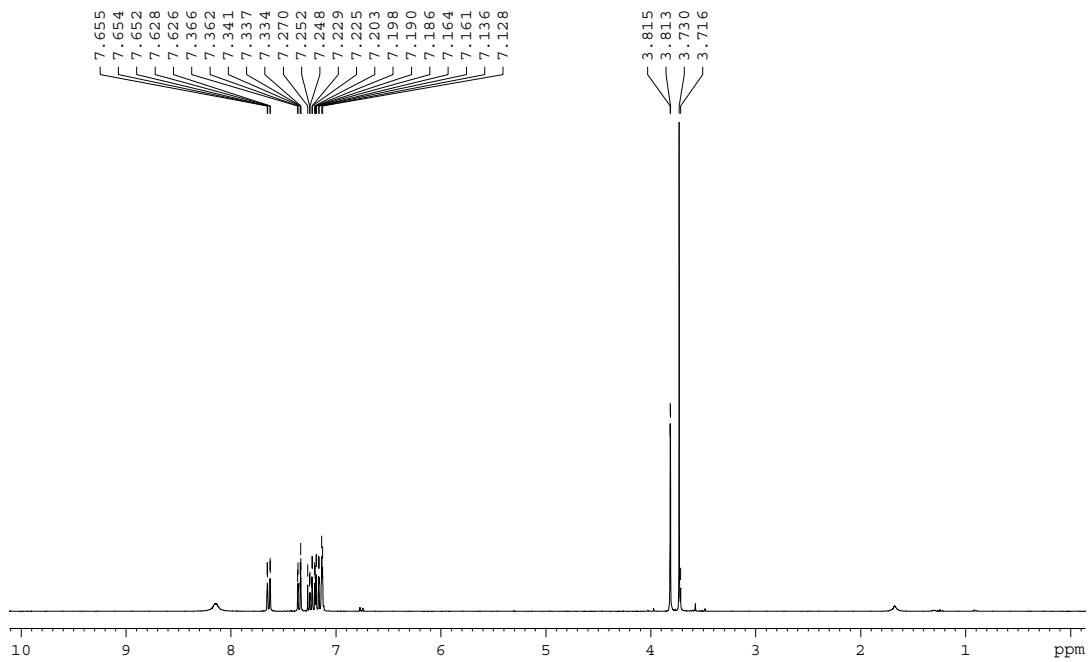
Representative procedure for the oxidation of octanal to methyl octanoate: To an oven-dried, argon purged Schlenk tube containing Ru(PPh₃)₃(CO)H₂ (92 mg, 0.1 mmol, 5 mol %) and Xantphos (56 mg, 0.1 mmol, 5 mol %) was added degassed anhydrous toluene (2 cm³) and the mixture heated at reflux for 1 hour then allowed to cool to room temperature. To the resultant deep-red solution was added octanal (256 mg, 313 μL, 2 mmol), crotononitrile (202 mg, 245 μL, 3 mmol), degassed anhydrous methanol (2 cm³), water (36 μL, 2 eq.) and the resultant yellow solution heated at 110 °C for 4 hours. The conversion was determined by ¹H NMR spectroscopy (96%).

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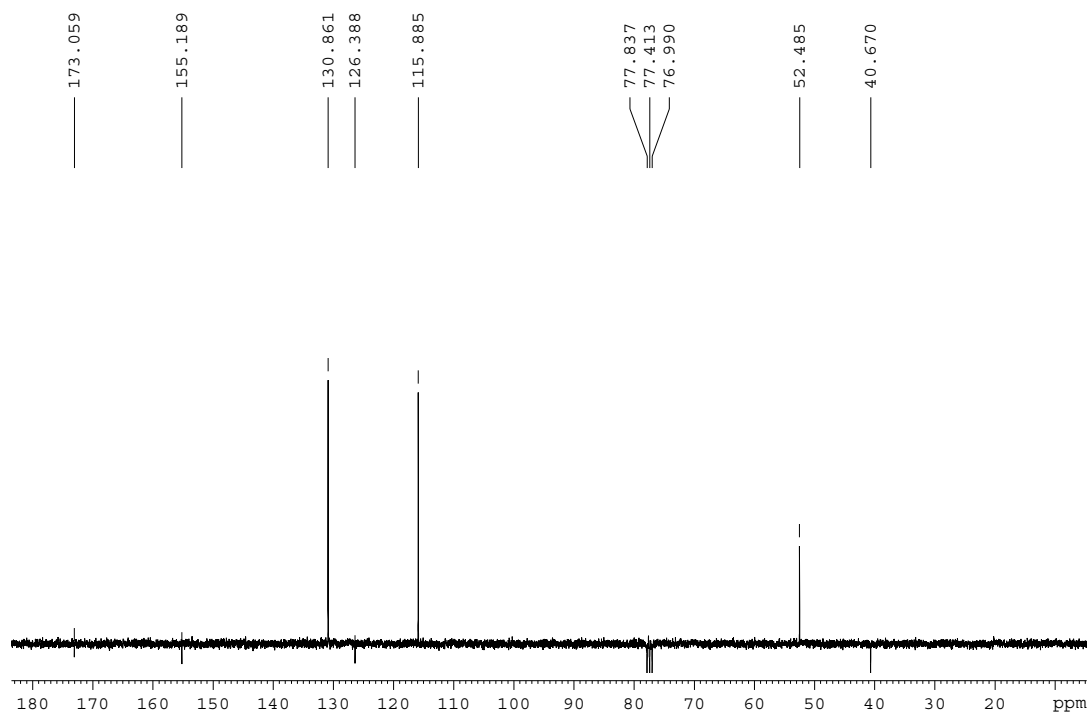
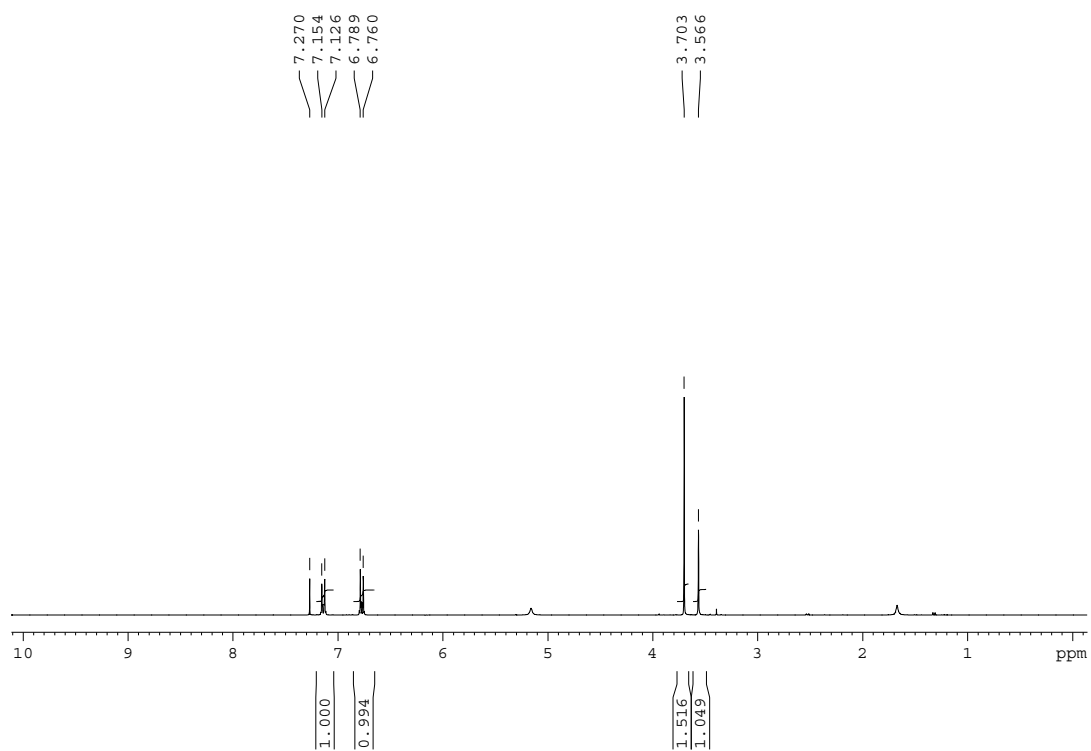
Methyl phenylacetate



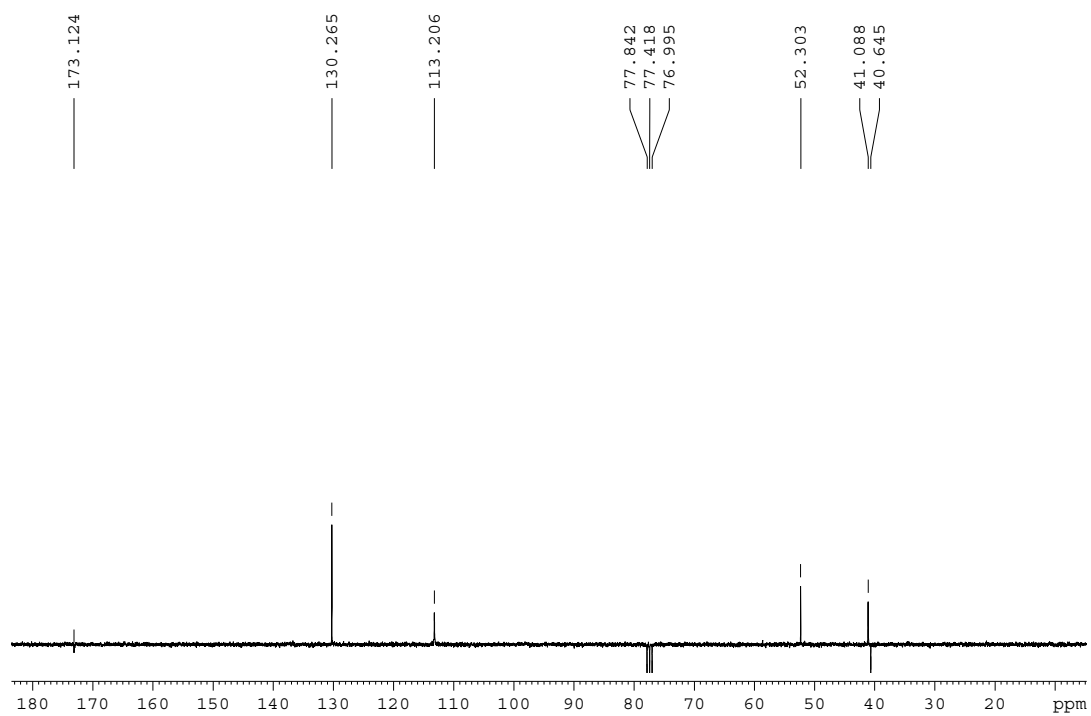
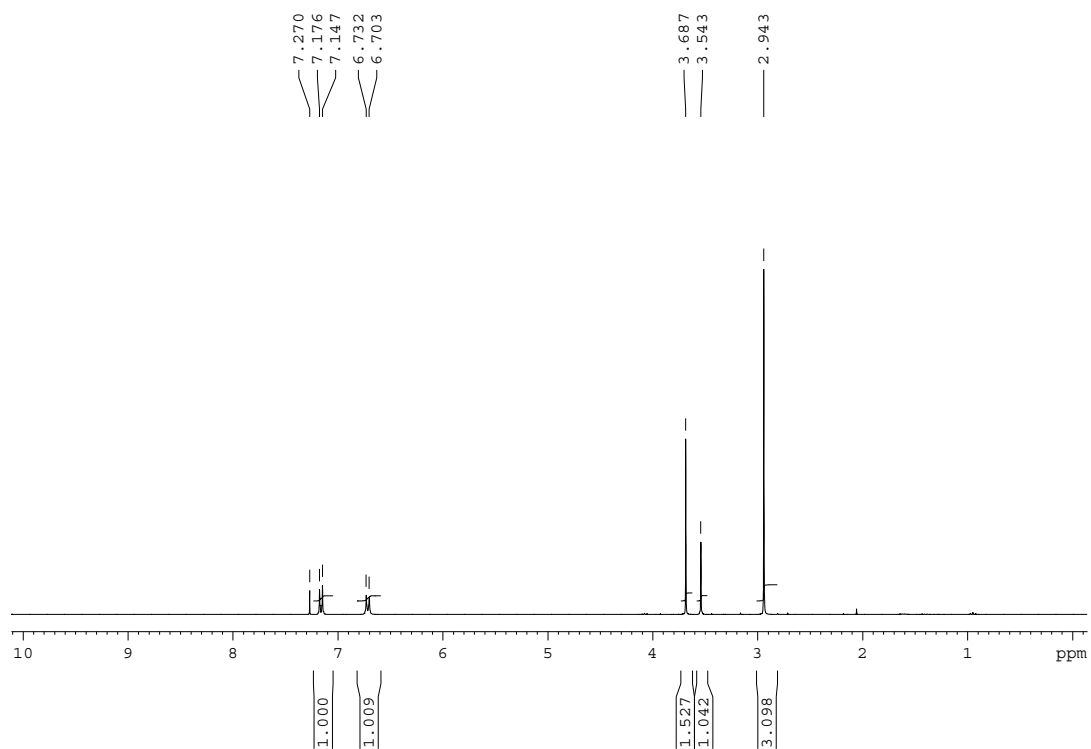
Methyl indole-3-acetate



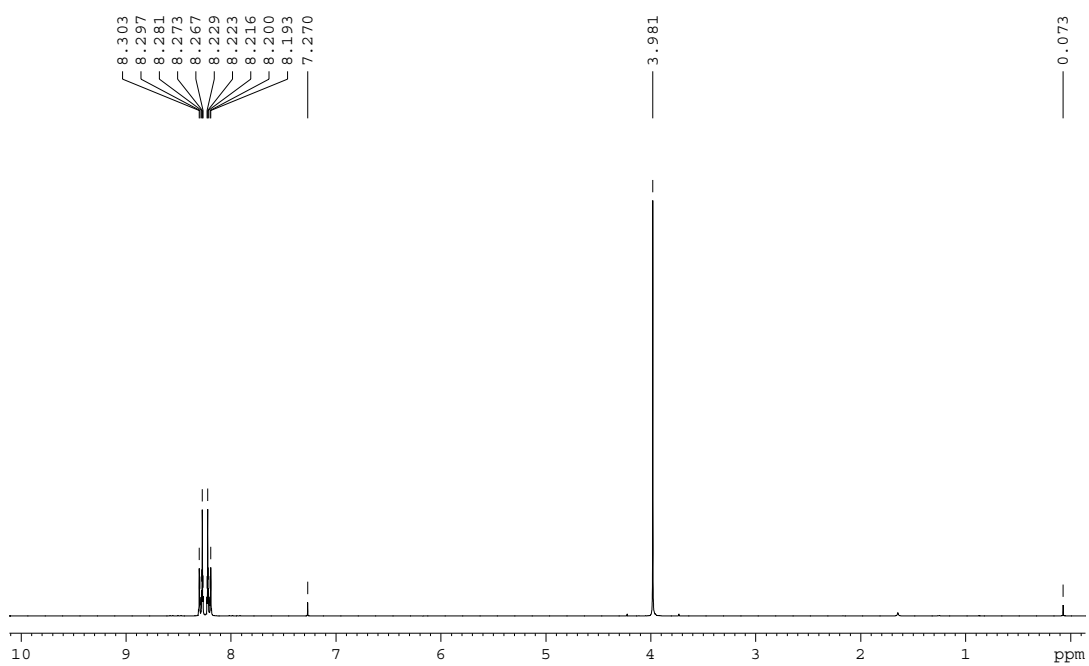
Methyl (4-hydroxyphenyl)acetate



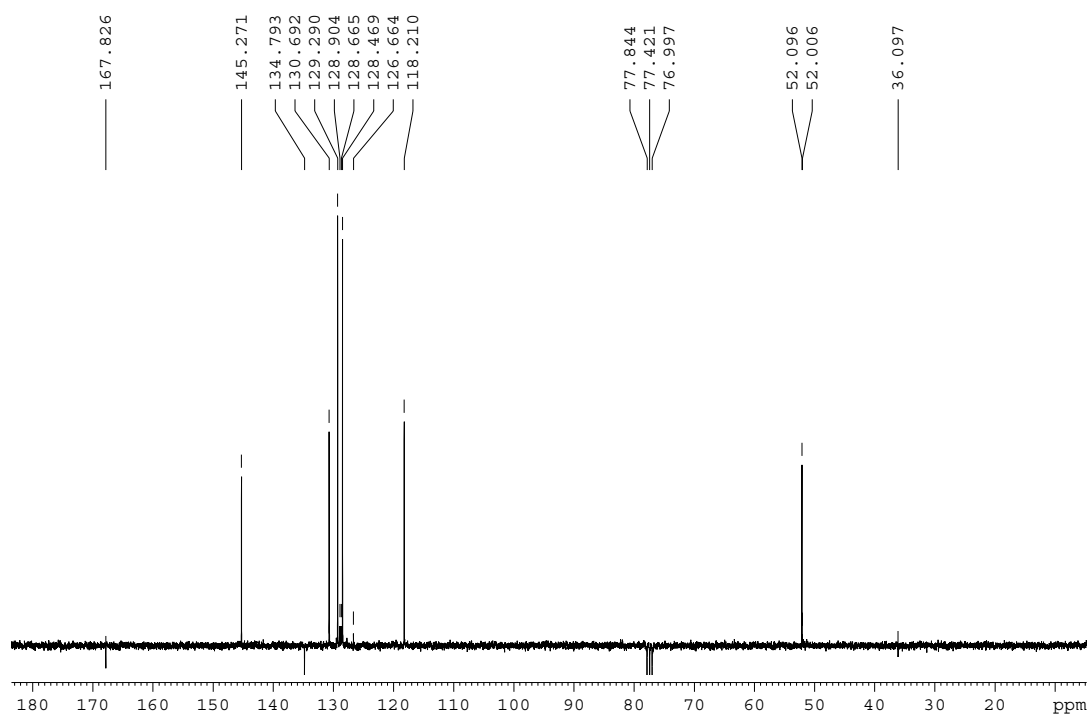
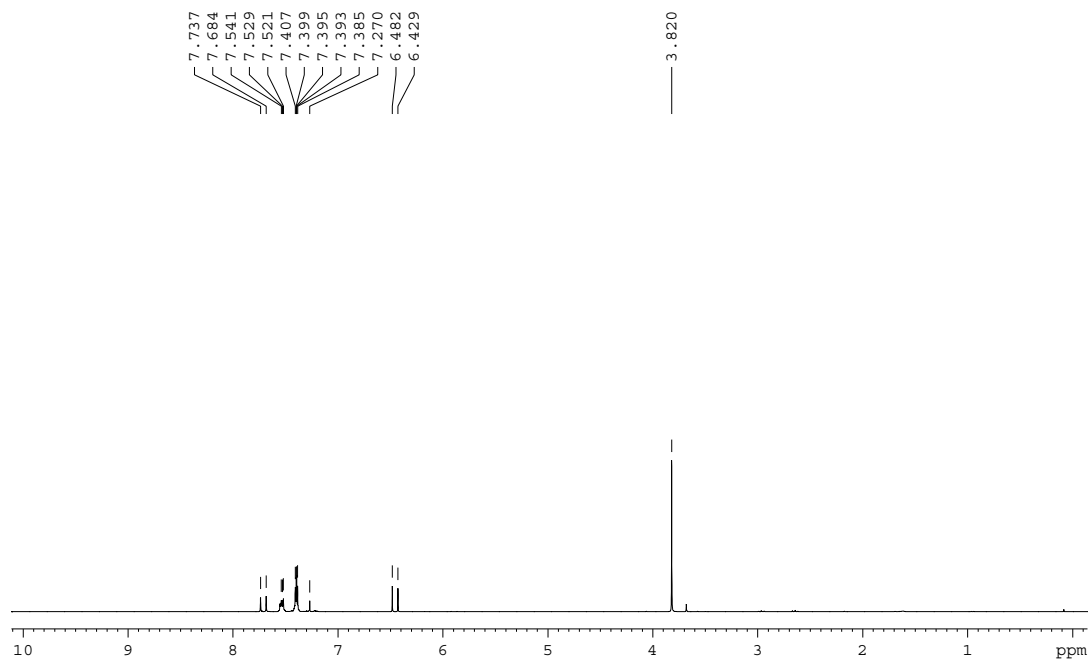
Methyl [2-(4-dimethylamino)phenyl]acetate



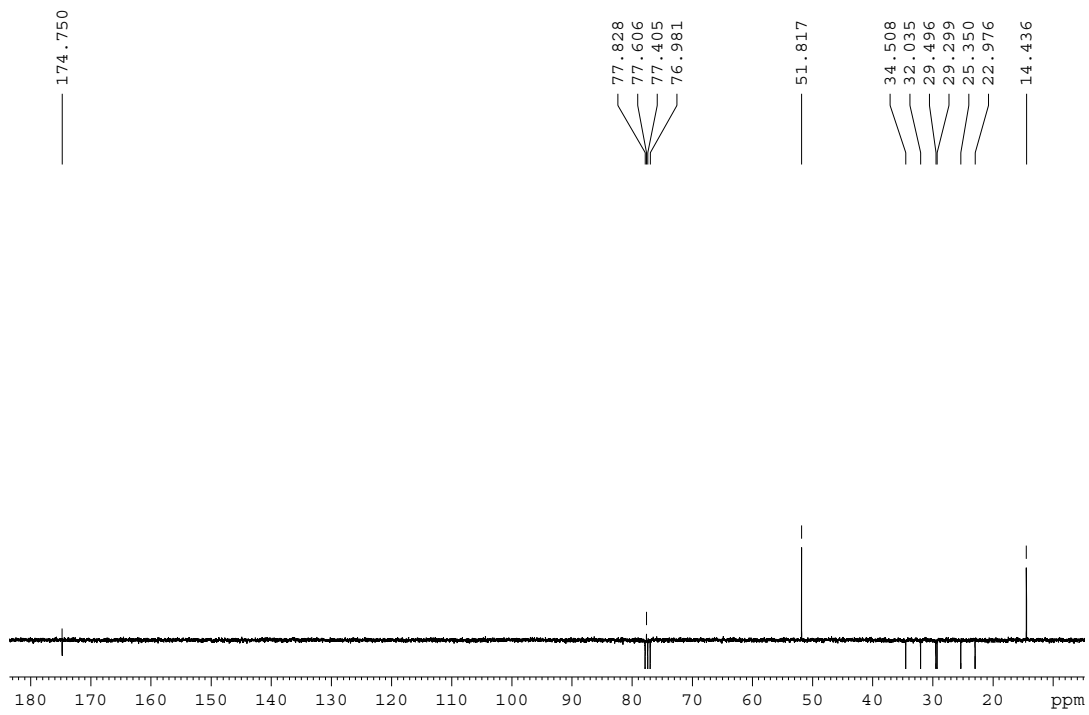
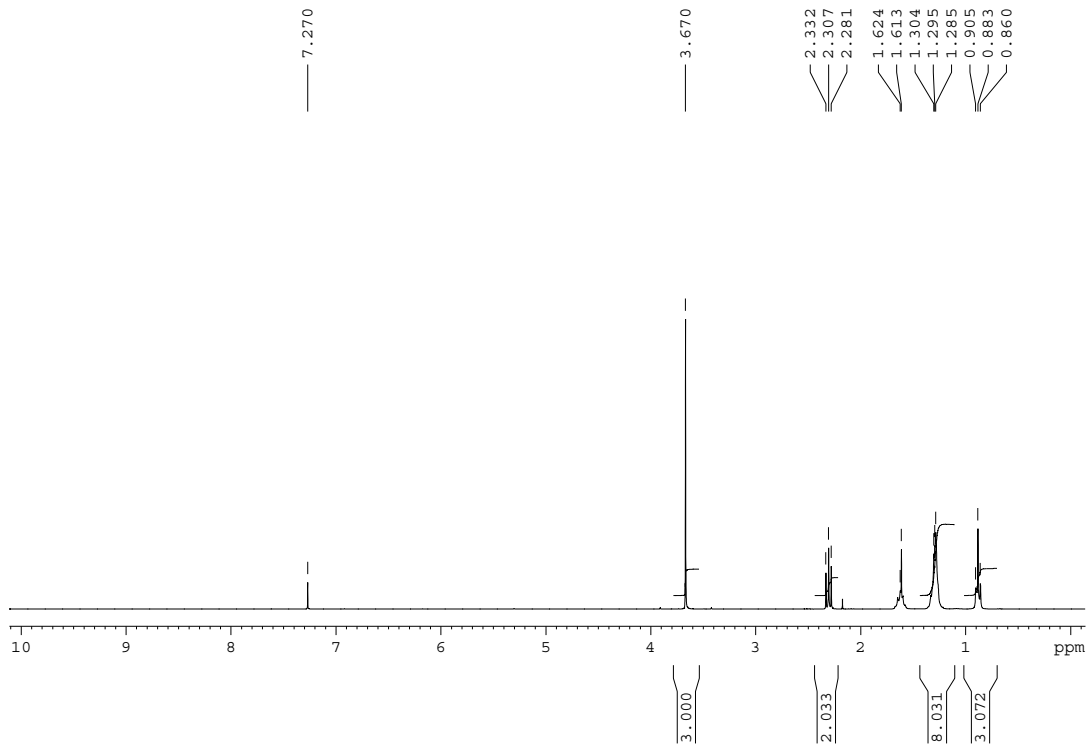
Methyl 4-nitrobenzoate



Methyl cinnamate



Methyl Octanoate



Methyl Hexadecanoate

