Development of a phosphine oxide-catalysed Appel reaction

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1.0 General experimental

Glassware was dried in an oven overnight before use. Thin layer chromatography was carried out on Polgram SIL $G/_{UV254}$ silica-aluminium plates and plates were visualised using ultra-violet light (254 nm) and $KMnO_4$ solution. For flash column chromatography Fluorochem silica gel 60, 35-70 μ was used. NMR data was collected at either 270, or 400 MHz. Data was manipulated directly from the spectrometer or via a networked PC with appropriate software. All samples were analysed in $CDCl_3$ unless otherwise stated. Reference values for residual solvent was taken as δ = 7.27 ($CDCl_3$) for ^{1}H-NMR; δ = 77.16 ($CDCl_3$) for ^{13}C-NMR. Multiplicities for coupled signals designated using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad signal, ap=apparent and are given in Hz. ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. High-resolution mass spectrometric data are quoted to four decimal places (0.1 mDa) with error limits for acceptance of +/-5.0 ppm (defined as calcd./found mass 10^{-6}). Mass spectra were acquired on a VG micromass 70E, VG autospec or micromass LCTOF. Infrared data was collected using sodium chloride discs or via analysis of neat samples using an ATR accessory. All solvents and reagents were used as supplied.

2.0 General experimental method for the chlorination of alcohols (Table 2)

To a solution of triphenylphosphine oxide (42 mg, 0.15 mmol) in either $CHCl_3$ or $CDCl_3$ (1.5 mL) was was added oxalyl chloride (0.012 mL, 0.142 mmol) and the reaction mixture stirred for 5 min. The appropriate alcohol (1.00 eq.) and oxalyl chloride (0.073 mL, 0.863 mmol) as solutions in either $CHCl_3$ or $CDCl_3$ (1.0 mL) were then added simultanesouly over 7 h *via* syringe pump. The solvent was removed *in vacuo.* The yield was determined using the procedure below:

The crude reaction mixture was dissolved in $CDCl_3$ and transferred to a volumetric flask (two washings of the original flask were done after transfer) that was subsequently made up to the correct volume with further $CDCl_3$. To a 1 mL aliquot of this solution was added tetrachloroethane (accurately approximately 30-80 mg). The ^{1}H NMR spectrum was recorded and the mass of the product calculated according to the equation below:

$$mass_{Cl} = (area_{Cl}/area_{standard}) \bullet (MW_{Cl}/MW_{standard}) \bullet mass_{standard} \bullet \text{purity factor} \bullet n \bullet m$$

where n corrects for the amount of the crude reaction mixture used and m corrects for the number of protons associated with the resonance used. The integral of the proton(s) adjacent to Cl was used in all cases. See example spectrum of crude reaction mixture plus internal standard for compound **14** below. Note that the volatility of certain chlorides as well as difficulties in observation *via* TLC resulted in some loss of material during evaporation and purification.

Further purification by flash chromatography (silica, 5-10 % Et_2O/pet. ether) gave the pure chlorides.

Data for chlorides is given below. NMR spectra are included for those chlorides that were further purified by flash column chromatography. Ether/petroleum ether 40-60 (5:95) was used as an eluent. Silica gel was used as the stationary phase.

2.1 Data for chlorides

1-chlorodecane 6[1] (147 mg, 83 % by NMR) further purification *via* flash chromatography afforded **5** as a colourless oil (120 mg, 68 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 6.8, C*H*$_3$), 1.23-1.50 (14H, m, 7xC*H*$_2$), 1.79 (2H, q, *J* 6.8, C*H*$_2$CH$_2$Cl), 3.55 (2H, t, *J* 6.8 C*H*$_2$Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 26.9 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 45.1 (CH_2).

Benzylchloride 9[2] (101 mg, 80 % by NMR) further purification *via* flash chromatography afforded **9** as a colourless oil (53 mg, 42 %);^{1}H NMR (270 MHz, $CDCl_3$) δ 4.62 (2H, s, C*H*$_2$), 7.30-7.43 (5H, m, Ar*H*); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 46.4 (CH_2), 128.5 (CH), 128.7 (CH), 128.9 (CH), 137.6 (Cq).

2-chlorooctane 14[3] (103 mg, 69 % by NMR) further purification *via* flash chromatography afforded **14** as a colourless oil (80 mg, 54 %);^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.7, C*H*$_3$), 1.28-1.48 (8H, m, 4xC*H*$_2$), 1.52 (3H, d, *J* 6.5, C*H*$_3$), 4.04 (1H, q, *J* 6.5, C*H*Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 26.6 (CH_2), 28.8 (CH_2), 31.7 (CH_2), 41.4 (CH_2), 58.9 (CH_2).

3-phenylpropylchloride 10[4] (113 mg, 73 % by NMR) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (2H, q, *J* 6.4, PhCH$_2$C*H*$_2$CH$_2$Cl), 2.84 (2H, q, *J* 6.4, PhC*H*$_2$CH$_2$CH$_2$Cl), 3.58 (2H, t, *J* 6.4, PhCH$_2$CH$_2$C*H*$_2$Cl), 7.21-7.30 (3H, m, Ar*H*), 7.31-7.40 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8 (CH_2), 34.1 (CH_2), 44.3 (CH_2), 126.2 (CH), 128.6 (CH), 128.7 (CH), 140.8 (Cq).

1-chloro-2-decyne 13[5] (113 mg, 67 % by NMR) further purification *via* flash chromatography afforded **14** as a colourless oil (90 mg, 52 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 6.8, C*H*$_3$), 1.22-1.44 (8H, m, 4xC*H*$_2$), 1.50 (2H, q, *J* 8.4, CH$_2$C*H*$_2$CH$_2$CC), 2.22 (2H, m, CH$_2$C*H*$_2$CC), 4.15 (2H, t, *J* 2.4, CCC*H*$_2$Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 18.8 (CH_2), 22.6 (CH_2), 28.4 (CH_2), 28.8 (2xCH_2), 31. 3 (CH_2), 31.7 (CH_2), 74.9 (Cq), 87.8 (Cq).

1-chloro-2-butene 11[6] **(**64 mg, 70 % by NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (3H, d, *J* 6.4, C*H*$_3$), 4.05 (2H, d, *J* 7.0, C*H*$_2$Cl), 5.68 (1H, dq *J* 15.0 and 6.4 CH$_3$C*H*CHCH$_2$Cl), 5.82 (1H, dt, *J* 15.0 and 6.6 CH$_3$CHC*H*CH$_2$Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 45.4 (CH_2), 129.1 (CH), 130.1 (CH).

2-chloro-1-octene 16[7] (94 mg, 64 % by NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 6.9, C*H*$_3$), 1.28-1.55 (6H, m, 3xC*H*$_2$), 1.61-1.91 (2H, m, CClHC*H*$_2$CH$_2$), 4.36 (1H, m, C*H*Cl), 5.14 (1H, d, J 10.1 C*H*$_2$CHCHCl), 5.27 (1H, d, J 16.8, C*H*$_2$CHCHCl), 5.90 (1H, ddd, *J* 16.8, 10.1 and 7.0, CH$_2$C*H*CHCl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_2), 26.1 (CH_2), 31.2 (CH_2), 45.5 (CH_2), 63.2 (CH_2), 114.4 (CH), 141.43 (CH).

cinnamylchloride 12[2] (134 mg, 88 % by NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (2H, d, *J* 6.9, C*H*$_2$), 6.36 (1H, dt, 15.6 and 7.2, C*H*CH$_2$Cl), 6.69 (1H, d, 15.6, PhC*H*CH), 7.30-7.49 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.5 (CH_2), 125.0 (CH), 126.7 (CH), 128.5 (CH), 128.7 (CH), 134.2 (CH), 136.4 (Cq).

1-bromodecane 17[8] (106 mg, 42 % by NMR) further purification *via* flash chromatography afforded **14** as a colourless oil (52 mg, 24 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 6.9, C*H*$_3$), 1.23-1.50 (14 H, m, 7xC*H*$_2$), 1.88 (2H, q, *J* 7.0, C*H*$_2$CH$_2$Br), 3.44 (2H, t, *J* 6.9, C*H*$_2$Br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.2 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 29.5 (2xCH_2), 31.9 (CH_2), 32.9 (CH_2), 34.0 (CH_2).

2.2 Experimental Procedures and data for new compounds

Bisoxalylester 8

An authentic sample was prepared for analysis:

To a solution of oxalyl chloride (63 mg, 0.50 mmol) was added decanol (158 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in *vacuo* affording bisoxalylester **8** (175 mg, 94 %) as a white solid.

IR ν_{max} ($CDCl_3$) 2928 (CH), 1763 (CO), 1739, (CO), 1467, 1318, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.9, C*H*$_3$), 1.23-1.49 (14H, m, 7xC*H*$_2$), 1.75 (2H, q, *J* 6.8, C*H*$_2$CH$_2$O), 4.30 (2H, t, *J* 6.8 C*H*$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 22.7 (CH_2), 29.5 (2 CH_2), 31.9 (CH_2), 67.2 (CH_2), 158.1 (Cq); HRMS (EI^+) $C_{22}H_{42}O_4$ calcd. 370.3083, found 370.3077.

Chloroglyoxalylate 7

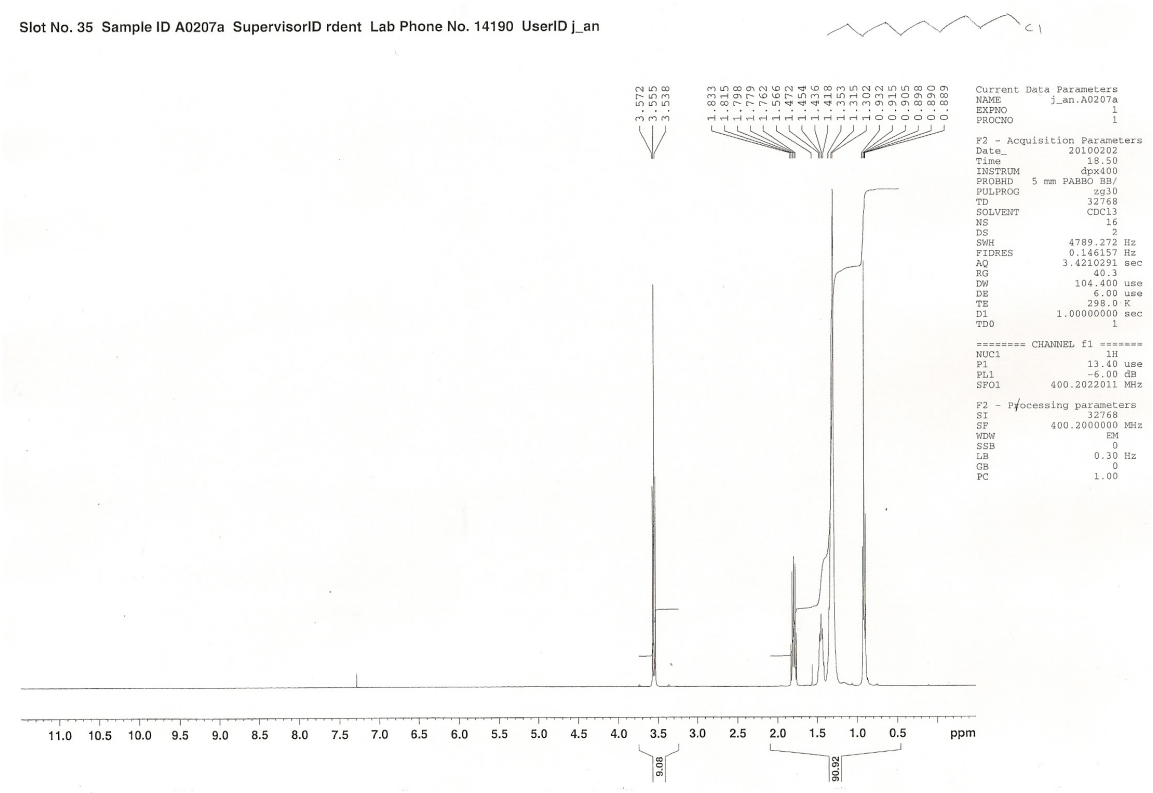
An authentic sample was prepared for analysis:

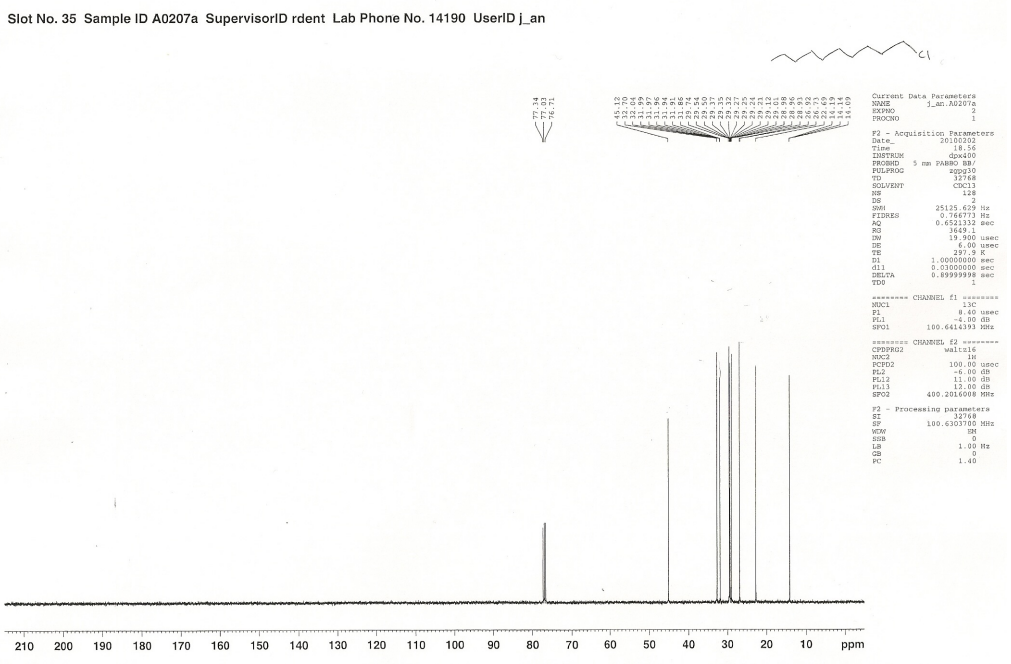
To a solution of oxalyl chloride (127 mg, 1.00 mmol) was added decanol (158 mg, 1.00 mmol) *via* syringe pump over 2 h. The solvent was removed *in vacuo* affording chloroglyoxalylate **7** (229 mg, 92 %) as a colourless oil.

IR ν_{max} ($CDCl_3$) 2909 (CH), 1780 (CO), 1467, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.4, C*H*$_3$), 1.23-1.50 (14H, m, 7xC*H*$_2$), 1.78 (2H, q, *J* 6.8, C*H*$_2$CH$_2$O), 4.36 (2H, t, *J* 6.8 C*H*$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 69.1 (CH_2), 155.8 (Cq), 161.0 (Cq). HRMS was obtained on the corresponding acid (EI^+) $C_{12}H_{21}O_2$ [$M^{+\cdot}$-CO_2H] calcd. 185.1542, found 185.1543.

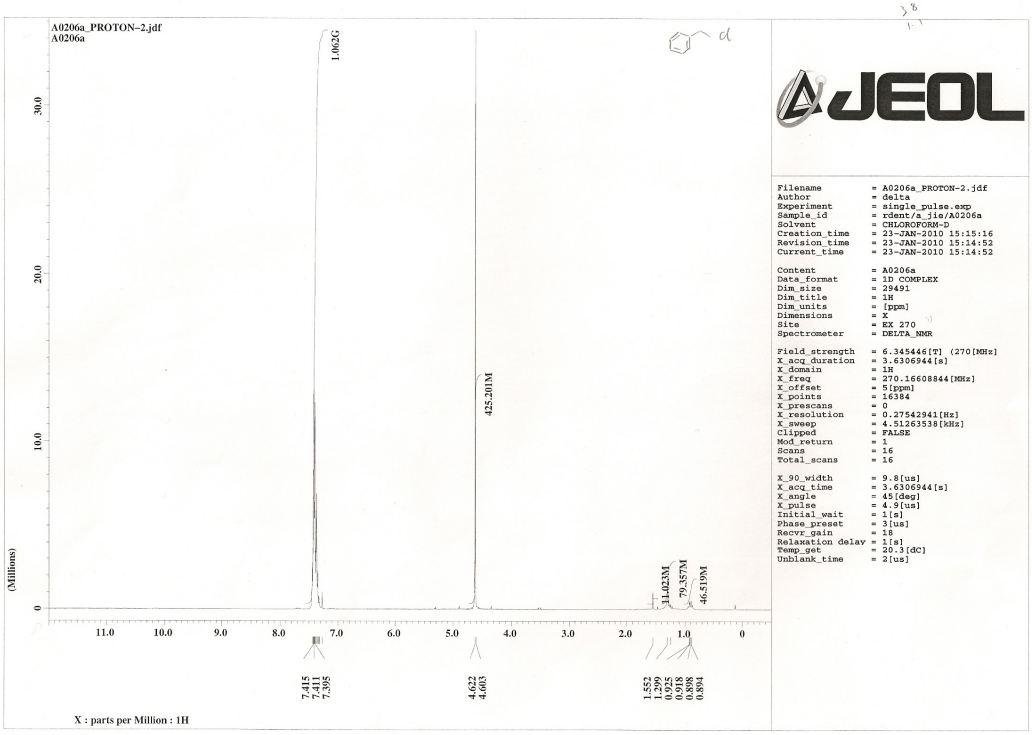
3.0 NMR spectra

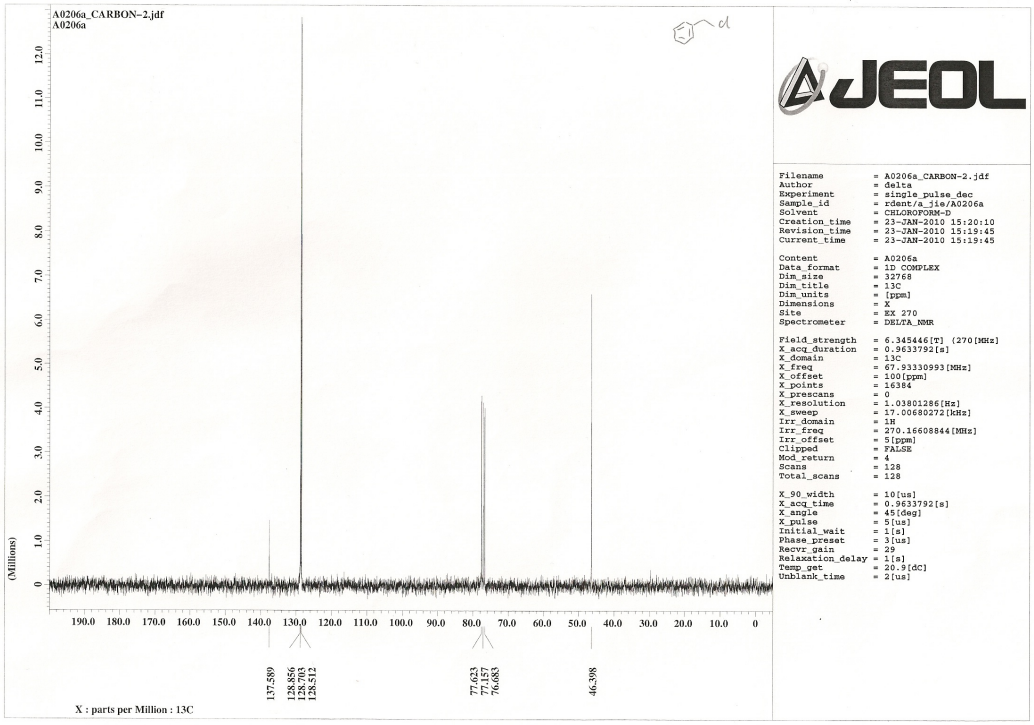
Chlorodecane **6**



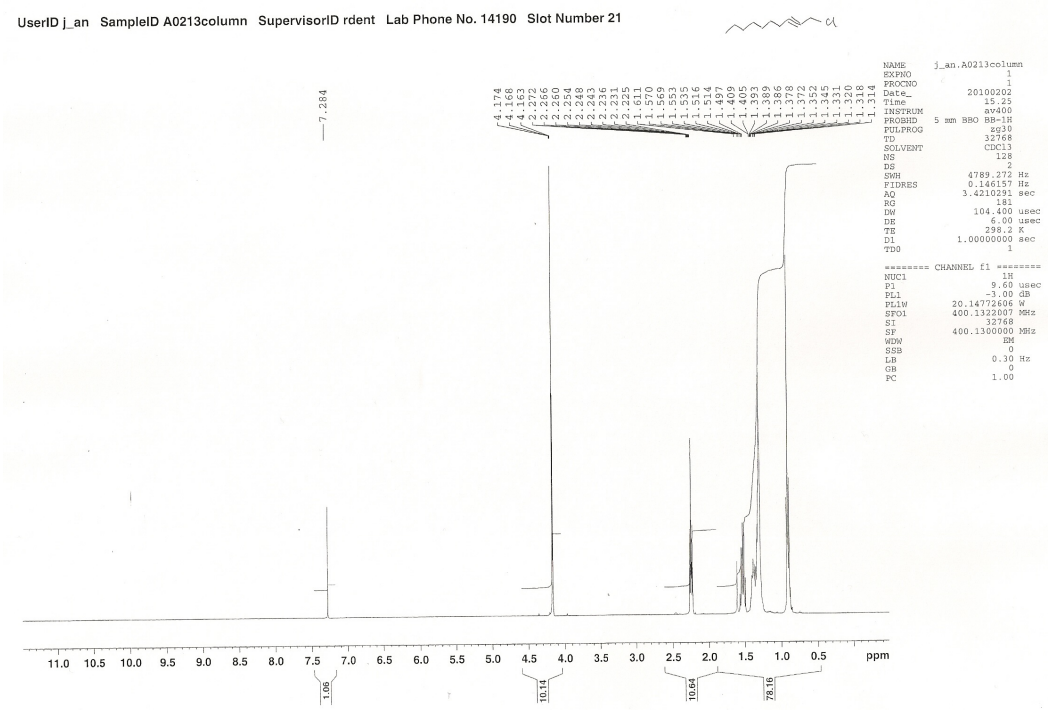


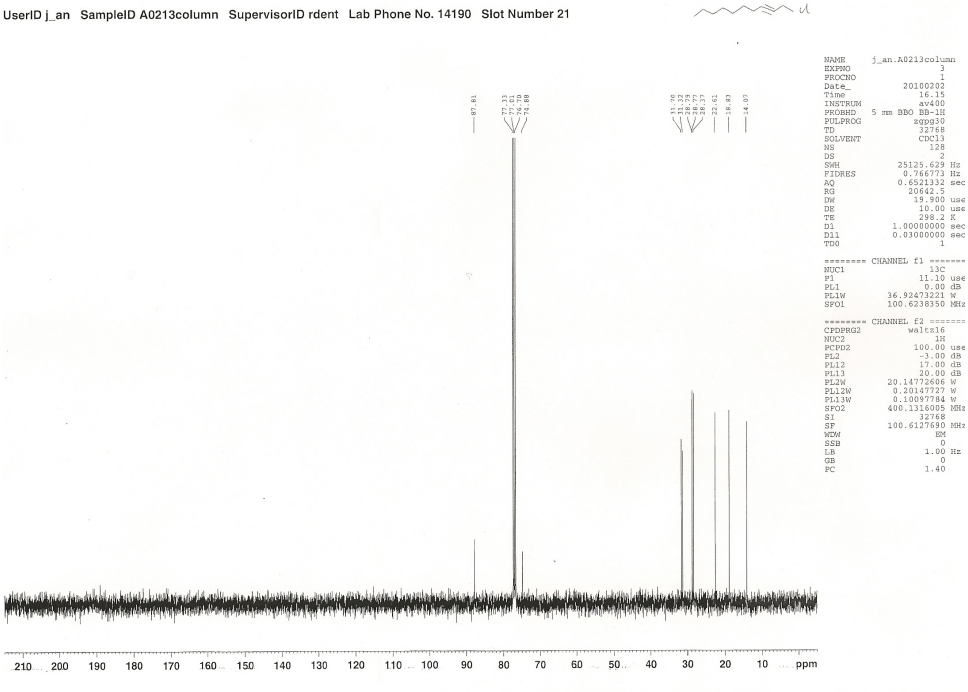
Benzylchloride 9





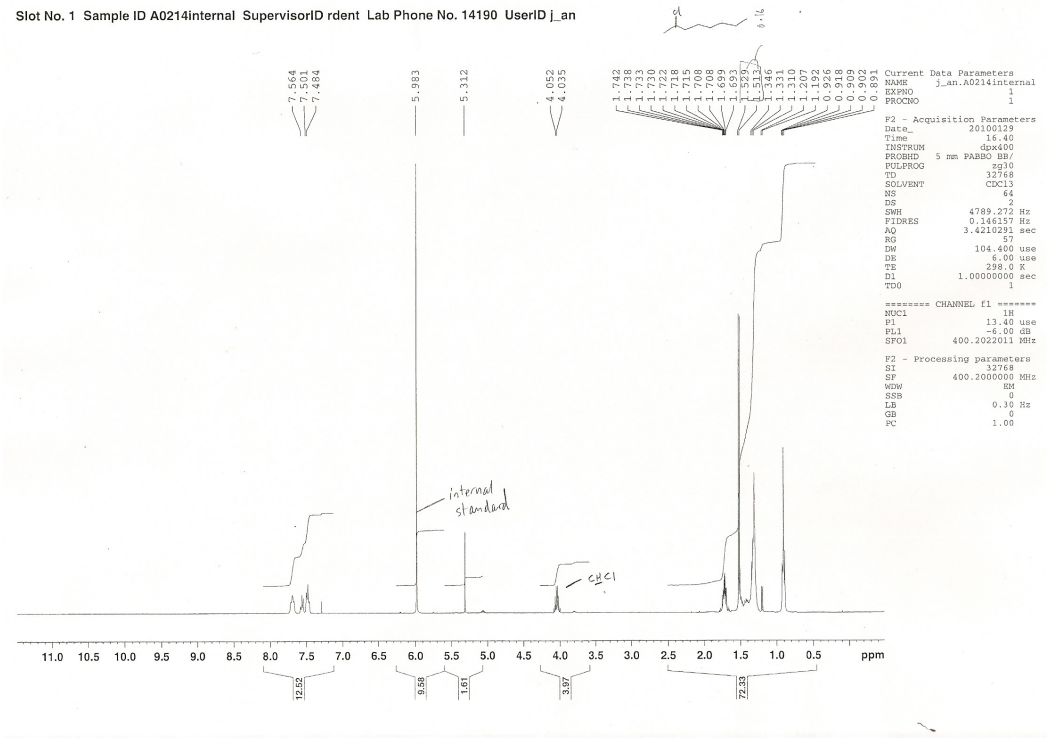
1-chloro-2-decyne 13

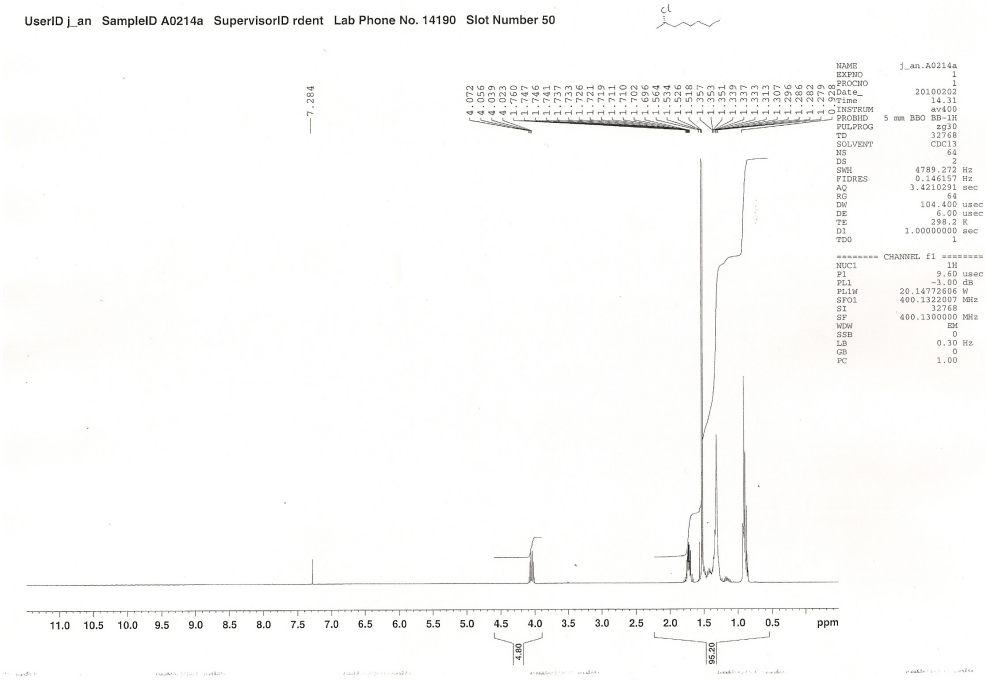


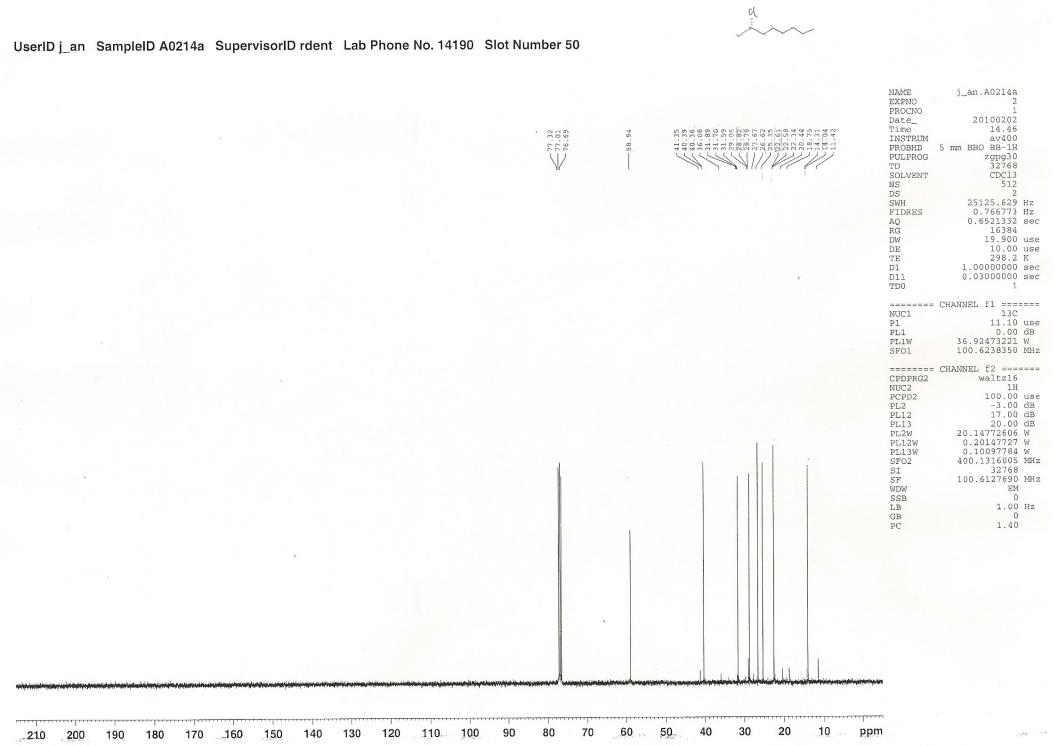


2-chlorooctane 14

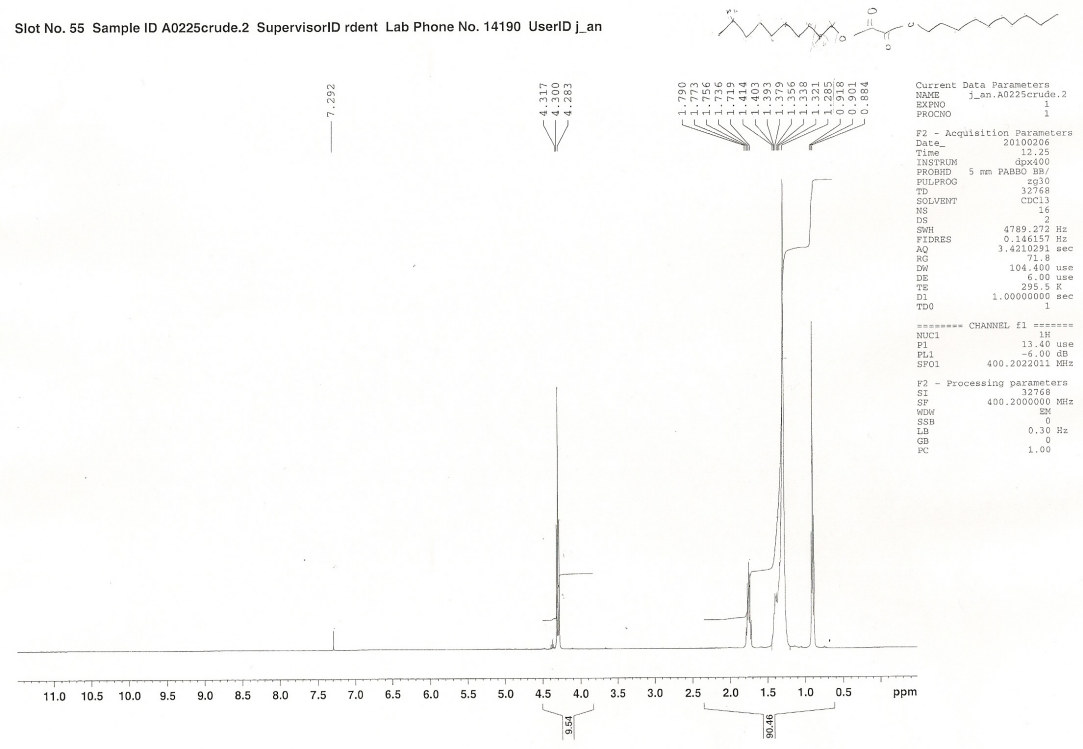
NMR below shows a representative crude reaction mixture + $C_2H_2Cl_4$ for determination of yield.

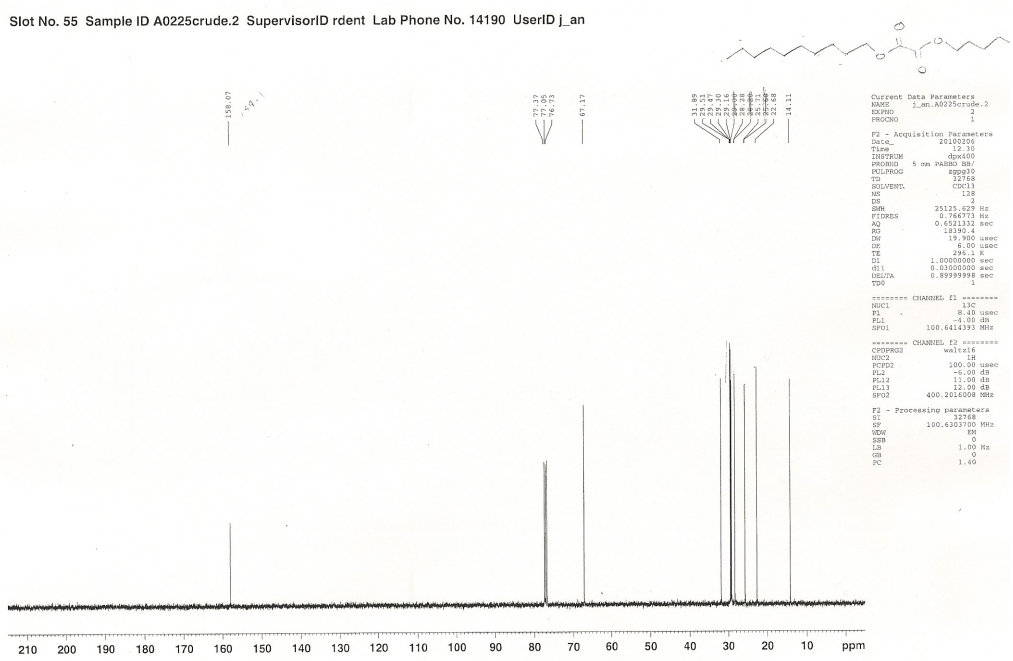




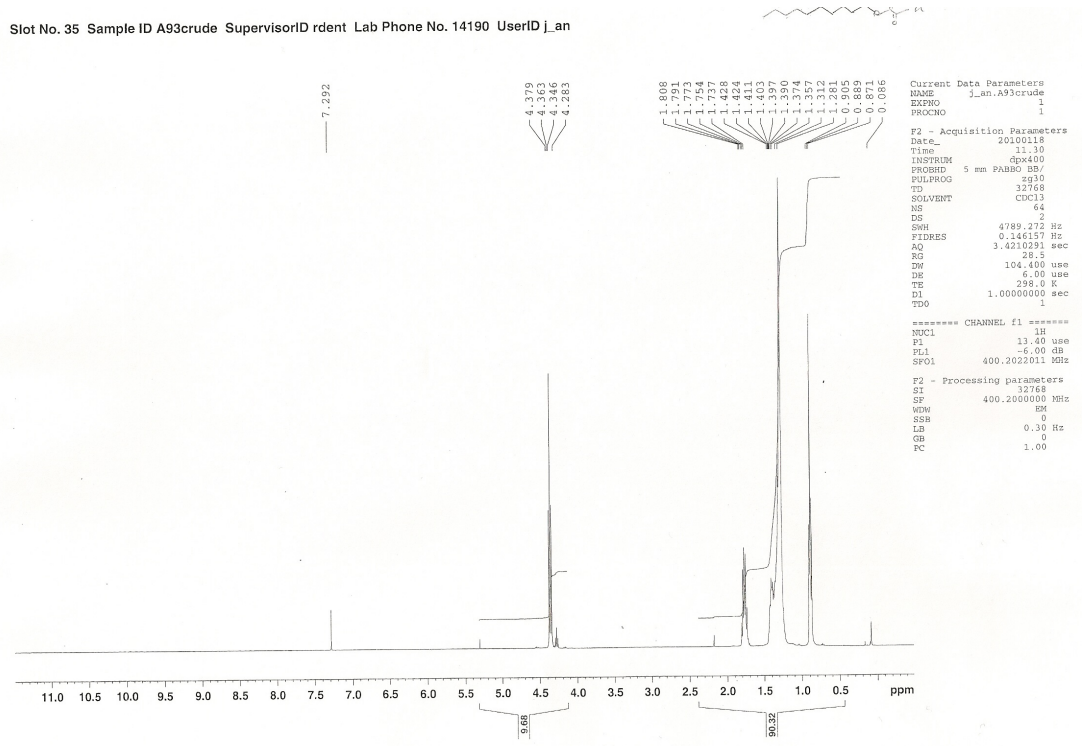


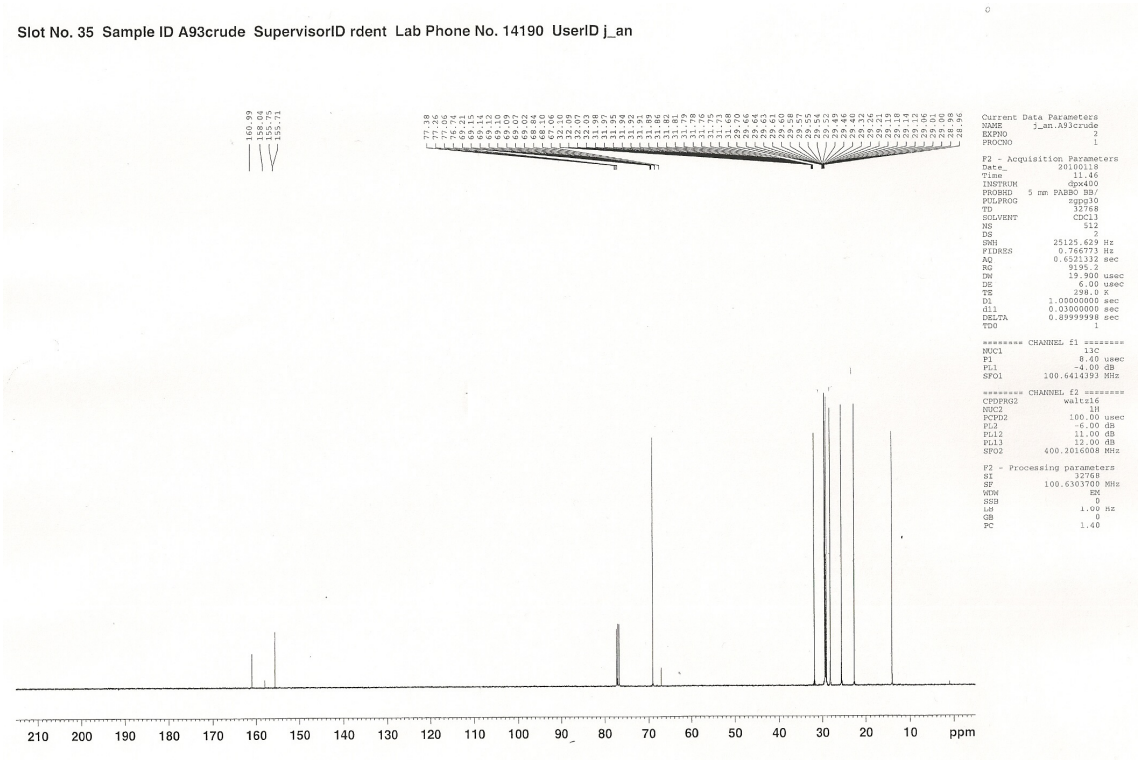
Bisoxalylester 8





Chloroglyoxalylate 7





4.0 References

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