A Silver Mediated One-Step Synthesis of Oxazoles

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Supporting Information

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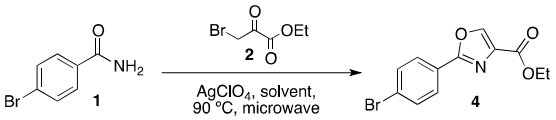
General Experimental

Melting points were recorded using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. High Resolution Mass Spectra were recorded on VG micron Autospec or Bruker microTOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin Elmer 1600 series or Bruker Tensor 27 spectrometer. All IR were taken in dry chloroform, unless specified. NMR spectra were recorded at 400 and 100 MHz, for ^{1}H and ^{13}C NMR respectively. Coupling constant are given in hertz (Hz), the shifts (δ) are given as parts per million (ppm) using tetramethylsilane as an internal standard. The following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent). Thin layer chromatography was performed on precoated silica gel aluminium plates (60F-254) and visualised using UV absorption and/or an appropriate stain. Column chromatography was performed using silica gel 60 (230-400 mesh). All reagents were used as received from commercial suppliers. Ethyl bromopyruvate was 90% pure, as indicated by GC, and this was taken into account (weight for weight) when calculating stoichiometery. Petrol ethers refer to petroleum ethers 40 - 60 $^{\circ}C$. Anhydrous THF was distilled from sodium wire/benzophenone and anhydrous DCM from CaH_2 immediately prior to use. MeCN and $CHCl_3$ were distilled from CaH_2 and stored over activated 4 Å MS. Toluene was dried by passing the solvent over an activated alumina column which was pressurised with dry N_2. Anhydrous DMF and 1,2-DCE were purchased and used as received. Microwave reactions were conducted on a CEM Discover Explorer microwave reactor in sealed tubes with stirring at a constant temperature for the indicated time. The reaction mixture temperatures were recorded using vertically-focused IR temperature sensor.

Results of Solvent Screen

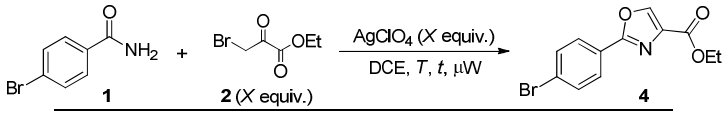
Table S1. Results of the solvent screen



entry	solvent	yield (%)[a]
1	DMF	17
2	THF	22
3	MeCN	54
4	toluene	59
5	DCM	70
6	$CHCl_3$	69
7	DCE	74
8	H_2O	nd[b]

[a] Isolated yield of **4**. [b] Not determined – complex mixture after the reaction. Conditions: **1** (0.3 mmol), **2** (1.8 equiv), anhydrous solvent (0.45 mL), $AgClO_4$ (1.0 equiv), 90 °C for 2 h in a sealed tube in a microwave.

Table S2. Optimization of reaction conditions



entry	vol. (mL)[a]	temp. (ºC)	time (h)	equiv. **2**	equiv. $AgClO_4$	yield (%)[b]
1	0.3	90	0.5	1.8	1	61
2	0.6	90	0.5	1.8	1	61
3	1.2	90	0.5	1.8	1	50
4	0.45	90	0.5	1.8	1	69
5	0.45	130	0.5	1.8	1	48
6	0.45	110	0.5	1.8	1	63
7	0.45	90	1.5	1.8	1	72
8	0.45	90	2	1.8	1	74
9	0.45	90	2	1.8	0.5	52
10	0.45	90	2	1.8	1.1	70
11	**0.45**	**90**	**2**	**1.0**	**1**	**74**

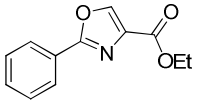
[a] Refers to volume of anhydrous DCE. [b] Isolated yield of **4**. Conditions: all reactions performed on 0.300 mmol of **1** in a sealed tube in a microwave.

Experimental Procedures

General microwave procedure for optimised conditions:

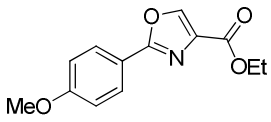
To a dry tube under Ar atmosphere was added the amide (0.30 mmol), β-bromo-α-oxoester (0.30 mmol), anhydrous 1,2-dichloroethane (0.45 mL) and $AgSbF_6$ (0.30 mmol, 103 mg). The mixture was stirred for 1 min then heated to 90 °C in a sealed tube in a microwave reactor for 2 h (3 h in the case of **27**) with stirring. After this time the reaction was cooled to room temperature and a saturated solution of $NaHCO_3$ (5 mL) was added and the product was extracted with EtOAc (2 × 7 mL). The combined organics were washed with a saturated solution of brine (4 mL), dried (Na_2SO_4), filtered and purified by flash chromatography or preparative TLC.

Ethyl 2-phenyloxazole-4-carboxylate (15)[1]



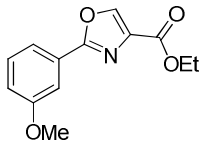
Colourless solid, 89%. Mp = 64-65 °C [Lit.[1] 66-67 °C]; R_F = 0.26 (4:1, petrol-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 8.12 (m, 2 H), 7.47 (m, 3 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 161.4, 143.7, 134.7, 131.1, 128.8, 126.9, 126.4, 61.3, 14.3; HRMS (ESI) calcd for $C_{12}H_{11}NNaO_3$ $[M+Na]^+$ 240.0637, found 240.0621.

Ethyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (16)[1]



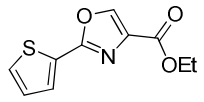
Colourless solid, 97%. Mp = 100-101 °C [Lit.[1] 102-103 °C]; R_F = 0.17 (4:1, petrol-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.09 (d, *J* = 9.0 Hz, 2 H), 7.01 (d, *J* = 9.0 Hz, 2 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 3.90 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 161.9, 161.5, 143.2, 134.5, 128.6, 119.1, 114.2, 61.2, 55.4, 14.3; HRMS (ESI) calcd for $C_{13}H_{13}NNaO_4$ $[M+Na]^+$ 270.0742, found 270.0734.

Ethyl 2-(3-methoxyphenyl)oxazole-4-carboxylate (17)[2]



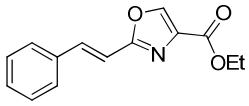
Colourless solid, 90%. Mp = 73.5-74.5 °C [Lit.[2] 76.7-77.8 °C]; R_F = 0.25 (4:1, petrol-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.72 (m, 1 H), 7.68 (m, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 7.07 (ddd, *J* = 8.3, 2.6, 0.7 Hz, 1 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 3.91 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.4, 159.9, 143.7, 134.6, 129.9, 127.6, 119.3, 117.9, 111.3, 61.3, 55.5, 14.3; HRMS (ESI) calcd for $C_{13}H_{13}NNaO_4$ $[M+Na]^+$ 270.0742, found 270.0725.

Ethyl 2-(thiophen-2-yl)oxazole-4-carboxylate (20)[1]



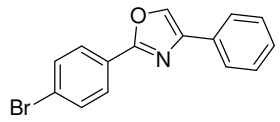
Colourless solid, 90%. Mp = 101-103 °C [Lit.[1] 100-101 °C]; R_F = 0.22 (4:1, petrol-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1 H), 7.81 (dd, *J* = 3.7, 1.2 Hz, 1 H), 7.51 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.16 (dd, *J* = 5.0, 3.7 Hz, 1 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 158.6, 143.1, 134.6, 129.5, 129.2, 128.6, 128.0, 61.3, 14.3; HRMS (ESI) calcd for $C_{10}H_9NNaO_3S$ $[M+Na]^+$ 246.0201, found 246.0196.

Ethyl (*E*)-2-cinnamyloxazole-4-carboxylate (25)[3]



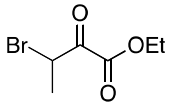
Colourless solid, 60%. Mp = 110-111 °C [Lit.[4] 110-112 °C]; R_F = 0.31 (4:1, petrol-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.65 (d, *J* = 16.5 Hz, 1 H); 7.55 (m, 2 H), 7.41 (m, 3 H), 6.97 (d, *J* = 16.4 Hz, 1 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 161.3, 143.3, 138.3, 135.0, 134.7, 129.7, 129.0, 127.4, 112.9, 61.3, 14.4; HRMS (ESI) calcd for $C_{14}H_{13}NNaO_3$ $[M+Na]^+$ 266.0793, found 266.0775.

2-(4-Bromo-phenyl)-4-phenyl-oxazole (26)[5]



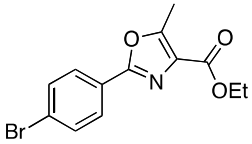
White solid, 81%. R_F = 0.48 (9:1, petrol-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7, 2 H), 7.99 (s, 1 H), 7.83 (dd, *J* = 8.4, 1.2, 2 H), 7.64 (d, *J* = 7.6, 2 H), 7.45 (m, 2 H), 7.36 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 142.3, 133.7, 132.1, 130.9, 128.8, 128.3, 128.0, 126.4, 125.7, 124.9; HRMS (ESI) calcd for $C_{15}H_{11}BrNO$ $[M+H]^+$ 300.0024, found 300.0017.

Ethyl 3-bromo-2-oxobutanoate (27)



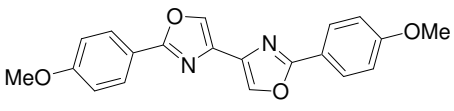
Prepared as previously reported.[6]

Ethyl 2-(4-bromophenyl)oxazole-4-carboxylate (28)[7]



Colourless solid, 74%. Mp = 131-134 ^{o}C; R_F = 0.27 (4:1, petrol-EtOAc); ν_{max}/cm^{-1} 3010, 2930, 2254, 1716, 1616; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 4.45 (q, *J* = 7.2 Hz, 2 H), 2.73 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.7, 156.3, 132.0, 129.0, 128.0, 125.5, 125.2, 61.1, 14.4, 12.2; HRMS (ESI) calcd for $C_{13}H_{12}BrNNaO_3$ $[M+Na]^+$ 331.9898, found 331.9888.

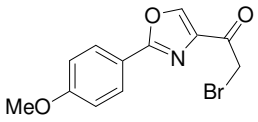
Synthesis of bis-oxazole – synthesis of 2,2'-bis-(4-methoxy-phenyl)-[4,4']bioxazolyl (29)[8]



4-Methoxybenzamide (0.6 mmol, 2.0 equiv) and $AgSbF_6$ (2.0 equiv) were transferred in a dry 5 mL microwave vial, equipped with a magnetic stirrer and kept under Argon. Then anhydrous 1,2-dichloroethane (0.9 mL) was added followed by 1,4-dibromo-2,3-butanedione

(**30**, 0.3 mmol, 1.0 equiv.). The resulting mixture was stirred for 5 min at ambient temperature and microwaved at 90 ^{o}C for 4 h under stirring conditions. After this time the reaction was cooled to ambient temperature, a saturated solution of $NaHCO_3$ (5 mL) was added and the product was extracted with EtOAc (2 x 7 mL). The organic layer were combined, dried over anhydrous Na_2SO_4, filtered and concentrated on a rotator evaporator. The crude product was further purified by flash silica-gel chromatography using EtOAc and petroleum-ether 40-60 ^{o}C. Pale yellow solid, 37%. Mp = 224-226 ^{o}C. ν_{max}/cm^{-1} (neat) 2923, 1611, 1499, 1249, 1095, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.07 (m, 6 H), 6.98-7.02 (m, 4 H), 3.89 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 161.5, 134.6, 134.4, 128.3, 120.1, 114.2, 55.4; HRMS (ESI) calcd for $C_{20}H_{16}N_2NaO_4$ $[M+Na]^+$ 371.1002, found 371.1014.

2-Bromo-1-[2-(4-methoxy-phenyl)-oxazol-4-yl]-ethanone (31)



White solid, 47%. Mp = 147-148 ^{o}C. ν_{max}/cm^{-1} (neat) 3124, 3072, 2956, 1697, 1462; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 8.01-8.03 (m, 2 H), 6.99-7.01 (m, 2 H), 4.53 (s, 2 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 162.3, 162.1, 142.5, 139.2, 128.6, 118.9, 114.3, 55.4, 32.1; HRMS (ESI) calcd for $C_{12}H_{10}BrNNaO_3$ $[M+Na]^+$ 317.9736, found 317.9728.

Reference

(1) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383-7386.

(2) Ackermann, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724-726.

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(4) Connell, R. D.; Tebbe, M.; Gangloff, A. R.; Helquist, P.; Akermark, B. *Tetrahedron* **1993**, *49*, 5445-5459.

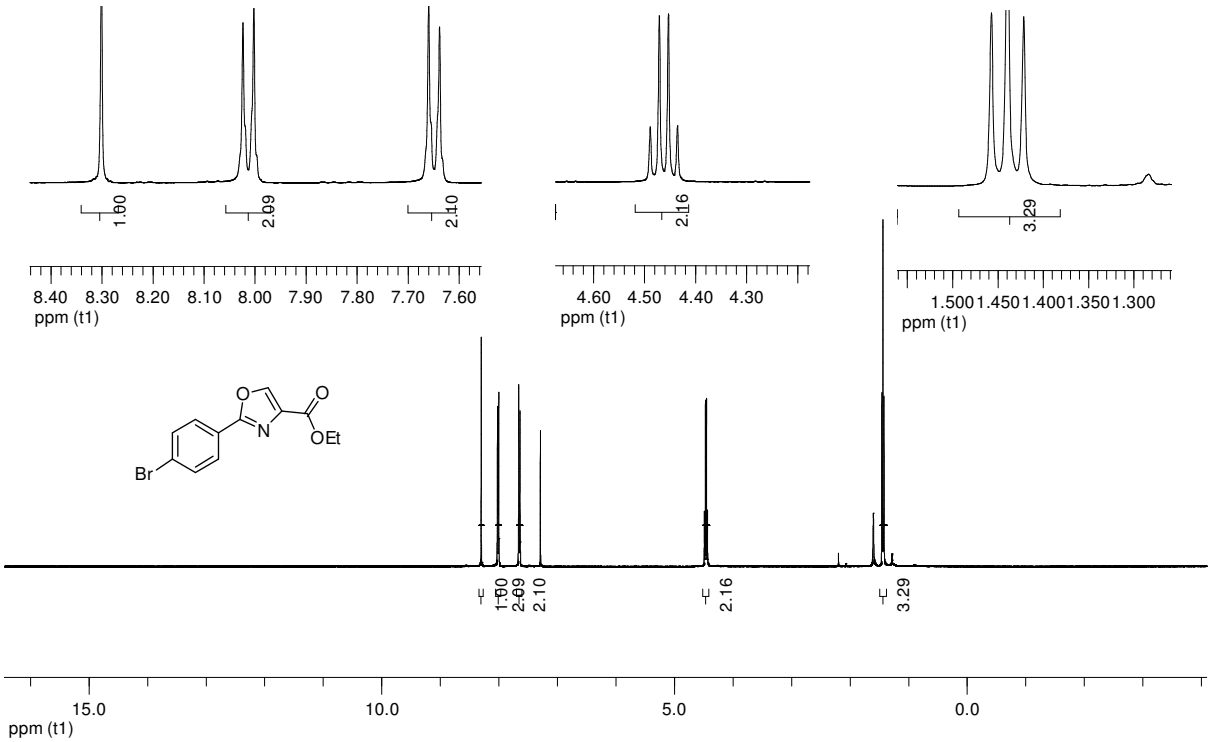
(5) Schuh, K.; Glorius, F. *Synthesis* **2007**, *15*, 2297-2306

(6) Okonya, J. F.; Hoffman, R. V.; Johnson, M. C. *J. Org. Chem.* **2002**, *67*, 1102-1108.

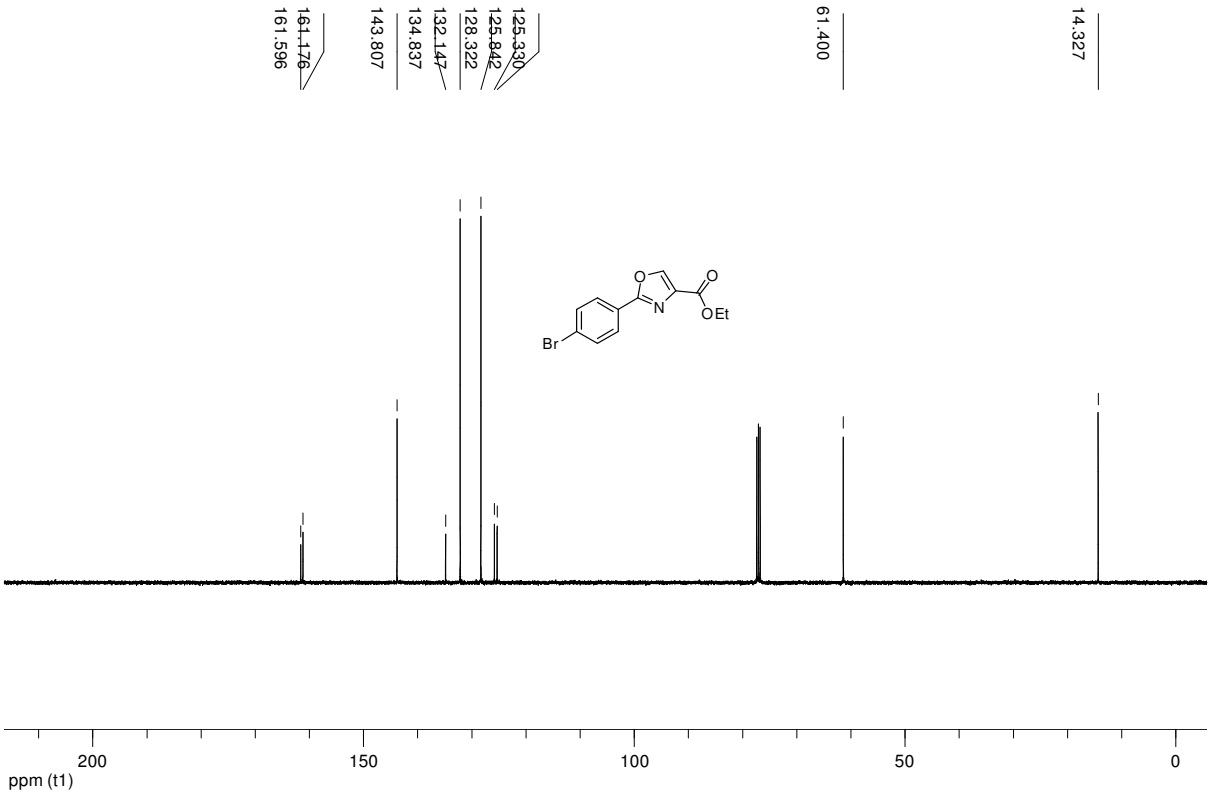
(7) Shafiee, A.; Kiaeay, G. *J. Het. Chem.* **1981**, *18*, 899-903.

(8) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495-2498.

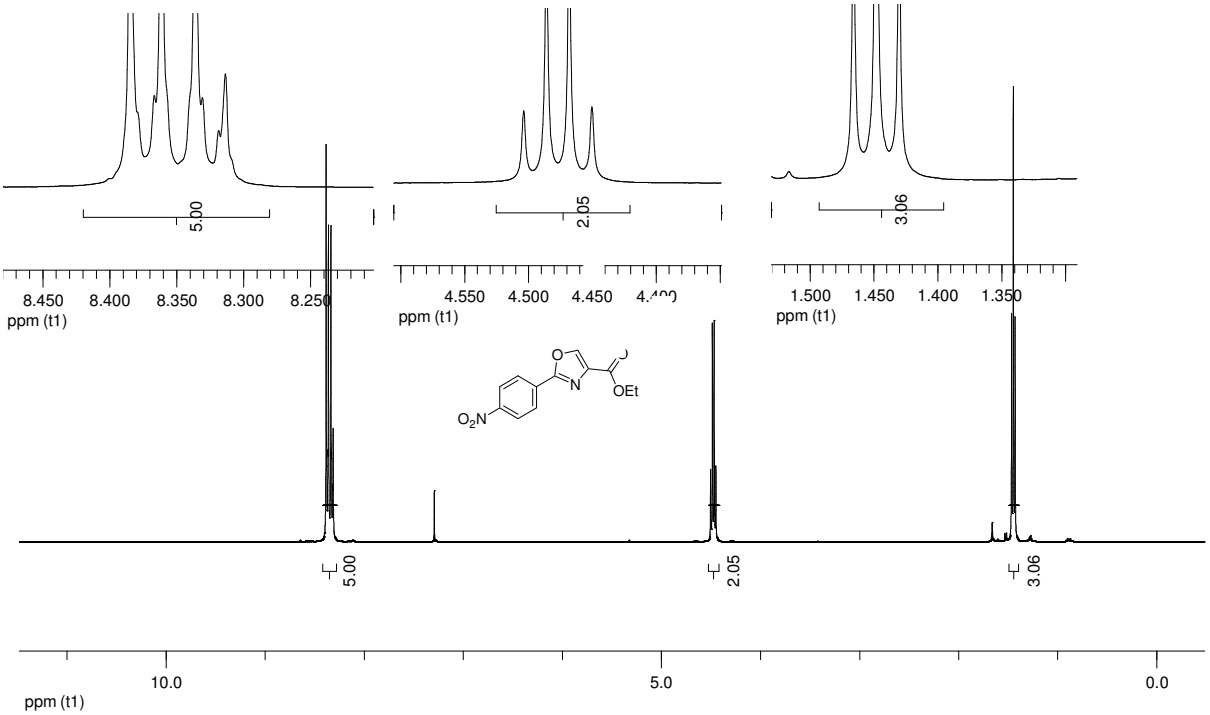
^{1}H NMR of ethyl 2-(4-bromophenyl)oxazole-4-carboxylate (4)



^{13}C NMR of ethyl 2-(4-bromophenyl)oxazole-4-carboxylate (4)



^{1}H NMR of ethyl 2-(4-nitrophenyl)oxazole-4-carboxylate (18)



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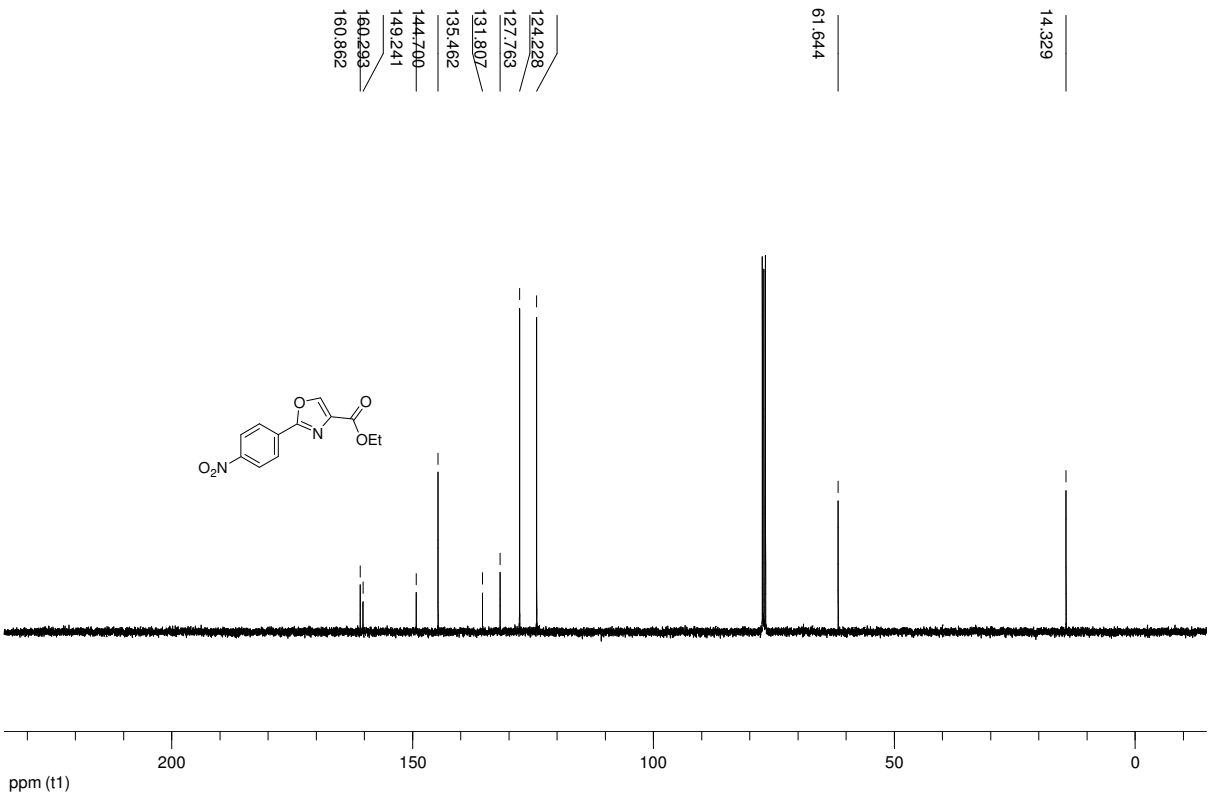
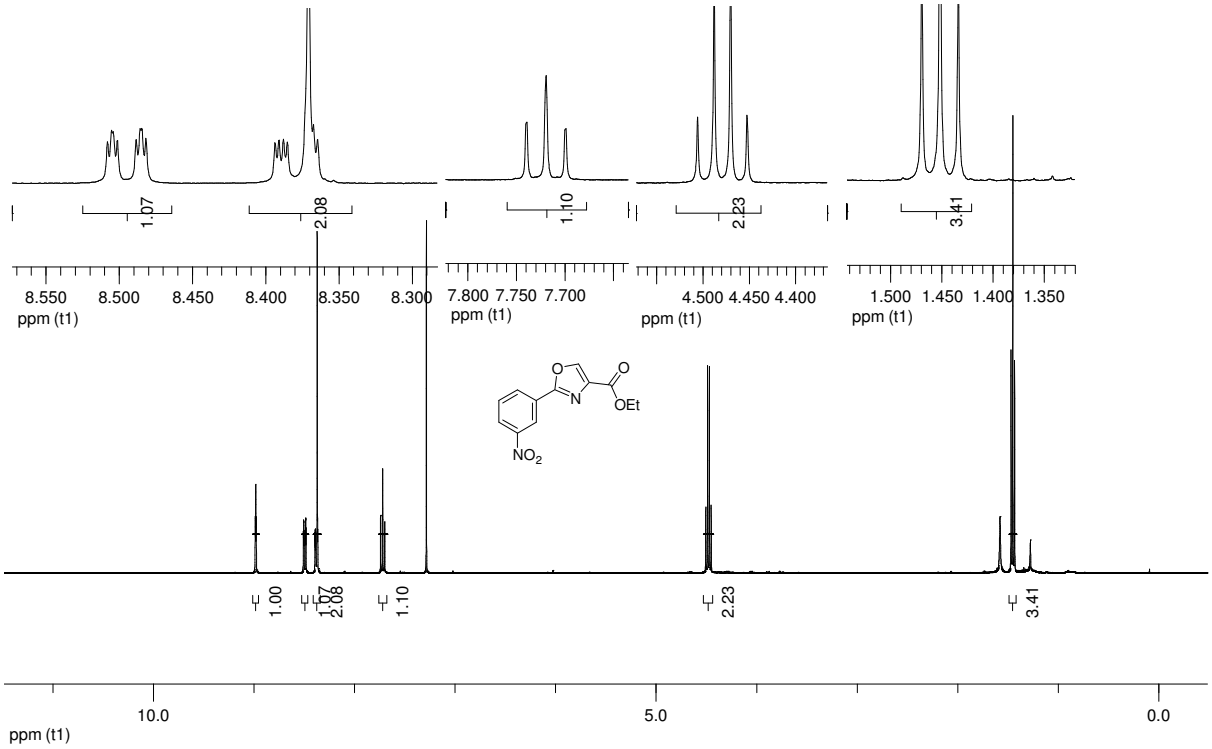
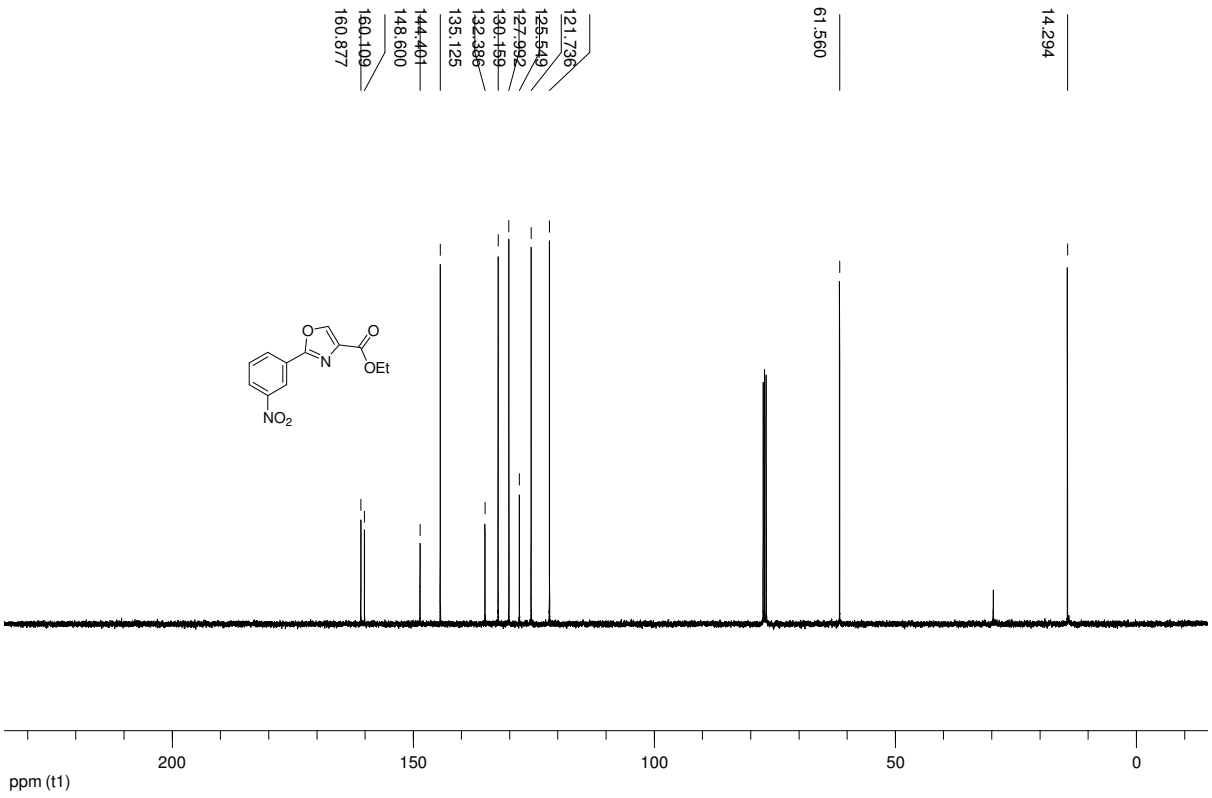


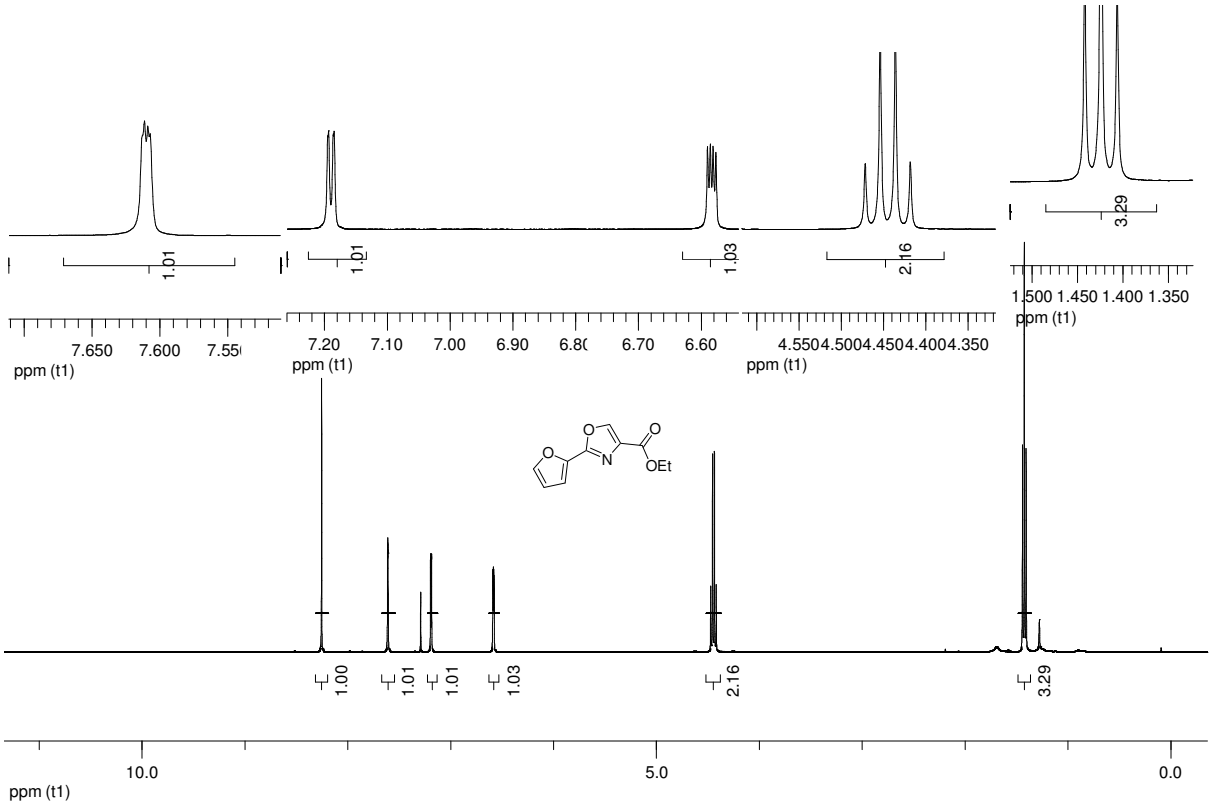
^{1}H NMR of ethyl 2-(3-nitrophenyl)oxazole-4-carboxylate (19)



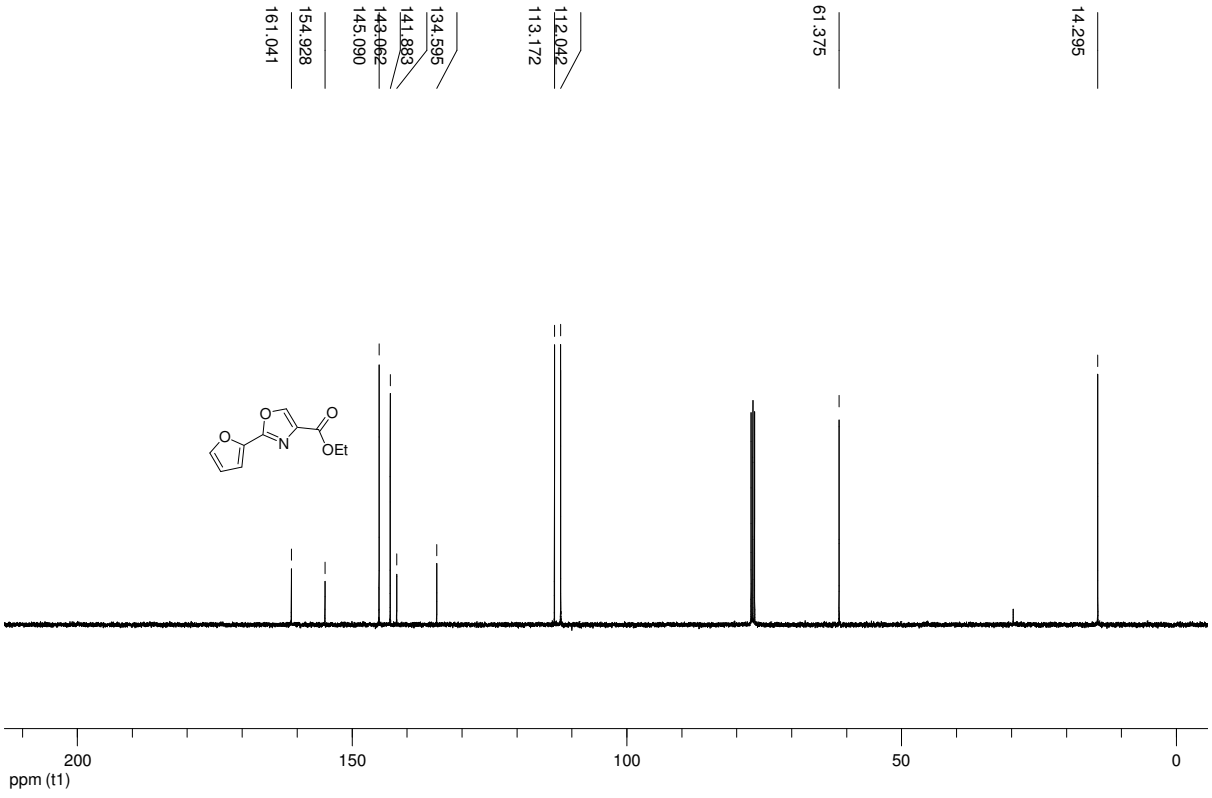
^{13}C NMR of ethyl 2-(3-nitrophenyl)oxazole-4-carboxylate (19)



^{1}H NMR of ethyl 2-(furan-2-yl)oxazole-4-carboxylate (21)



^{13}C NMR of ethyl 2-(furan-2-yl)oxazole-4-carboxylate (21)



^{1}H NMR of 2,2'-bis-(4-methoxy-phenyl)-[4,4']bioxazolyl (29)

04/03/2011 17:40:32

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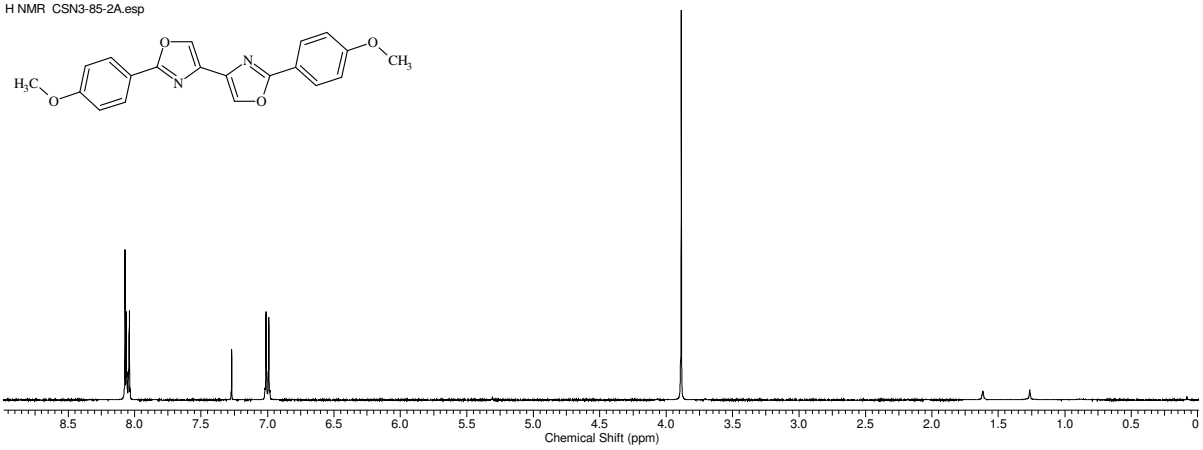

^{13}C NMR of 2,2'-bis-(4-methoxy-phenyl)-[4,4']bioxazolyl (29)

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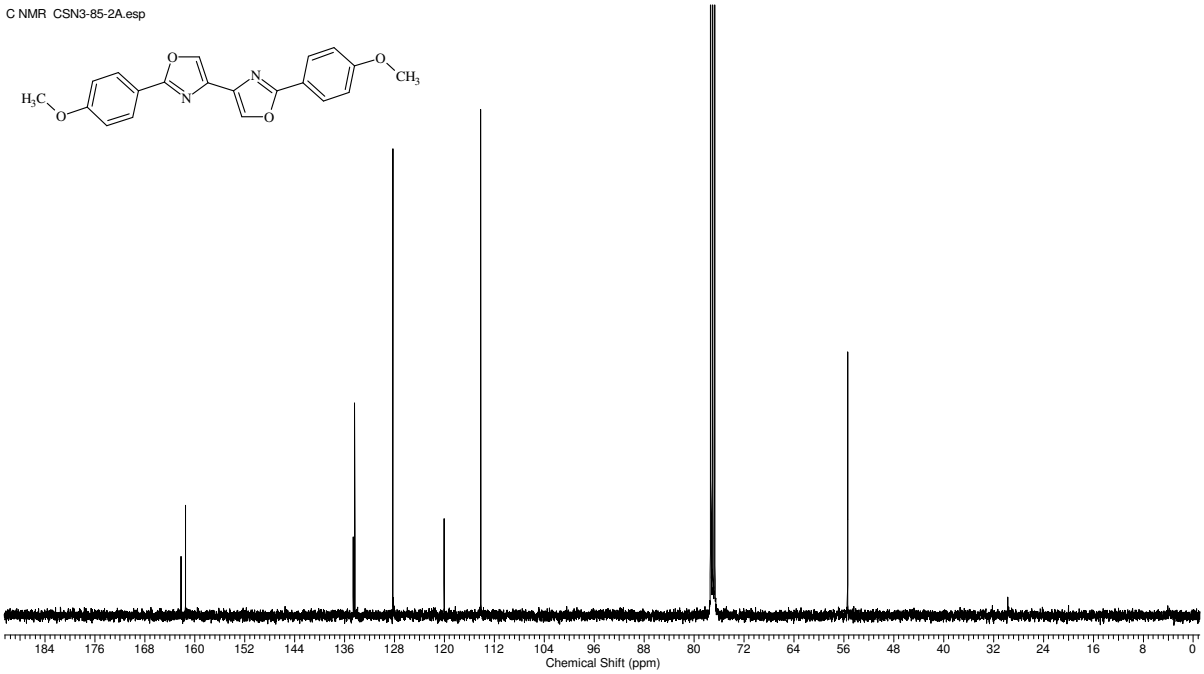
C NMR CSN3-85-2A.esp

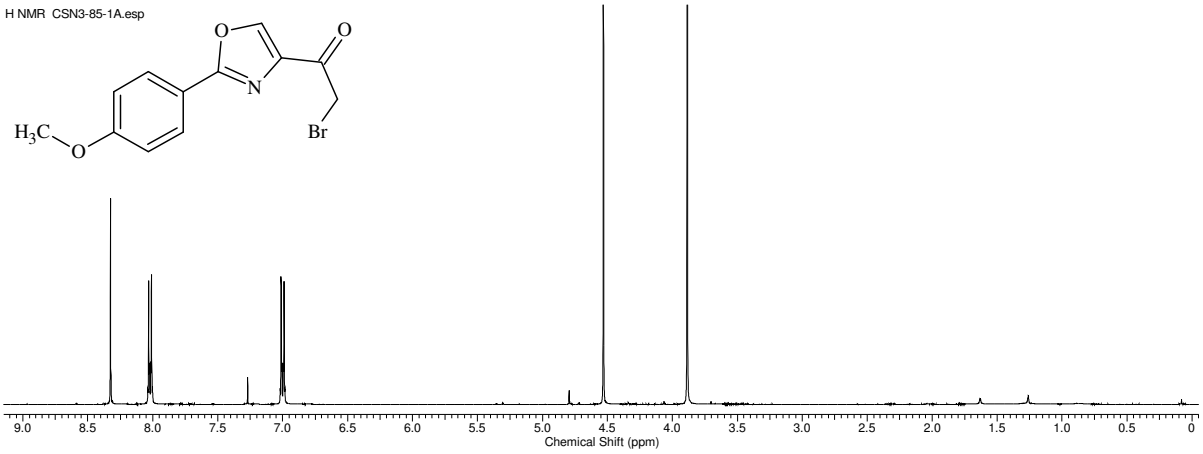


^{1}H NMR of 2-bromo-1-[2-(4-methoxy-phenyl)-oxazol-4-yl]-ethanone (31)

04/03/2011 17:58:17

Formula $C_{12}H_{10}BrNO_3$	***FW***	296.1167					
Acquisition Time (sec)	3.9846	***Comment***	Slot No. 58 Sample ID CSN3-85-1A SupervisorID moses Lab Phone No. 13540 UserID c_spi				
Date	03 Mar 2011 11:09:52			***Date Stamp***	03 Mar 2011 11:09:52		
File Name	\\brukdpx400\nmr_data\C_SPI\NMR\C_SPI.CSN3-85-1A\1\PDATA\1\1R					***Frequency (MHz)***	400.20
Nucleus	1H	***Number of Transients***	16	***Origin***	dpx400	***Original Points Count***	32768
Owner	nmruser	***Points Count***	65536	***Pulse Sequence***	zg30	***Receiver Gain***	322.50
SW(cyclical) (Hz)	8223.68	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	2462.4192	***Spectrum Type***	STANDARD
Sweep Width (Hz)	8223.56	***Temperature (degree C)***	24.900				

H NMR CSN3-85-1A.esp



^{13}C NMR of 2-bromo-1-[2-(4-methoxy-phenyl)-oxazol-4-yl]-ethanone (31)

04/03/2011 18:06:37

Formula $C_{12}H_{10}BrNO_3$	***FW***	296.1167					
Acquisition Time (sec)	0.6521	***Comment***	Slot No. 58 Sample ID CSN3-85-1A SupervisorID moses Lab Phone No. 13540 UserID c_spi				
Date	03 Mar 2011 11:16:16			***Date Stamp***	03 Mar 2011 11:16:16		
File Name	\\brukdpx400\nmr_data\C_SPI\NMR\C_SPI.CSN3-85-1A\2\PDATA\1\1R					***Frequency (MHz)***	100.63
Nucleus	13C	***Number of Transients***	128	***Origin***	dpx400	***Original Points Count***	16384
Owner	nmruser	***Points Count***	32768	***Pulse Sequence***	zgpg30	***Receiver Gain***	9195.20
SW(cyclical) (Hz)	25125.63	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	11064.4502	***Spectrum Type***	STANDARD
Sweep Width (Hz)	25124.86	***Temperature (degree C)***	25.000				

C NMR CSN3-85-1A.esp