The name and structure of compounds **S1** and **S2** have been changed from *R* to *S* at the relevant stereogenic center (p S-4). The revised file was published February 4, 2013.

Amines bearing tertiary substituents by tandem enantioselective carbolithiation–rearrangement of vinyl ureas

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SUPPORTING INFORMATION

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GENERAL INFORMATION

NMR spectra were recorded on a Bruker Ultrashield 300, 400 or 500 MHz spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (*J*) reported in hertz and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sep), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ H: $CDCl_3$ 7.26 ppm, MeOD 3.31 ppm, C_6D_6 7.16 ppm; δ C: $CDCl_3$ 77.0 ppm, MeOD 49.0 ppm, C_6D_6 128.4 ppm).

Low and high resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Micromass Trio 2000; ES and APCI spectra were recorded on a Micromass Platform II; high resolution mass spectra (HRMS, EI and ES) were recorded on a Thermo Finnigan MAT95XP mass spectrometer.

Infrared spectra were recorded on a Perkin Elmer Spectrum RX I FTIR spectrometer as a film on a sodium chloride plate. Absorptions reported are sharp and strong, only absorption maxima of interest are reported.

Melting points (m.p.) were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotations were measured on an Optical Activity AA-100 polarimeter with a 0.5 ml, 0.25 dm cell at 25 °C with the solvent and concentration stated.

Chiral HPLC measurements were carried out on a Hewlett Packard Series 1050 instrument with a Diode Array Detector, using Daicel Chiralcel AD-H chiral stationary phases using a mixture of hexane and *i*-PrOH as eluent.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram Sil G/UV254) and visualised with UV light at 254 nm or phosphomolybdic acid dip (5 % in ethanol). Flash chromatography was carried out using Fluorochem Davisil 40-63um 60 Å.

All reactions were conducted under an atmosphere of dry nitrogen or argon in oven dried glassware. Tetrahydrofuran (THF) was distilled under nitrogen from sodium using benzophenone as indicator. Cumene was obtained by distillation from calcium hydride under nitrogen. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures. (–)-Sparteine and (+)-sparteine surrogate were both distilled using a kugelrohr just before used. When stored under argon in a –32 °C freezer, enantiomeric ratios appeared to decrease significantly after few days. (+)-Sparteine surrogate has been synthesised following O'Brien's procedure[1] starting from *Laburnum anagyroides* seeds.

[1] A. J. Dixon, M. J. McGrath and P. O'Brien, *Org. Synth.*, **2006**, *83*, 141

GENERAL PROCEDURES

I. Synthesis of ureas

Using the method of Clayden et. al.[2] CH_3NH_2 (8 M in EtOH, 4 equiv.), the ketone (1 equiv.) and 4Å M.S. (250 mg/mmol) were combined and stirred for 48 h at r.t. before filtering over celite and washing with CH_2Cl_2.* The organic phases were combined and concentrated under reduce pressure to give the imine (quantitative) as a pale yellow oil. To a solution of the imine in dry THF (0.3 M), aryl isocyanate (1 equiv.) was added dropwise. After stirring for 24 h at r.t. to the mixture NaH (2 equiv.) and MeI (2 equiv.) were sequentially added at 0 °C. The reaction was stirred for 24 h at r.t., quenched with methanol and NH_4Cl (sat. sol.) and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (SiO_2, Petrol/EtOAc : 9/1 + 1% Et_3N) to give the urea **1**.

* Alternatively, the imine can be obtained using a microwave reactor with the same mixture at 125 °C for 30 to 60 min followed by the same work up.

II. Carbolithiation-rearrangement of ureas

A. Racemic reaction

Using the method of Clayden et. al.[2],to a stirred solution of the urea **1** (1 equiv.) in dry THF (0.2 M) at –78 °C, RLi (2 equiv.) was added, resulting in a red-orange solution. The reaction was stirred at the same temperature for 1.5 h, then quenched with MeOH and NH_4Cl (sat. sol.), and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Petrol/EtOAc : 8:2 + 1% Et_3N) to afford the rearranged product **3**.

B. Enantioselective reaction with (–)-sparteine in cumene

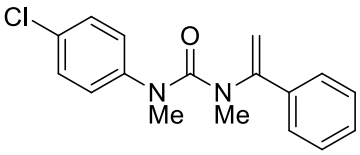
To a stirred solution of freshly distilled (–)-sparteine (1 equiv.) in dry cumene (1.5 mL) at –50 °C, RLi (2 equiv.) was added resulting in a pale yellow solution. The reaction was left to stir at the same temperature for 15 min. before the urea **1** (0.17 mmol, 1 equiv.) in solution in dry cumene (1 mL) was slowly added dropwise resulting in a red-orange solution. The reaction was stirred at the same temperature for 1.5 h, then DMPU (10 equiv.) was added dropwise and the mixture was let to stir for an additional 1.5 h. To finish, the reaction was quenched slowly with MeOH and NH_4Cl (sat. sol), and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Petrol/EtOAc : 8:2 + 1% Et_3N) to afford the rearranged product **3**.

C. Enantioselective reaction with (+)-sparteine surrogate

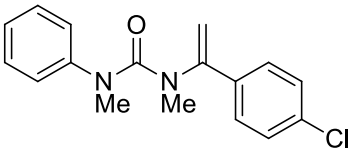
To a stirred solution of freshly distilled (+)-sparteine surrogate (2 equiv.) in dry THF (1.5 mL) at –78 °C, RLi (2 equiv.) was added resulting in a pale yellow solution. The reaction was left to stir at the same temperature for 15 min. before the urea **1** (0.17 mmol, 1 equiv.) in solution in dry THF (1 mL) was slowly added dropwise resulting in a red-orange solution. The reaction was stirred at the same temperature for 1.5 h, then DMPU (10 equiv.) was added dropwise and the mixture was let to stir for an additional 1.5 h. To finish, the reaction was quenched slowly with MeOH and NH_4Cl (sat. sol), and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Petrol/EtOAc : 8:2 + 1% Et_3N) to afford the rearranged product **3**.

Characterisation data

The following compounds **1a-1e** were reported in Clayden *et. al. J. Am. Chem. Soc*. **2010**, *132*, 6624-6625.[2]



1-(4-Chlorophenyl)-1,3-dimethyl-3-(1-phenylvinyl)urea (1a)



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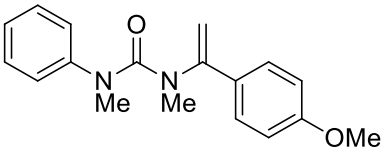

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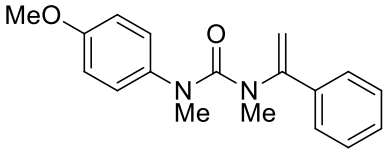

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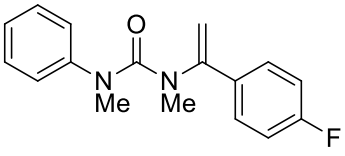
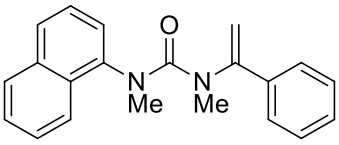
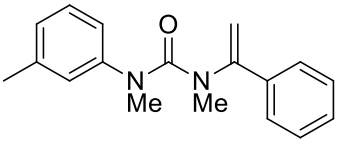


1-(1-(4-Fluorophenyl)vinyl)-1,3-dimethyl-3-phenylurea (1e)



1,3-Dimethyl-1-(naphthalen-1-yl)-3-(1-phenylvinyl)urea (1f)

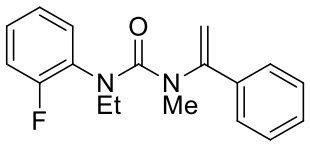
Synthesised following the general procedure **I** starting from 1 g (8.3 mmol) of acetophenone. The purification gave the desired product (1.11 g, 42%) as a brown oil. **IR** υ_{max} ($CHCl_3$)/cm^{-1}: 3053, 2931, 1651, 1614, 1594, 1494; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.82-7.74 (m 1H), 7.64-7.55 (m, 2H), 7.49-7.37 (m, 2H), 7.25-7.05 (m, 4H), 6.97 (dd, *J*=7.3, 1.3), 6.86-6.79 (m, 2H), 4.80 (s, 1H), 4.43 (s, 1H), 3.27 (s, 3H), 3.07 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 161.9, 149.6, 141.3, 136.5, 134.4, 130.2, 128.3, 128.1, 127.9, 126.9, 126.3, 125.8, 125.6, 125.5, 125.4, 122.8, 108.3, 39.9, 39.3; **HRMS** (ESI): calcd for $C_{21}H_{21}N_2O$ ($M+H^+$) 317.1649, found 317.1642



1,3-Dimethyl-3-(1-phenylvinyl)-1-(m-tolyl)urea (1g)

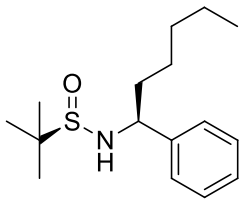
Synthesised following the general procedure **I** starting from 1 g (8.3 mmol) of acetophenone. The purification gave the desired product (887 mg, 38%) as a yellow oil. **IR** υ_{max} ($CHCl_3$)/cm^{-1}: 3034, 2948, 1647, 1615, 1599, 1495; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.24-7.01 (m, 5H), 6.95-6.87 (m, 2H), 6.85-6.78 (m, 2H), 4.84 (s, 1H), 4.59 (s, 1H), 3.22 (s, 3H), 3.00 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.7, 150.2, 144.8, 138.0, 137.4, 128.9, 128.4,

127.8, 126.4, 125.0, 124.5, 122.9, 106.4, 39.1, 38.3, 21.3; **HRMS** (ESI): calcd for $C_{18}H_{21}N_2O$ ($M+H^+$) 280.1649, found 280.1642



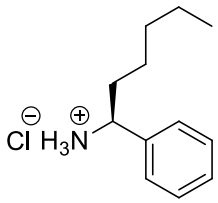
1-(2-Fluorophenyl)-1,3-dimethyl-3-(1-phenylvinyl)urea (1h)

Synthesised following the general procedure **I** starting from 1 g (8.3 mmol) of acetophenone. The purification gave the desired product (1.36 g, 55%) as a pale yellow oil. **IR υ_{max}** ($CHCl_3$)/cm^{-1}: 3026, 2945, 1648, 1618, 1596, 1493; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.18 (m, 2H), 7.13-7.08 (m, 2H), 7.08-7.01 (m, 1H), 6.97-6.90 (m, 2H), 6.81-6.76 (m, 2H), 4.92 (s, 1H), 4.69 (s, 1H), 3.48 (q, *J*=7.1 , 2H), 3.15 (s, 3H), 1.00 (t, *J*=7.1 , 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.3, 158.1 (d, J^F=249.2), 149.8, 137.0, 129.6 (d, J^F=0.9), 129.2, 128.3, 127.9, 127.3 (d, J^F=7.4), 125.8, 123.9 (d, J^F=3.7), 115.9 (d, J^F=21.2), 107.0, 45.9, 39.0, 13.0; **HRMS** (ESI): calcd for $C_{18}H_{20}N_2OF$ ($M+H^+$) 299.1555, found 299.1554



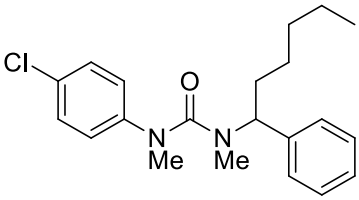
(R)-2-Methyl-N-((S)-1-phenylhexyl)propane-2-sulfinamide (S1)

(*R,E*)-N-Benzylidene-2-methylpropane-2-sulfinamide (686 mg, 3.27 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (0.2 M) and cooled to −78 °C. Pentyl magnesium bromide solution (2 equiv) was then added dropwise and the mixture stirred for 4 h. The reaction was quenched with NH_4Cl (sat. soln.), extracted with CH_2Cl_2 and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Petrol/EtOAc : 8:2 + 1% Et_3N) to afford the desired product **S1** (599 mg, 65%) as a pale yellow oil. **IR υ_{max}** ($CHCl_3$)/cm^{-1}: 1603, 1592, 1569; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.22 (m, 5H), 4.36-4.28 (m, 1H), 3.37 (d, *J*=2.0, 1H), 1.81-1.69 (m, 2H), 1.27-1.19 (m, 6H), 1.15 (s, 9H), 0.84-.78 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.1, 128.3, 127.6, 127.5, 59.1, 55.4, 38.8, 31.5, 25.6, 22.5, 22.4, 13.9; **HRMS** (ESI): calcd for $C_{16}H_{27}NONaS$ ($M+Na^+$) 304.1706, found 304.1693



(S)-1-Phenylhexan-1-aminium chloride (S2)

S1 (549 mg, 1.95 mmol) was dissolved in MeOH (0.2 M) and HCl (2 M in Et_2O, 10 equiv.) added dropwise. The mixture was stirred at room temperature for 1 h before evaporating to dryness. Et_2O was added and the resultant precipitate filtered and washed with Et2O to gived the desired product **S2** (412 mg, 99%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.75 (bs, 2H), 7.46-7.39 (m, 2H), 7.37-7.32 (m, 3H), 4.12-4.07 (m, 1H), 2.12-2.02 (m, 1H), 2.00-1.88 (m, 1H), 1.29-1.07 (m, 6H), 0.85-0.80 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 136.4, 129.1, 128.9, 127.3, 56.4, 34.5, 31.1, 25.3, 22.3, 13.9; **HRMS** (ESI): calcd for $C_{12}H_{20}N$ ($M+H^+$) 177.1517, found 177.1521

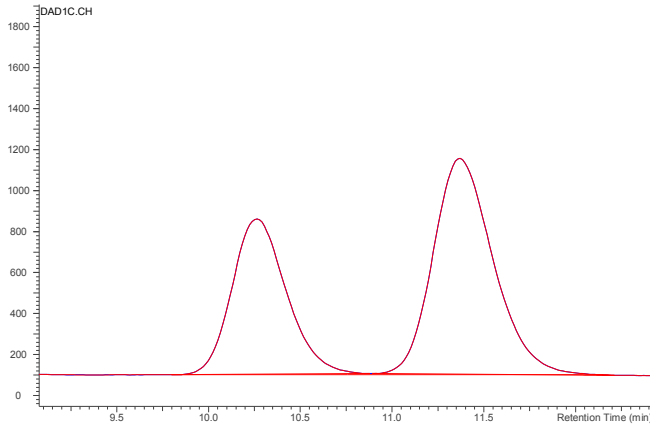


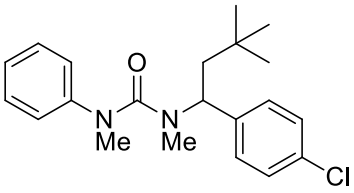
1-(4-Chlorophenyl)-1,3-dimethyl-3-(1-phenylhexyl)urea (2a)

To a stirred solution of freshly distilled (–)-sparteine (39 mg, 0.17 mmol, 1 equiv.) in dry cumene (1.5 mL) at –50 °C, *n*-BuLi (0.34 mmol, 2 equiv.) was added resulting in a pale yellow solution. The reaction was left to stir at the same temperature for 15 min. before the urea **1a** (50 mg, 0.17 mmol, 1 equiv.) in solution in dry cumene (1 mL) was slowly added dropwise resulting in a red-orange solution. The reaction was stirred at the same temperature for 1.5 h. To finish, the reaction was quenched slowly with MeOH and NH_4Cl (sat. sol), and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 9:1 Petrol/ EtOAc) to afford the corresponding urea (32 mg, 54%) as a yellow oil.

Alternatively, **2a** was synthesised by dissolving **S2** (460 mg, 2.15 mmol, 1 equiv.) in CH_2Cl_2 (0.2 M) and adding Et_3N (1.5 equiv.) and *p*-chlorophenyl isocyanate (1 equiv.). After stirring for 24 h at r.t. to the mixture NaH (5 equiv.) and MeI (5 equiv.) were sequentially added at 0 °C. The reaction was stirred for 24 h at r.t., quenched with methanol and NH_4Cl (sat. sol.) and then extracted with EtOAc. The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography (SiO_2, Petrol/EtOAc : 9/1 + 1% Et_3N) to give the desired urea **2a** (583 mg, 75%). **IR** υ_{max} ($CHCl_3$)/cm^{-1}: 2963, 1641, 1489; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.15 (m, 7H), 6.95-6.89 (m, 2H), 5.35 (dd, *J*=8.8, 7.1 , 1H), 3.15 (s, 3H), 2.26 (s, 3H), 1.92-1.81 (m, 1H), 1.77-1.67 (m, 1H) 1.35-1.17 (m, 6H), 0.86 (t, *J*=6.9 , 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.0, 145.6, 139.9, 129.6, 129.4, 128.3, 127.8, 127.3, 125.2, 58.5, 40.1, 31.7, 30.8, 30.3, 26.4, 22.6, 14.0; **HRMS** (ESI): calcd for $C_{21}H_{27}N_2OClNa$ ($M+Na^+$) 381.1704, found 381.1710

Enantioenriched product from procedure **II.B** gave 65:35 er determined by HPLC : Chiralcel AD-H 95:5 hexane:*i*-PrOH 1mL/min. $[\alpha]_D^{25} = +12.8$ (c. 1.00 in $CDCl_3$)

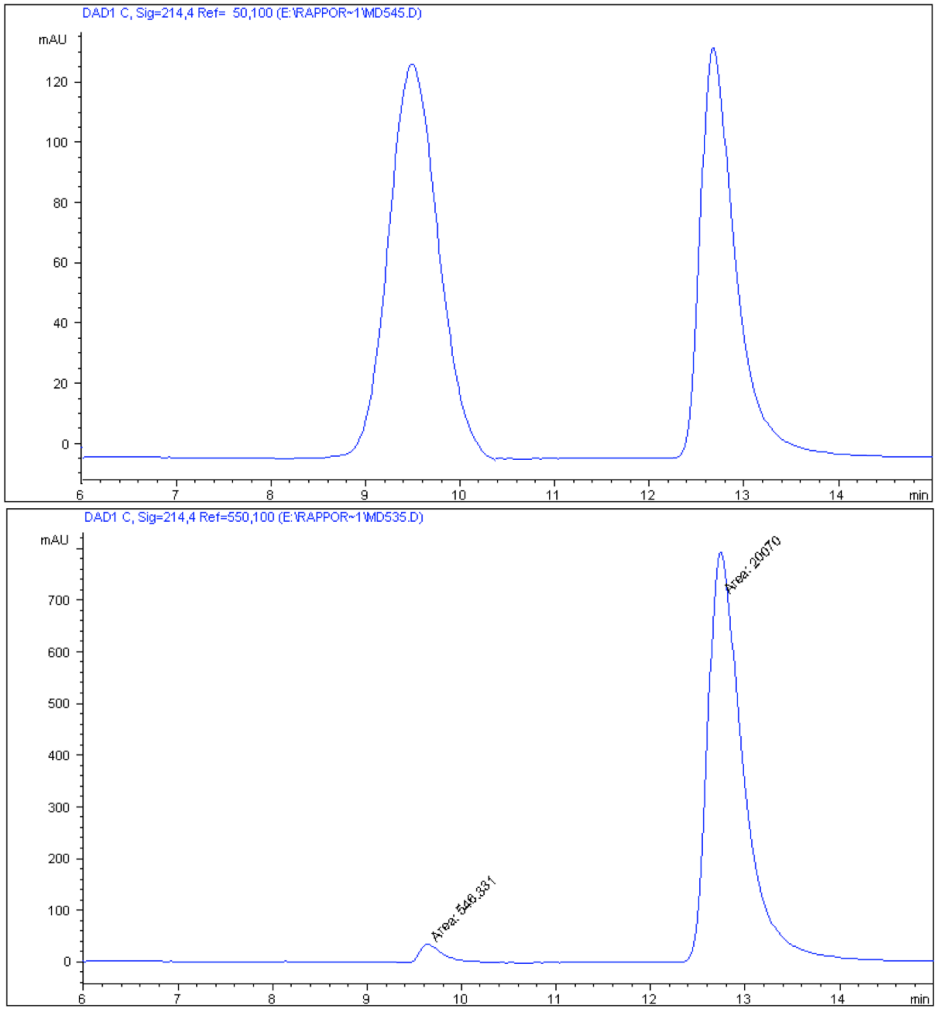


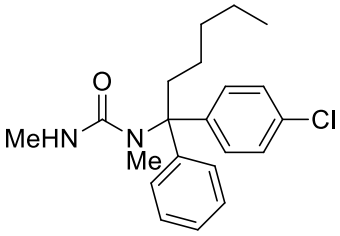


1-(1-(4-Chlorophenyl)-3,3-dimethyl-1-phenylbutyl)-1,3-dimethylurea (2c)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea **1b**. The purification gave the desired product (**A:** 48 mg, 78%; **B**: 44 mg, 72%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 2960, 1635, 1494**;** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 4 H), 7.11 (t, *J*= 7.6 , 2H), 6.96 (t, *J*= 7.6 , 1H), 6.85 (d, *J*= 7.6 , 2H), 5.53 (t, *J*= 6.8 , 1H), 3.13 (s, 3H), 2.23 (s, 3H), 1.95 (dd; *J*= 6.8, 7.2 , 2H, A of AB), 1.68 (dd; *J*= 6.8, 7.2 , 2H, B of AB), 0.82 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.1, 146.9, 141.0, 138.7, 129.2, 128.1, 127.1, 124.2, 123.8, 56.4, 43.7, 40.2, 31.1, 30.7, 30.0; **HRMS** (ESI): calcd for $C_{21}H_{27}N_2OClNa$ ($M+Na^+$) 381.1710, found 381.1717

Enantioenriched product from procedure **II.B** gave 94:6 er determined by HPLC : Chiralcel AD-H 95:5 hexane:*i*-PrOH 1mL/min.

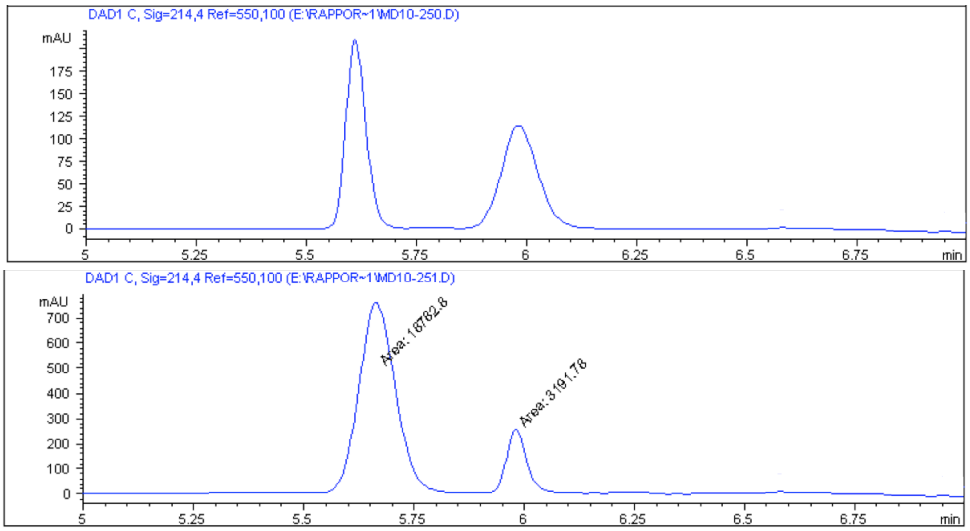


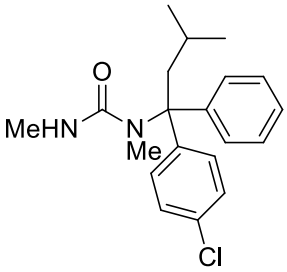


1-(1-(4-Chlorophenyl)-1-phenylhexyl)-1,3-dimethylurea (3a)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea **1a**. The purification gave the desired product (**A:** 44 mg, 72%; **B**: 43 mg, 75%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3350, 2953, 2924, 1635, 1530**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 9H), 4.16 (bq, -NH), 2.91 (s, 3H), 2.60 (d, *J*= 4.8 , 3H), 2.55 (m, 2H), 1.32-1.25 (m, 6H), 0.85 (d, *J*= 6.8 , 3H); **^{13}C NMR** (100 MHz, MeOD): δ 162.1, 146.1, 145.8, 132.8, 129.9, 129.0, 128.7 **(4C)**, 127.6, 71.5, 40.4, 36.7, 33.3, 27.6, 23.7, 14.4; **HRMS** (ESI): calcd for $C_{21}H_{27}ClN_2ONa$ ($M+Na^+$) 381.1710, found 381.1708

Enantioenriched product from procedure **II.B** gave 88:12 er determined by HPLC : Chiralcel AD-H 90:10 hexane:*i*-PrOH 1mL/min. $[\alpha]_D^{25}$ = - 8.1 (c. 1.45 in $CDCl_3$)

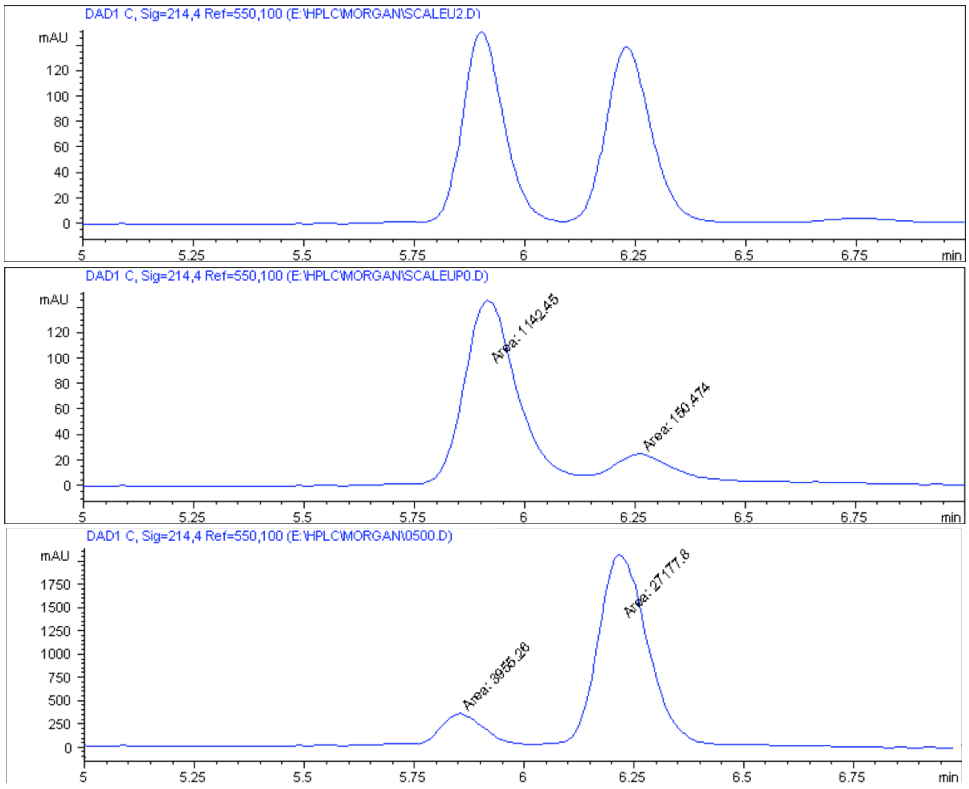


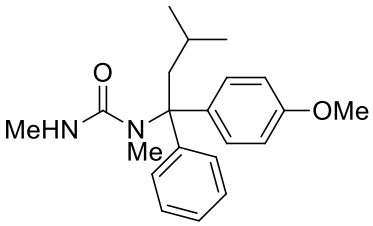


1-(1-(4-Chlorophenyl)-3-methyl-1-phenylbutyl)-1,3-dimethylurea (3b)

Synthesised following the general procedure **II.A, II.B** or **II.C** starting from 50 mg (0.17 mmol) of the urea **1b**. The purification gave the desired product (**A :** 41 mg, 72%; **B** : 48 mg, 86%; **C :** 45 mg, 74%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3362, 3056, 2947, 1634, 1520; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.17 (m, 9H), 4.18 (bq, -NH), 2.89 (s, 3H), 2.59 (d, *J*= 4.8 , 3H), 2.50 (m, 2H), 1.58 (m, 1H), 0.73 (t, *J*= 6.8 , 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.7, 142.3, 137.7, 131.1, 129.7, 128.4, 128.3, 128.1, 127.1, 60.5, 28.8, 27.4, 23.2, 14.3; **HRMS** (ESI): calcd for $C_{20}H_{25}N_2OClNa$ ($M+Na^+$) 367.1553, found 367.1561

Enantioenriched product from procedure **II.B** gave 90:10 er from **1a** and 92:8 er from **1b** determined by HPLC : Chiralcel AD-H 90:10 hexane:*i*-PrOH 1mL/min. From **1a** : $[\alpha]_D^{25} = +7.8$ (c. 1.35 in $CDCl_3$); from **1b :** $[\alpha]_D^{25} = -8.0$ (c. 1.20 in $CDCl_3$). Enantioenriched product from procedure **II.C** gave 95:5 er from **1b**

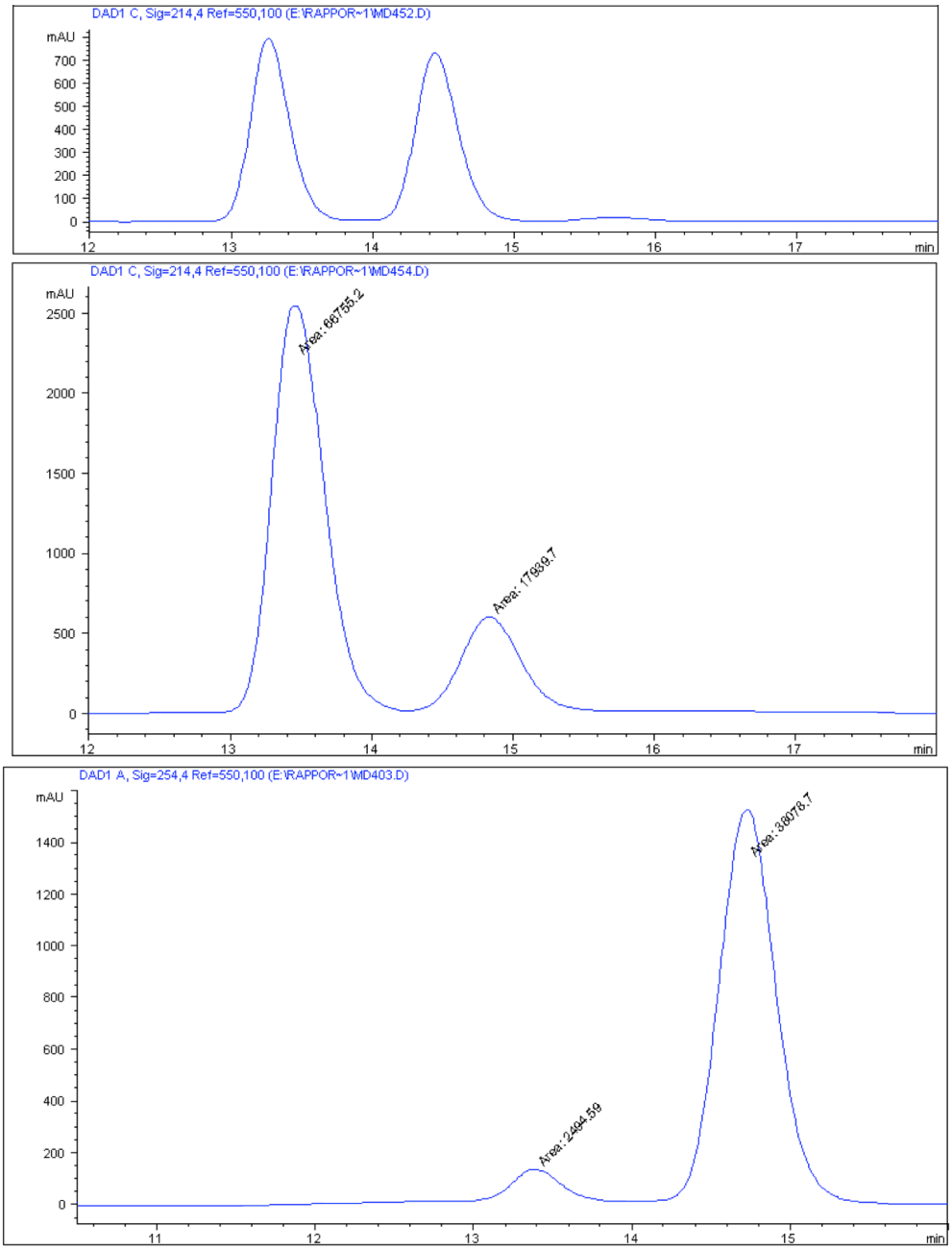


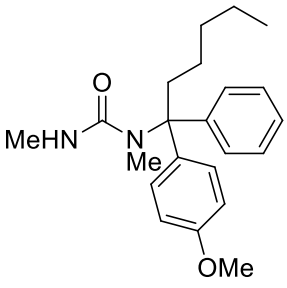


1-(1-(4-Methoxyphenyl)-3-methyl-1-phenylpentyl)-1,3-dimethylurea (3c)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea (**1c** or **1d**). The purification gave the desired product (*from **1c*** : **A** : 44 mg, 76%; **B** : 42 mg, 72%; from **1d** : **A** : 43 mg, 75%; **B** : 44 mg, 76%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3359, 3060, 2950, 1635**;** **^{1}H NMR** (400 MHz, C_6D_6): δ 7.58-7.56 (m, 2H), 7.51-7-48 (m, 2H), 7.29-7.25 (m, 2H), 7.17-7.13 (m, 1H), 6.86-6.84 (m, 2H), 3.99-3.98 (bq, -NH), 3.41 (s, 3H), 2.75-2.73 (m, 2H), 2.74 (s, 3H), 2.60 (d, *J*= 4.8 , 3H), 1.79-1.76 (m, 1H), 0.90 (d, *J*= 6.8 , 3H), 0.89 (d, *J*= 6.8 , 3H); **^{13}C NMR** (100 MHz, C_6D_6): δ 158.4, 157.0, 148.6, 140.2, 123.0, 128.1, 126.2, 113.4, 65.2, 54.7, 45.2, 29.5, 28.7, 25.0, 24.9, 23.8; **HRMS** (ESI): calcd for $C_{21}H_{28}N_2O_2Na$ (M+Na$^+$) 363.2048, found 363.2059

Enantioenriched product from procedure **II.B** gave 89:11 er from **1c** and 78:22 er from **1d** determined by HPLC : Chiralcel AD-H 90:10 hexane:*i*-PrOH 1mL/min. From **1c** : $[\alpha]_D^{25}$ =- 7.4 (c. 1.5 in $CDCl_3$) ; from **1d** : $[\alpha]_D^{25}$ =+ 6.2 (c. 1.5 in $CDCl_3$)

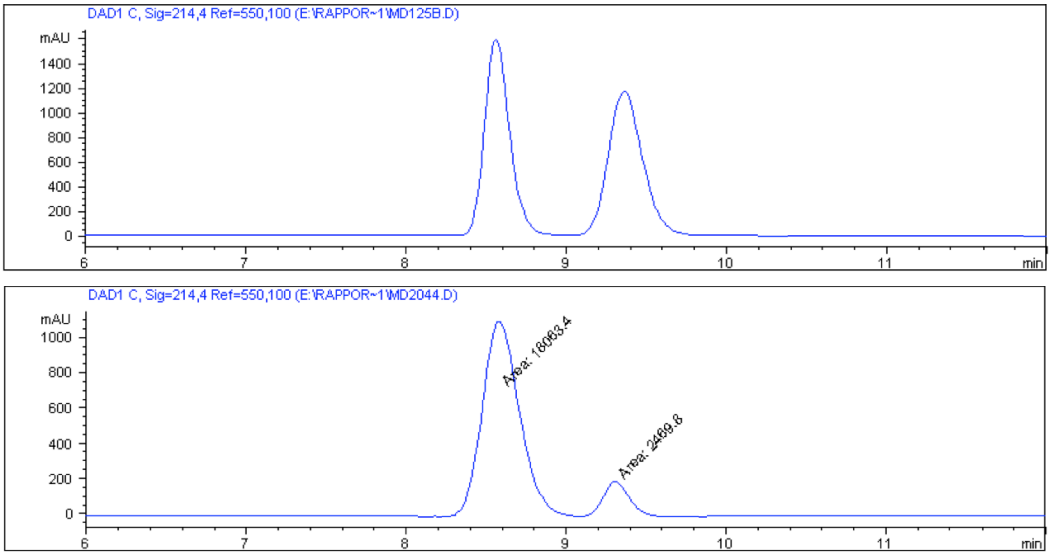


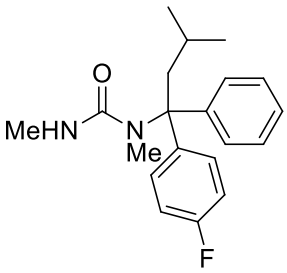


1-(1-(4-Methoxyphenyl)-1-phenylhexyl)-1,3-dimethylurea (3d)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea **1c**. The purification gave the desired product (**A** : 40 mg, 66%; **B** : 44 mg, 73%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3362, 3055, 2960**;** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=7.2 , 2H), 7.44 (d, *J*=8.8 , 2H), 7.25-7-07 (m, 3H), 6.84 (d, *J*=8.8 , 2H), 3.84 (bq, -NH), 3.40 (s, 3H), 2.81 (s, 3H), 2.79-2.75 (m, 2H), 2.60 (d, *J*= 4.8 , 3H), 1.47-1.29 (m, 6H), 0.94 (t, *J*= 7.2 , 3H); ^{13}**C NMR** (100 MHz, C_6D_6): δ 159.8, 158.7, 145.7, 136.7, 129.6, 126.7, 113.7, 70.4, 54.7, 41.7, 35.4, 32.7, 27.6, 25.8, 22.9, 14.3; **HRMS** (ESI): calcd for $C_{22}H_{30}N_2O_2Na$ ($M+Na^+$) 377.2205, found 377.2209

Enantioenriched product from procedure **II.B** gave 90:10 er determined by HPLC : Chiralcel AD-H 90:10 hexane:*i*-PrOH 1mL/min. $[\alpha]_D^{25}$ = - 7.2 (c. 1.24 in CDCl3)

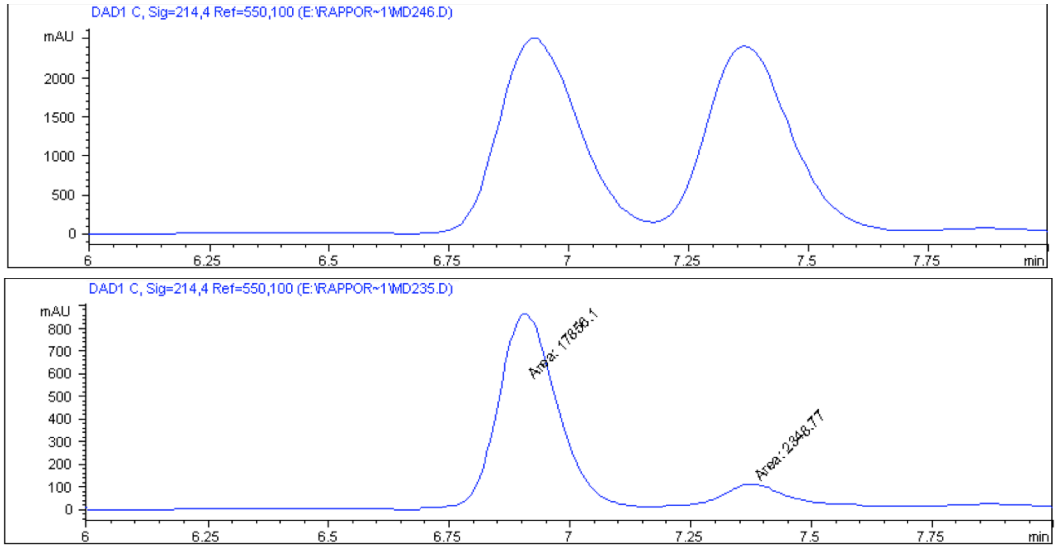


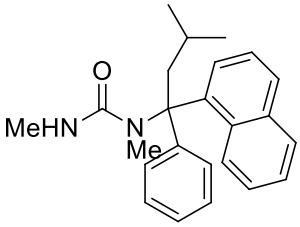


1-(1-(4-Fluorophenyl)-3-methyl-1-phenylbutyl)-1,3-dimethylurea (3e)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.18 mmol) of the urea **1e**. The purification gave the desired product (**A** : 48 mg, 81%; **B** : 47 mg, 79%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3432, 2958, 1633**;** ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 4H), 7.32-7-29 (m, 2H), 7.24-7.22 (m, 1H), 7.04-6.96 (m, 2H), 4.18 (bq, -NH), 2.92 (s, 3H), 2.59 (d, *J*= 4.4 , 3H), 2.51 (d, *J*= 4.8 , 2H), 1.62-1.57 (m, 1H), 0.74 (d, *J*= 6.8 , 3H), 0.73 (d, *J*= 6.8 , 3H); ^{13}**C NMR** (100 MHz, C_6D_6): δ 159.9, 143.8, 139.8, 129.5, 128.2 (d, J^F=249.5), 128.1, 127.7, 114.7 (d, J^F=21.1), 70.3, 48.3, 35.3, 27.5, 24.7, 24.6, 24.5; **HRMS** (ESI): calcd for $C_{20}H_{25}N_2OFNa$ ($M+Na^+$) 351.4135, found 351.4135

Enantioenriched product from procedure **II.B** gave 91:9 er determined by HPLC : Chiralcel AD-H 90:10 hexane:*i*-PrOH 1mL/min. $[\alpha]_D^{25}$ = - 2.2 (c. 1.20 in $CDCl_3$)

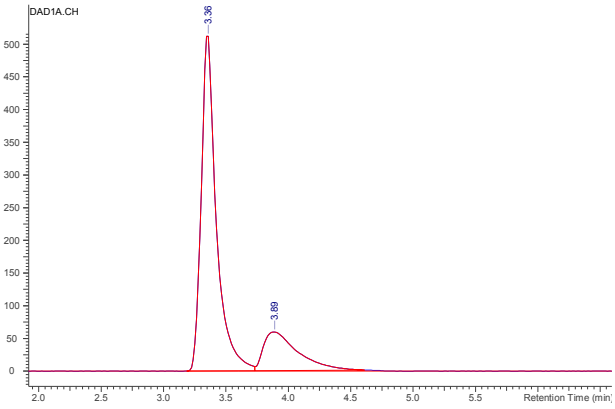


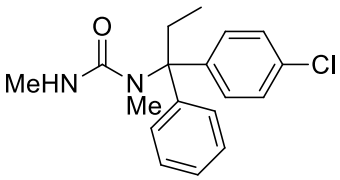


1,3-Dimethyl-1-(3-methyl-1-(naphthalen-1-yl)-1-phenylbutyl)urea (3f)

Synthesised following the general procedure **II.A** or **II.B** starting from 48 mg (0.15 mmol) of the urea **1f**. The purification gave the desired product (30 mg, 55%) as a brown oil.**IR** μ_{max} (film)/cm^{-1}: 3349, 2982, 1645; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.45-8.38 (m, 1H), 7.84-7.79 (m, 1H), 7.73 (d, *J*=8.3, 1H), 7.59 (d, *J*=8.1, 2H), 7.43-7.36 (m, 2H), 7.34-7.21 (m, 4H), 7.13 (d, *J*=6.8, 1H), 3.15 (d, *J*=15.4, 1H), 2.82 (s, 3H), 2.71 (dd, *J*=14.9, 6.3, 1H), 2.51 (s, 3H), 1.32-1.23 (m, 2H), 0.81 (d, *J*=6.8, 3H), 0.03 (d, *J*=6.6, 3H); ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 162.1, 146.1, 140.9, 136.1, 134.8, 130.4, 129.9, 128.7, 128.4, 127.9, 127.6, 126.6, 126.3, 125.6, 79.6, 74.6, 46.9, 27.7, 27.4, 25.6, 24.2; **HRMS** (ESI): calcd for $C_{24}H_{29}N_2O$ ($M+H^+$) 261.2274, found 261.2278

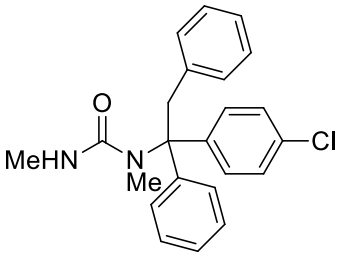
Enantioenriched product from procedure **II.B** gave 88:12 er determined by HPLC : Chiralcel AD-H 97:3 hexane:*i*-PrOH 1mL/min.





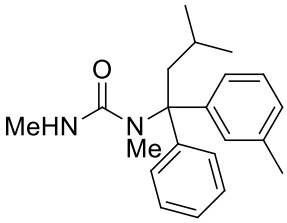
1-(1-(4-Chlorophenyl)-1-phenylpropyl)-1,3-dimethylurea (3g)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea **1a**. The purification gave the desired product (31 mg, 58%) as a pale yellow oil.**IR** μ_{max} (film)/cm^{-1}: 3351, 2973, 2938, 1636, 1529, 1490; **^{1}H NMR** (400 MHz, MeOD): δ 7.38-7.22 (m, 8H), 7.21-7.16 (m, 1H), 2.82 (s, 3H), 2.74 (q, *J*=7.3 , 2H), 2.63 (3H, s), 0.88 (t, *J*=7.3); **^{13}C NMR** (MeOD, 100 MHz): δ 162.3, 146.0, 145.7, 133.0, 130.2, 129.2, 128.9, 128.9, 127.7, 72.0, 36.9, 33.0, 27.8, 10.6; **HRMS** (ESI): calcd for $C_{18}H_{22}N_2OCl$ (M+H$^+$) 317.1415, found 317.1413



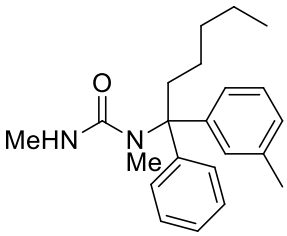
1-(1-(4-Chlorophenyl)-1,2-diphenylethyl)-1,3-dimethylurea (3h)

Synthesised following the general procedure **II.A** or **II.B** starting from 50 mg (0.17 mmol) of the urea **1a**. The purification gave the desired product (48 mg, 74%) as a pale yellow oil. **IR** μ_{max} (film)/cm^{-1}: 3356, 3026, 2937, 1634, 1566; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.07 (m, 14H), 4.10 (bq, -NH), 4.07 (s, 2H), 2.81 (s, 3H), 2.65 (d, J= 4.8 ,3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.2, 156.6, 144.0, 137.6, 131.3, 127.9, 127.7, 127.5, 126.9, 126.3, 74.1, 45.3, 31.0, 27.3; **HRMS** (ESI): calcd for $C_{23}H_{23}N_2OClNa$ (M+Na+) 401.1397, found 401.1406



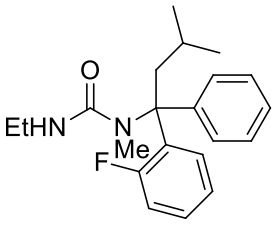
1,3-Dimethyl-1-(3-methyl-1-phenyl-1-(m-tolyl)butyl)urea (3i)

Synthesised following the general procedure **II.A** or **II.C** starting from 40 mg (0.14 mmol) of the urea **1g**. The purification gave the desired product (37 mg, 82%) as a pale brown oil.**IR** μ_{max} (film)/cm^{-1}: 2984, 1663; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.42 (m, 2H), 7.34-7.28 (m, 2H), 7.26-7.17 (m, 4H), 7.03 (d, *J*=7.1 , 1H), 4.14 (q, *J*=4.3 , 1H), 2.98 (s, 3H), 2.55 (d, *J* =4.5, 3H), 2.52 (d, *J*=5.6 , 2H), 2.33 (s, 3H), 1.75-1.64 (m, 1H), 0.77 (dd, *J*=6.7, 3.3 , 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.0, 143.9, 143.8, 137.6, 128.3, 128.0, 127.9, 127.7, 127.5, 126.7, 124.8, 70.4, 48.2, 35.4, 27.4, 24.7, 24.6, 24.6, 21.7; **HRMS** (ESI): calcd for $C_{21}H_{28}N_2ONa$ (M + Na$^+$) 347.2094, found 347.2104



1,3-Dimethyl-1-(1-phenyl-1-(m-tolyl)hexyl)urea (3j)

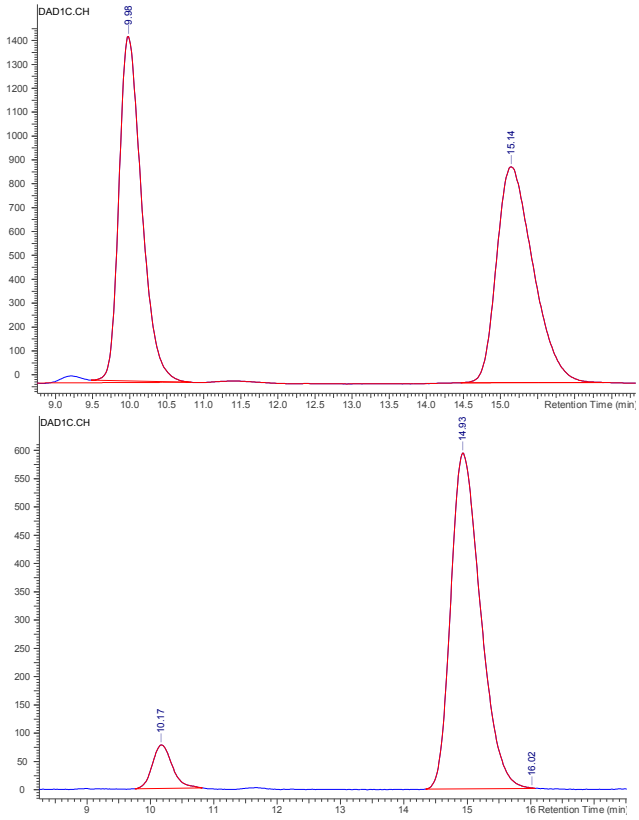
Synthesised following the general procedure **II.A** or **II.C** starting from 41 mg (0.15 mmol) of the urea **1g**. The purification gave the desired product (42 mg, 83%) as a pale yellow oil.**IR** μ_{max} (film)/cm^{-1}: 1654; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 2H), 7.34-7.29 (m, 2H), 7.25-7.16 (m, 4H), 7.06-7.02 (m, 1H), 4.07 (q, *J*=4.5 , 1H), 2.96 (s, 3H), 2.56-2.50 (m, 5H), 2.33 (s, 3H), 1.34-1.24 (m, 6H), 0.86 (t, *J*=6.3 , 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.1, 144.1, 144.0, 137.7, 128.1, 128.1, 128.0, 127.6, 127.6, 126.8, 124.6, 69.9, 41.1, 35.2, 32.3, 27.5, 25.2, 21.8, 21.8, 14.0; **HRMS** (ESI): calcd for $C_{22}H_{31}N_2O$ (M+H$^+$) 339.2431, found 339.2420

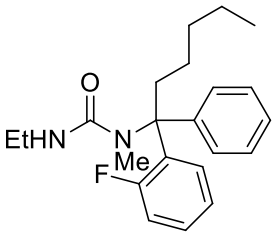


3-Ethyl-1-(1-(2-fluorophenyl)-3-methyl-1-phenylbutyl)-1-methylurea (3k)

Synthesised following the general procedure **II.A** or **II.C** starting from 60 mg (0.20 mmol) of the urea **1h**. The purification gave the desired product (47 mg, 69%) as a pale yellow oil.**IR** μ_{max} (film)/cm^{-1}: 3423, 1659; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.42 (m, 2H), 7.34-7.28 (m, 3H) 7.27-7.21 (m, 2H), 7.08 (ddd, *J*=7.6, 7.6, 1.4 , 1H), 7.00 (ddd, *J*=12.6, 8.1, 1.3 , 1H), 4.19 (t, *J*=5.3 , 1H), 3.11-3.02 (m, 2H), 3.00 (d, *J*=1.0 , 3H), 2.60 (dd, *J*=10.1, 5.4 , 2H, A and B of AB), 1.65-1.53 (m, 1H), 0.89 (t, *J*=7.3 , 3H), 0.75 (dd, *J*=14.5, 6.7 , 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.6 (d, J^F=248.3), 158.6, 143.2, 131.0 (d, J^F=10.2), 129.4 (d, J^F=4.6), 128.8 (d, J^F=9.2), 127.8, 127.8, 126.9, 123.5 (d, J^F=2.8), 116.5 (d, J^F=24.9), 69.7 (d, J^F=3.7), 46.6 (d, J^F=2.8), 35.4, 34.4 (d, J^F=1.9), 25.1, 24.5, 24.4, 15.2; **HRMS** (ESI): calcd for $C_{21}H_{28}N_2OF$ ($M+H^+$) 343.2180, found 343.2194

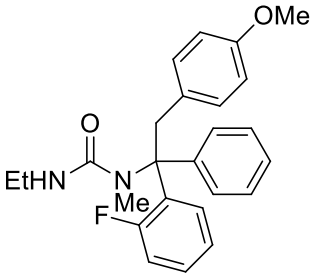
Enantioenriched product from procedure **II.C** gave 92:8 er determined by HPLC : Chiralcel OD-H 95:5 hexane:*i*-PrOH 1mL/min. $[\alpha]_D^{25} = +5.6$ (c. 1.00 in $CDCl_3$)





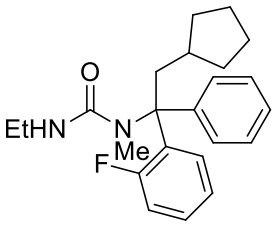
3-Ethyl-1-(1-(2-fluorophenyl)-1-phenylhexyl)-1-methylurea (3l)

Synthesised following the general procedure **II.A** or **II.C** starting from 55 mg (0.18 mmol) of the urea **1h**. The purification gave the desired product (39 mg, 61%) as a colourless oil.**IR** μ_{max} (film)/cm^{-1}: 1638; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39-7.19 (m, 7H), 7.10 (ddd, *J*=8.1, 8.1, 1.3 , 1H), 7.04 (ddd, *J*=12.4, 8.1, 1.3 , 1H), 4.11 (t, *J*=5.3 , 1H), 3.08-2.94 (m, 5H), 2.72-2.53 (m, 2H), 1.33-1.20 (m, 4H), 1.18-1.08 (m, 2H), 0.83 (t, *J*=7.1 , 3H), 0.81 (t, *J*=7.3 , 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.4 (d, J^F=248.3), 158.7, 143.6, 130.6 (d, J^F=11.1), 129.3 (d, J^F=4.6), 129.0 (d, J^F=9.2), 128.1, 127.5, 127.0, 123.8 (d, J^F=2.8), 116.5 (d, J^F=24.0), 69.5 (d, J^F=3.7), 39.9 (d, J^F=3.7), 35.4, 34.1 (d, J^F=1.9), 32.1, 25.9, 22.4, 15.0, 14.0; **HRMS** (ESI): calcd for $C_{22}H_{29}N_2OFNa$ ($M+Na^+$), 379.2157, found 379.2167



3-Ethyl-1-(1-(2-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylethyl)-1-methylurea (3m)

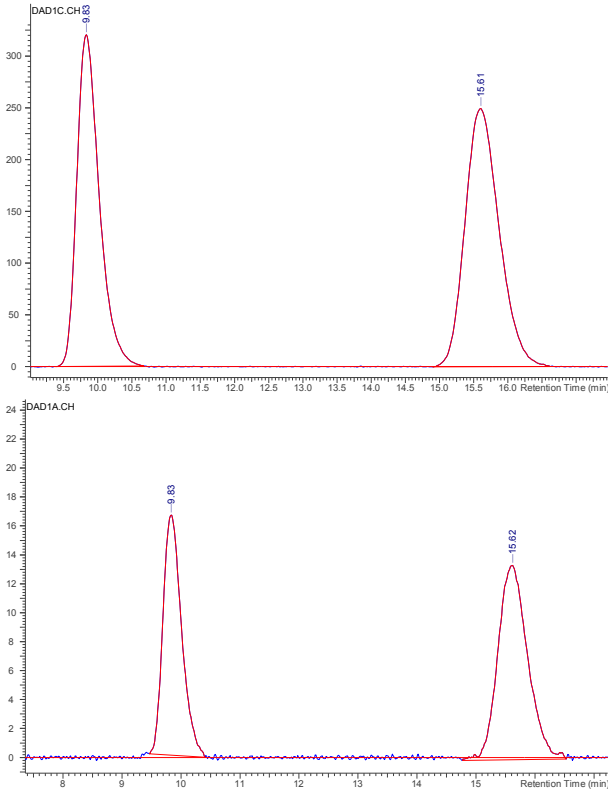
Synthesised following the general procedure **II.A** or **II.C** starting from 54 mg (0.18 mmol) of the urea **1h**. The purification gave the desired product (57 mg, 78%) as a brown oil.**IR** μ_{max} (film)/cm^{-1}: 1653; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (td, *J*=8.1, 1.8 , 1H), 7.29-7.16 (m, 6H), 6.99 (m, 1H), 6.88-6.82 (m, 2H), 6.70-6.65 (m, 2H), 4.22 (t, *J*=5.3 , 1H), 4.20 (d, *J*=13.9 , A of AB, 1H), 4.03 (d, *J*=13.9 , B of AB, 1H), 3.76 (s, 3H), 3.21-3.09 (m, 2H), 2.71 (d, *J*=1.5 , 3H), 0.99 (t, *J*=7.1 , 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.0 (d, J^F=248.3), 159.0, 158.1, 142.2, 132.3 (d, J^F=10.2), 132.1, 129.5 129.2 (d, J^F=3.7), 128.6 (d, J^F=8.3), 128.0 (d, J^F=1.9), 127.6, 126.8, 123.6 (d, J^F=2.8), 116.7 (d, J^F=24.9), 113.0, 70.8 (d, J^F=2.8), 55.1, 42.0 (d, J^F=3.7), 36.0 (d, J^F=3.7), 35.5, 15.4; **HRMS** (ESI): calcd for $C_{25}H_{27}N_2O_2FNa$ (M+Na$^+$) 429.1949, found 429.1939

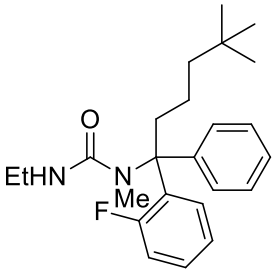


1-(2-Cyclopentyl-1-(2-fluorophenyl)-1-phenylethyl)-3-ethyl-1-methylurea (3n)

Synthesised following the general procedure **II.A** or **II.C** starting from 46 mg (0.15 mmol) of the urea **1h**. The purification gave the desired product (49 mg, 88%) as a colourless oil.**IR** μ_{max} (film)/cm^{-1}: 3032, 1648; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48-7.40 (m, 2H), 7.36-7.19 (m, 5H), 7.08 (ddd, *J*=7.6, 7.6, 1.4 , 1H), 7.01 (ddd, *J*=11.5, 8.1, 1.1 , 1H), 4.17 (t, *J*=5.3 , 1H), 3.11-2.99 (m, 2H), 3.03 (s, 3H), 2.77 (d, *J*=4.9 , 2H), 1.72-1.23 (m, 7H), 1.10-0.94 (m, 2H), 0.86 (t, *J*=7.2 , 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.7 (d, J^F = 248.5), 158.6, 143.3, 131.0 (d, J^F = 10.9), 129.6 (d, J^F = 4.4), 128.9 (d, J^F = 9.3), 127.9, 127.9, 126.9, 123.6 (d, J^F = 3.3), 116.5 (d, J^F = 24.5), 69.6 (d, J^F = 3.3), 45.0 (d, J^F = 2.7), 37.7, 35.5, 34.3, 34.2, 34.1 (d, J^F = 2.7), 24.8, 24.8, 15.1; **HRMS** (ESI): calcd for $C_{23}H_{29}N_2OFNa$ (M+Na$^+$) 391.2157, found 391.2159

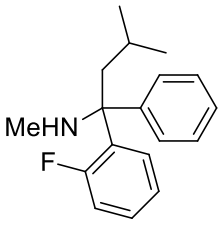
Enantioenriched product from procedure **II.C** gave 53:47 er determined by HPLC : Chiralcel OD-H 95:5 hexane:*i*-PrOH 1mL/min.





3-Ethyl-1-(1-(2-fluorophenyl)-5,5-dimethyl-1-phenylhexyl)-1-methylurea (3o)

Synthesised following the general procedure **II.A** or **II.C** starting from 67 mg (0.22 mmol) of the urea **1h**. The purification gave the desired product (60 mg, 70%) as a brown oil.**IR** μ_{max} (film)/cm^{-1}: 1638; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.31-7.12 (m, 7H), 7.03 (t, *J*=7.6 , 1H), 6.98 (dd, *J*=12.5, 8 , 1H), 4.04 (t, *J*=5.0 , 1H), 3.02-2.88 (m, 5H), 2.60-2.44 (m, 2H), 1.15-0.98 (m, 4H), 0.73 (t, *J*=7.3 , 3H), 0.70 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 160.4 (d, J^F=248.0), 158.7, 143.6, 130.5 (d, J^F=11.8), 129.3 (d, J^F=3.6), 129.1 (d, J^F=8.2), 128.1, 127.5, 127.1, 123.8 (d, J^F=2.7), 116.5 (d, J^F=24.5), 69.6, (d, J^F=3.6), 44.4, 40.7 (d, J^F=3.6), 35.4, 34.0, 30.2, 29.2, 21.3, 15.0; **HRMS** (ESI): calcd for $C_{24}H_{33}N_2OFNa$ (M+Na$^+$) 407.2475, found 407.2472

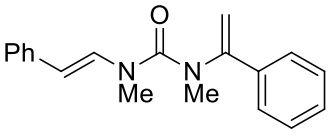


1-(2-Fluorophenyl)-N,3-dimethyl-1-phenylbutan-1-amine (8k)

To urea **3k** (1 equiv.) was added a 1:1 v/v mixture of EtOH and 2 M NaOH (10 equiv.). The resultant mixture was heated to 130 ºC under microwave irradiation. After cooling, the mixture was extracted with EtOAc and the solvent removed under reduced pressure to yield the desired product.

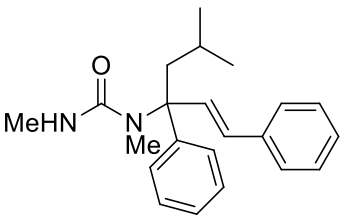
IR μ_{max} (film)/cm^{-1}: 3240; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.65 (td, *J*=8.1, 1.7 , 1H), 7.32-7.14 (m, 7H), 6.90 (ddd, *J*=12.4, 7.9, 1.5 , 1H), 2.25 (dd, *J*=13.6, 5.7, A of AB, 1H), 2.11 (s, 3H), 2.03, (dd, *J*=13.6, 5.1 , B of AB, 1H), 1.68-1.54 (m, 1H), 0.75 (d, *J*=6.8 , 3H), 0.64 (d, *J*=6.6 , 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.6 (d, J^F=247.4), 146.8, 134.5 (d, J^F=10.4), 128.7, (d, J^F=3.8), 128.4 (d, J^F=8.7), 127.7, 126.4 (d, J^F=1.6), 126.2, 123.3 (d, J^F=3.3), 116.2 (d, J^F = 22.3), 63.9, 43.6, 29.4, 24.7, 24.4, 23.2; **HRMS** (ESI): calcd for $C_{18}H_{23}NF$ (M+H$^+$) 272.1810, found 272.1805

Enantioenriched product gave 92:8 er determined by HPLC : Chiralcel OD-H 95:5 hexane:*i*-PrOH 1mL/min.



(E)-1,3-Dimethyl-3-(1-phenylvinyl)-1-styrylurea (9)

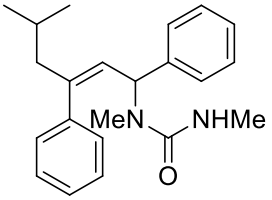
Synthesised following the general procedure **I** starting from 805 mg (6.7 mmol) of acetophenone and freshly prepared styrene isocyante using the procedure of Greco et. al.[4]. Purification by recrystallisation from Et_2O gave the desired product as a white solid. (490 mg, 25%).**IR** μ_{max} (film)/cm^{-1}: 1633; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51-7.46 (m, 3H), 7.41-7.35 (m, 3H), 7.24-7.08 (m, 5H), 5.56 (d, *J*=14.5), 5.31 (s, 1H), 4.94 (s, 1H), 3.18 (s, 3H), 2.96 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.8, 150.4, 137.4, 136.8, 130.6, 128.9,128.7, 128.5, 125.9, 125.6, 125.0, 107.8, 106.4, 38.4, 32.6; **HRMS** (ESI): calcd for $C_{19}H_{21}N_2O$ (M+H)$^+$ 293.1649, found 293.1645



(E)-1,3-Dimethyl-1-(5-methyl-1,3-diphenylhex-1-en-3-yl)urea (10)

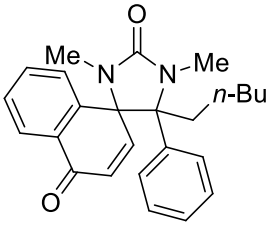
Synthesised following the general procedure **II.A** except the temperature was raised to −30 °C after 90 mins and left at that temperature for a further 90 minns before quenching to give the desried product (32 mg, 55%) as a colourless oil. Alternatively synthesised using general procedure **II.B** except the temperature was set to −35 °C to give the desried product (16 mg, 27%). Alternatively synthesised using general procedure **II.C** except the temperature was set to −45 °C, the solvent changed to Et2O and the reaction left to run for 4 h to give the desried product (18 mg, 32%). **IR** μ_{max} (film)/cm^{-1}: 2953, 1634, 1529; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32-7.17 (m, 10H), 6.75 (d, *J*=16.2 , 1H), 6.16 (d, *J*=16.2), 4.06 (br s, 1H), 3.08 (s, 3H), 2.45 (d, *J*=4.7 , 3H), 2.11 (ddd, *J*=39.9, 14.1, 5.3 , 2H), 1.61-1.70 (m, 1H), 0.81 (d, *J*=6-8), 0.72 (d, *J*=6-8); **^{13}C NMR** Unable to get clean ^{13}C NMR due to product's instability δ ; **HRMS** (ESI): calcd for $C_{22}H_{28}N_2O$ (M+Na)$^+$ 359.2099, found 359.2105

Enantioenriched product from procedure **II.B** gave 75:25 er determined by NMR using the chemical shift reagent ((*R*)-2,2,2-Trifluoro-1-anthracen-9-yl-ethanol). Enantioenriched product from procedure **II.C** gave 88:12 er



(Z)-1,3-Dimethyl-1-(5-methyl-1,3-diphenylhex-2-en-1-yl)urea (11)

Attempts at purification of **10**, or prolonged standing in $CDCl_3$ resulted in **11 IR** μ_{max} (film)/cm^{-1}: 2953, 2928, 1624, 1537; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.15 (m, 10H), 6.37 (d, *J*=9.2 , 1H), 5.80 (d, *J*=9.2 , 1H), 4.31 (d, *J*=4.5 , 1H), 2.80 (d, *J*=4.5 , 3H), 2.63 (s, 3H), 2.36-2.58 (m, 2H), 1.47-1.56 (m, 1H), 0.73 (d, *J*=6-8); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 158.9, 144.8, 143.0, 141.1, 128.5 128.3,127.2, 127.1, 127.0, 126.8, 126.1, 55.1, 39.2, 29.3, 27.84, 27.0, 22.5, 22.4; **HRMS** (ESI): calcd for $C_{19}H_{21}N_2O$ $(M+Na)^+$ 337.2280, found 337.2275.

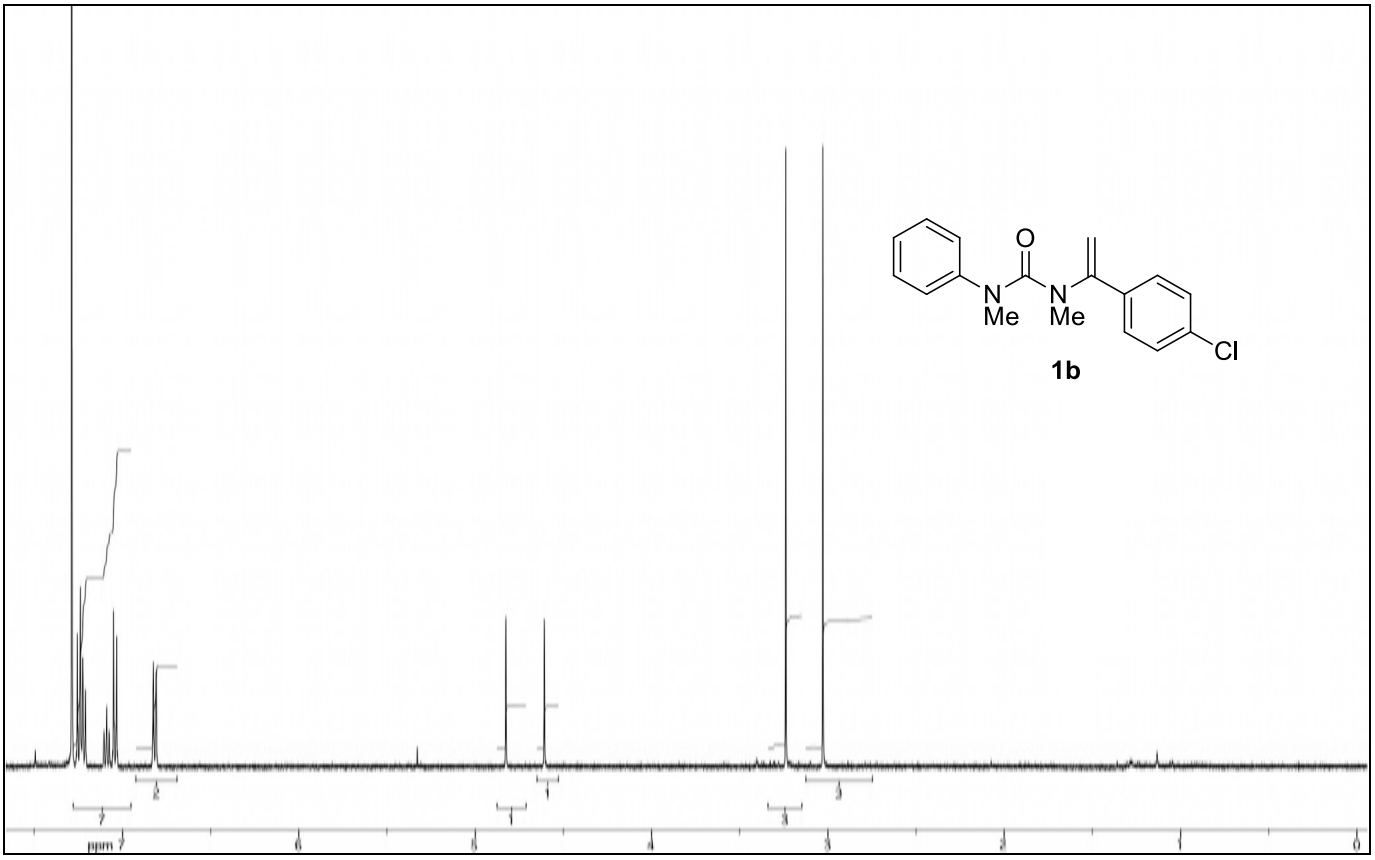


1,3-Dimethyl-5-pentyl-5-phenyl-4'H-spiro[imidazolidine-4,1'-naphthalene]-2,4'-dione (12)

Urea **1f** (50 mg, 0.16mmol) was solubilised in THF (0.1 M) and cooled to –78 °C. *n*-BuLi (2 equiv.) was then added to the mixture and the reaction was stirred for 1 h. The reaction was then put under oxygen atmosphere (balloon) and stirred for 16 h increasing slowly the temperature to r.t. The reaction was diluted with EtOAc, extracted with, H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The titled compound was obtained in 56% yield as an oil after flash chromatography on silica gel (Pet. ether/EtOAc: 8/2). The compound was isolated as a mixture of diastereoisomers.**IR** μ_{max} (film)/cm^{-1}: 2951, 1706, 1669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36-8.34 (m, 1H, major dia.), 7.87 (dd, *J*=7.6, 1.2 , 1H, minor dia.), 7.39-7.36 (m, 1H, major dia.), 7.16 (m, 1H, major dia.), 7.07-6.96 (m, 5H, major dia. and 2H, minor dia.), 6.93 (d, *J*=7.2 , 1H, minor dia.), 6.81 (dt, *J*=7.6, 1.6 , 2H, minor dia.), 6.75-6.71 (m, 1H, major dia. and 1H, minor dia.), 6.73 (d, *J*=10.4 , 1H, minor dia.), 6.55-6.53 (m, 2H, minor dia.), 6.38 (d, *J*=10.4 , 1H, minor dia.), 6.05 (d, *J*=10.4 , 1H, major dia.), 5.54 (d, *J*=10.4 , 1H, major dia), 2.85 (s, 3H, major dia.), 2.73 (s, 3H, minor dia.), 2.57 (s, 3H, minor dia.), 2.45 (s, 3H, major dia.), 1.97 (ddd, *J*=15.6, 11.6, 3.8 , 1H, minor dia.), 1.65 (ddd, *J*=16.4, 12.8, 3.6 , 1H, minor dia.), 1.49-1.41 (m, 1H, major dia. and 1H, minor dia.), 1.30-1.23 (m, 1H, major dia. and 1H, minor dia.), 1.17-0.97 (m, 2H, major dia. and 2H, minor dia.), 0.93-0.83 (m, 3H, major dia. and 2H, minor dia.), 0.74-0.68 (m, 2H, major dia. and 3H, minor dia.) 0.62 (t, *J*=7.2, 3H, major dia.); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 183.9 (major dia.), 182.8 (minor dia.), 162.0 (minor dia.), 161.7 (major dia.), 151.0 (major dia.), 147.4 (minor dia.), 140.5 (minor dia.), 139.6 (major dia.), 137.6 (minor dia.), 137.5 (major dia.), 133.4 (minor dia.), 132.9, 132.4, 132.1, 131.4, 131.0 (major dia.), 128.9, 128.6, 127.9, 127.9, 127.4, 127.3, 127.3, 126.8, 126.4, 4.5 (minor dia.), 73.7 (major dia.), 69.0 (minor dia.), 68.5 (major dia.), 36.8 (minor dia.), 35.2 (major dia.), 32.7 (major dia), 32.4 (minor dia), 29.5 (major dia.), 28.9 (minor dia.), 28.1 (minor dia.), 27.8 (major dia.), 24.6 (minor dia.), 24.5 (major dia.), 22.4 (minor dia.), 22.2 (major dia.), 14.1 (minor dia.), 13.8 (major dia).; **HRMS** (ESI): calcd for $C_{25}H_{29}N_2O_2$ $(M+H)^+$ 389.2224, found 389.2221

References

1. A. J. Dixon, M. J. McGrath and P. O'Brien, *Org. Synth.*, **2006**, *83*, 141
2. Clayden, J. et. al. *J. Am. Chem. Soc.* **2010**, *132*, 6624-6625
3. Ellman, J. A. et. al. *J. Am. Chem. Soc.* **119**, 9913-9914 (1997)
4. Greco et. al. *J. Med. Chem.* **2007**, *50*, 1727-1730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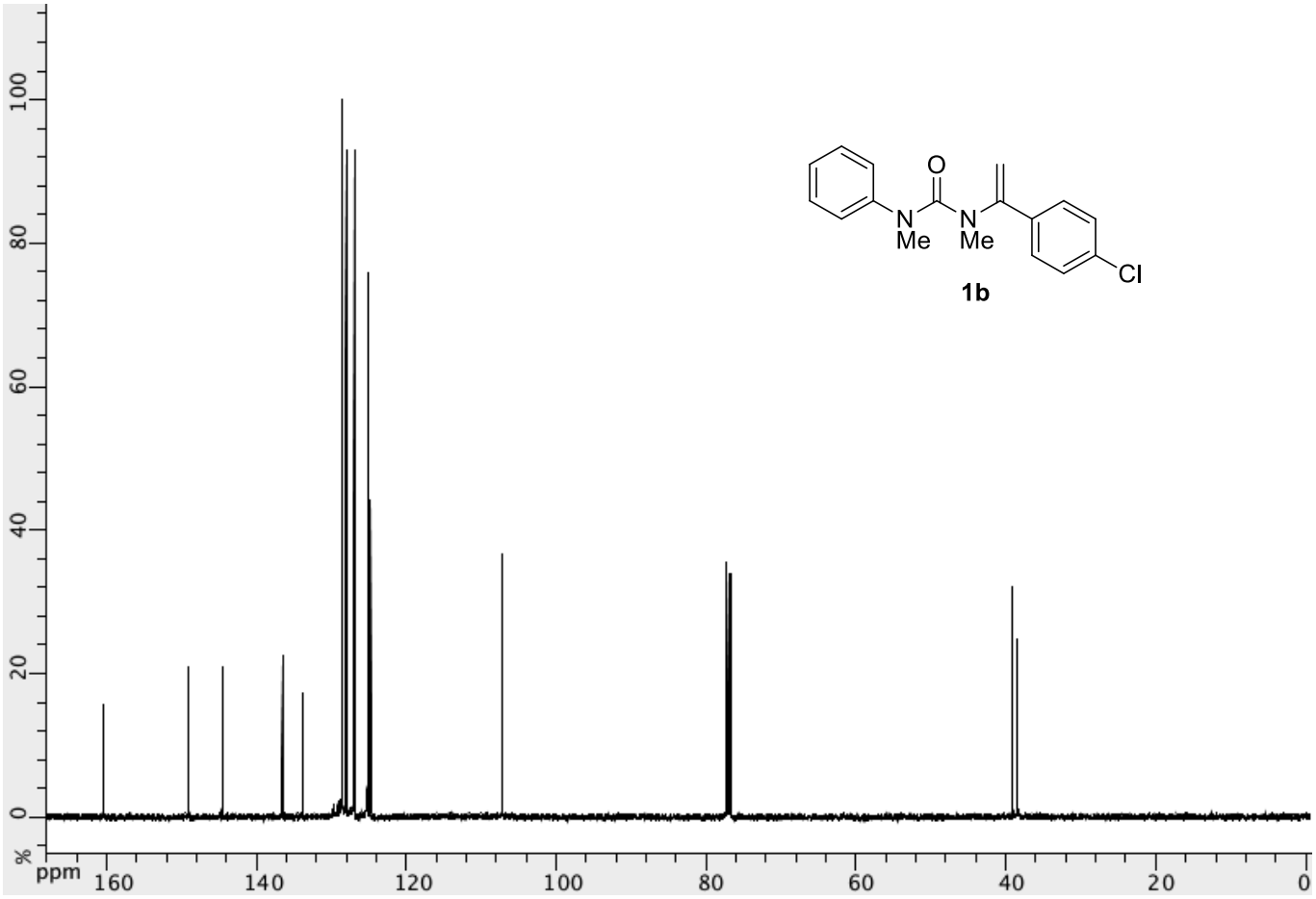
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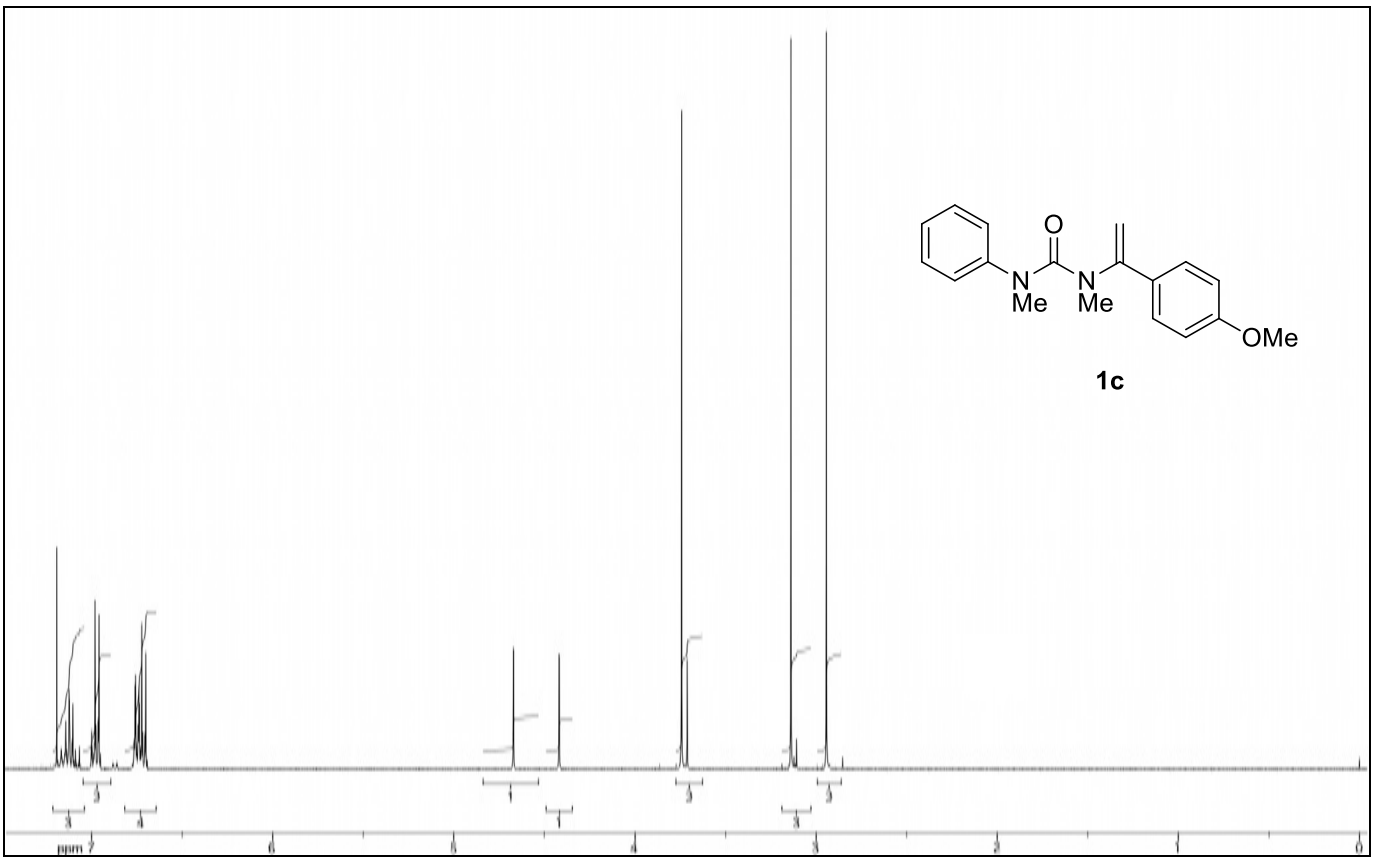
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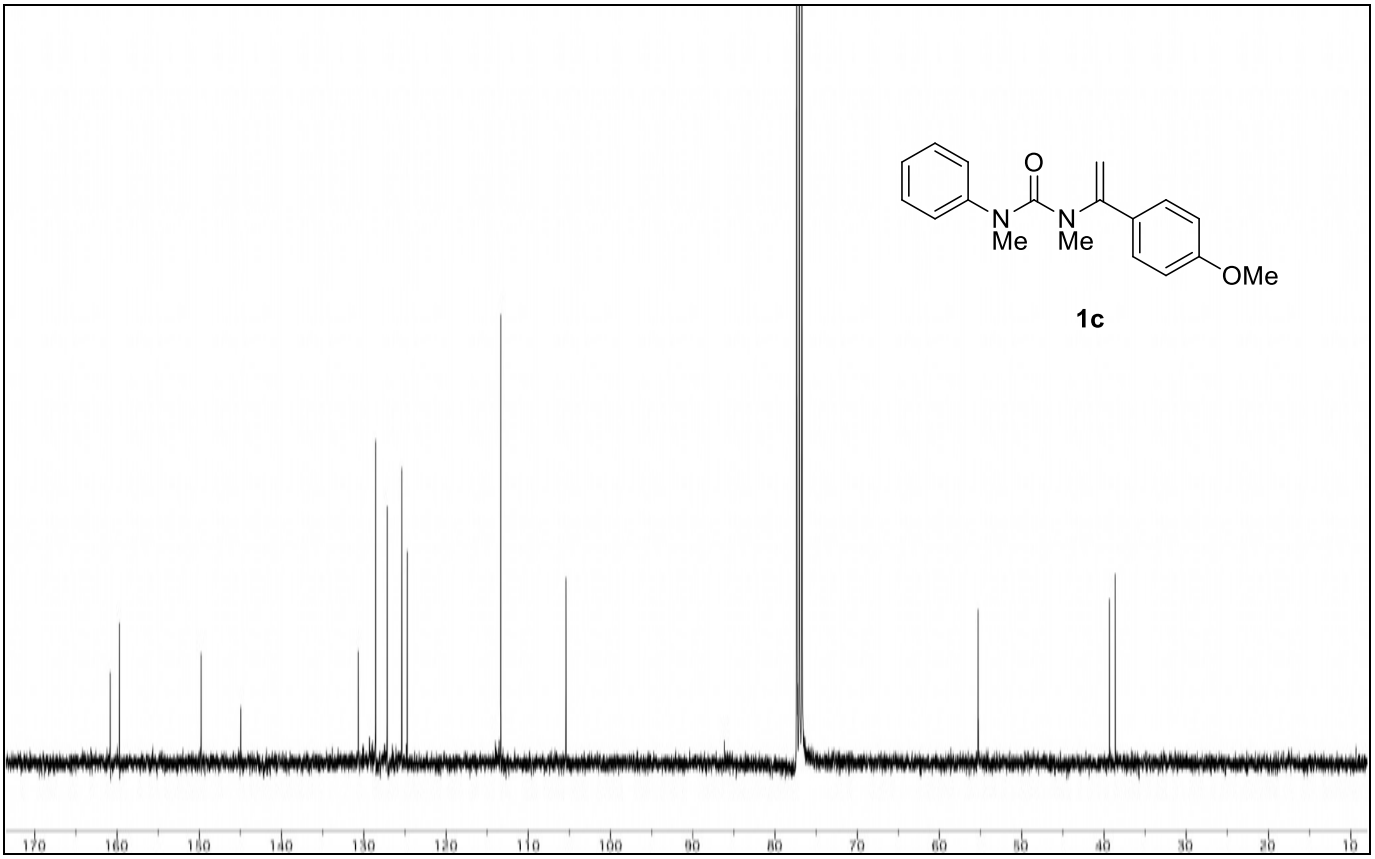
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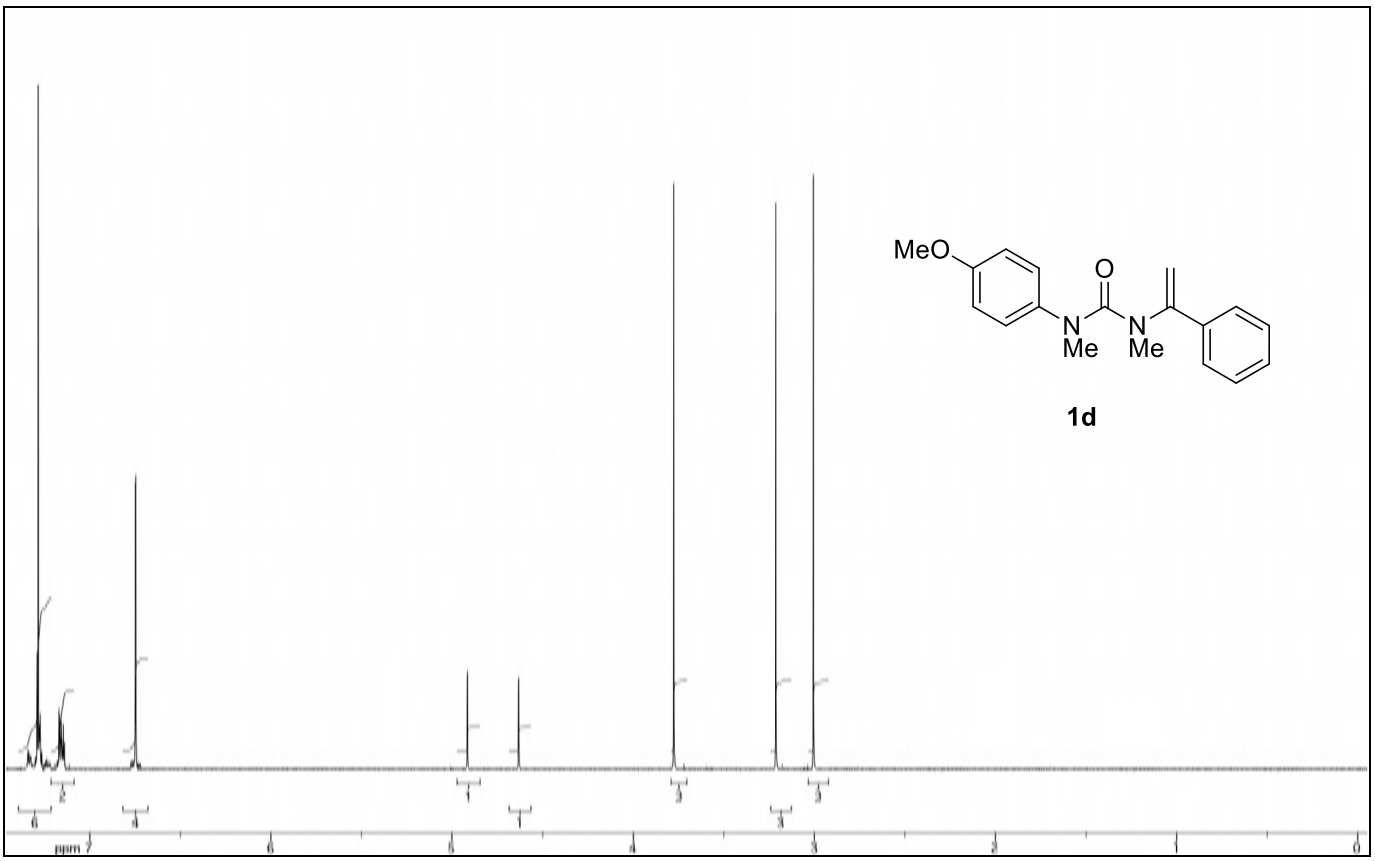
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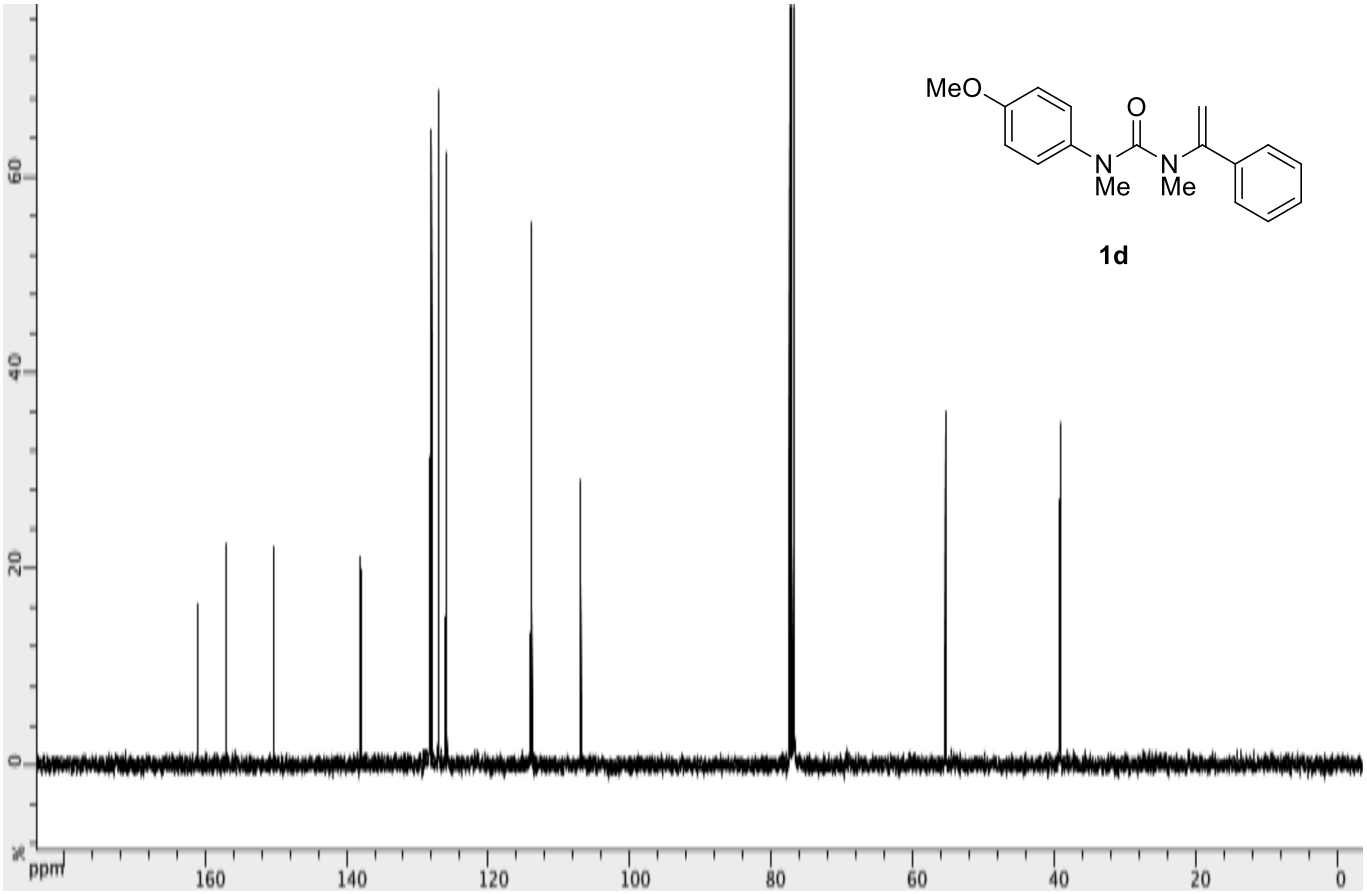
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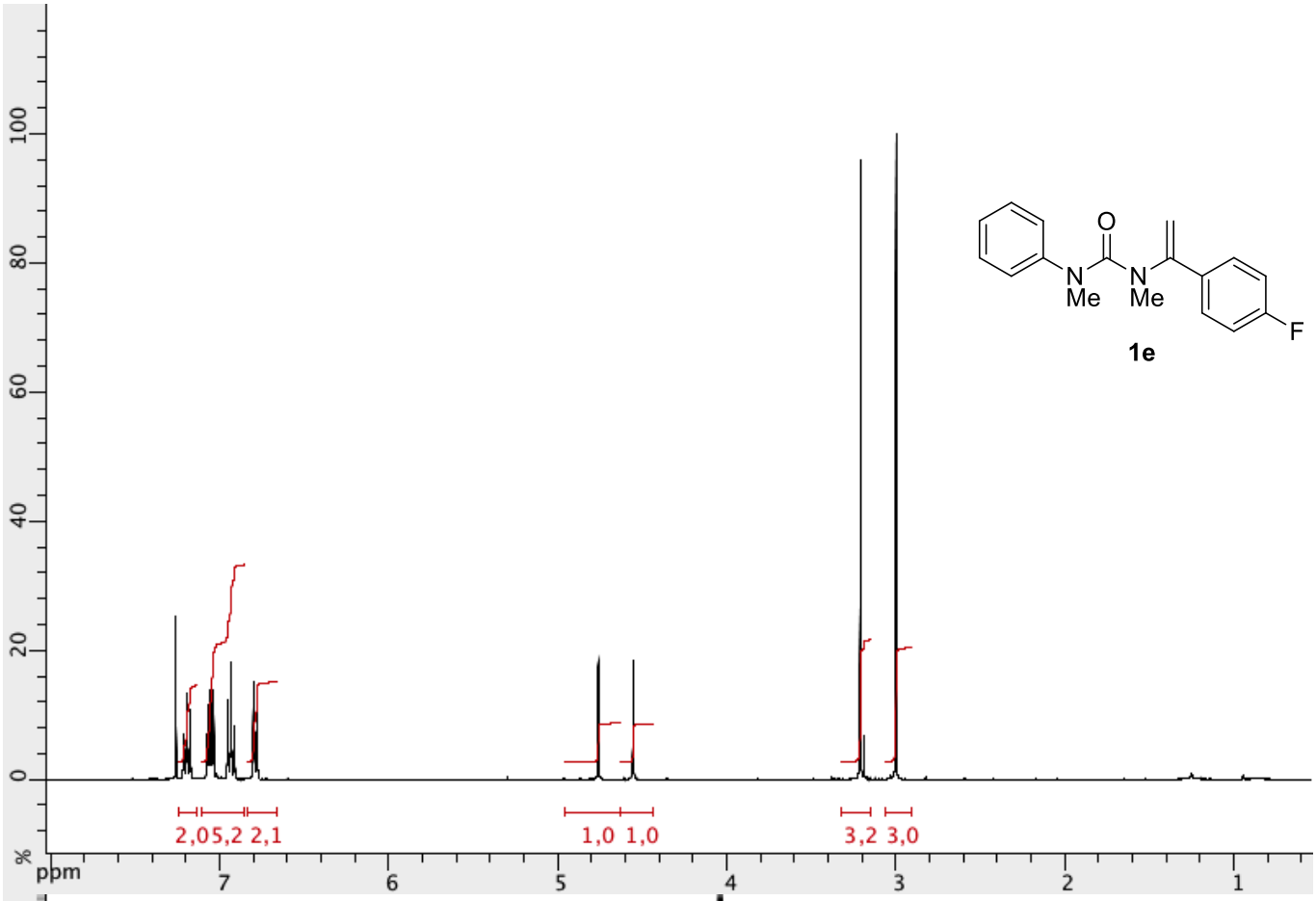
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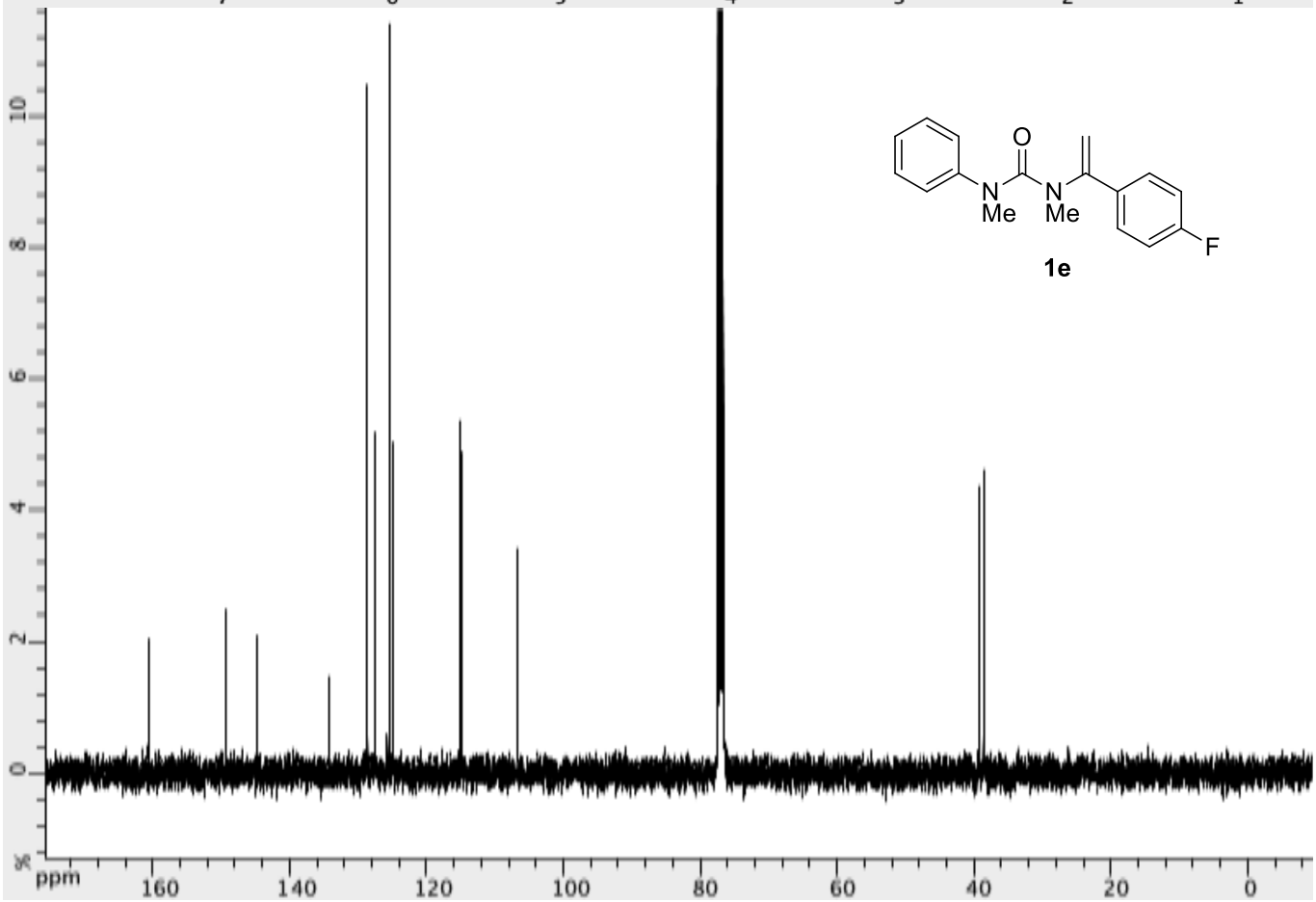
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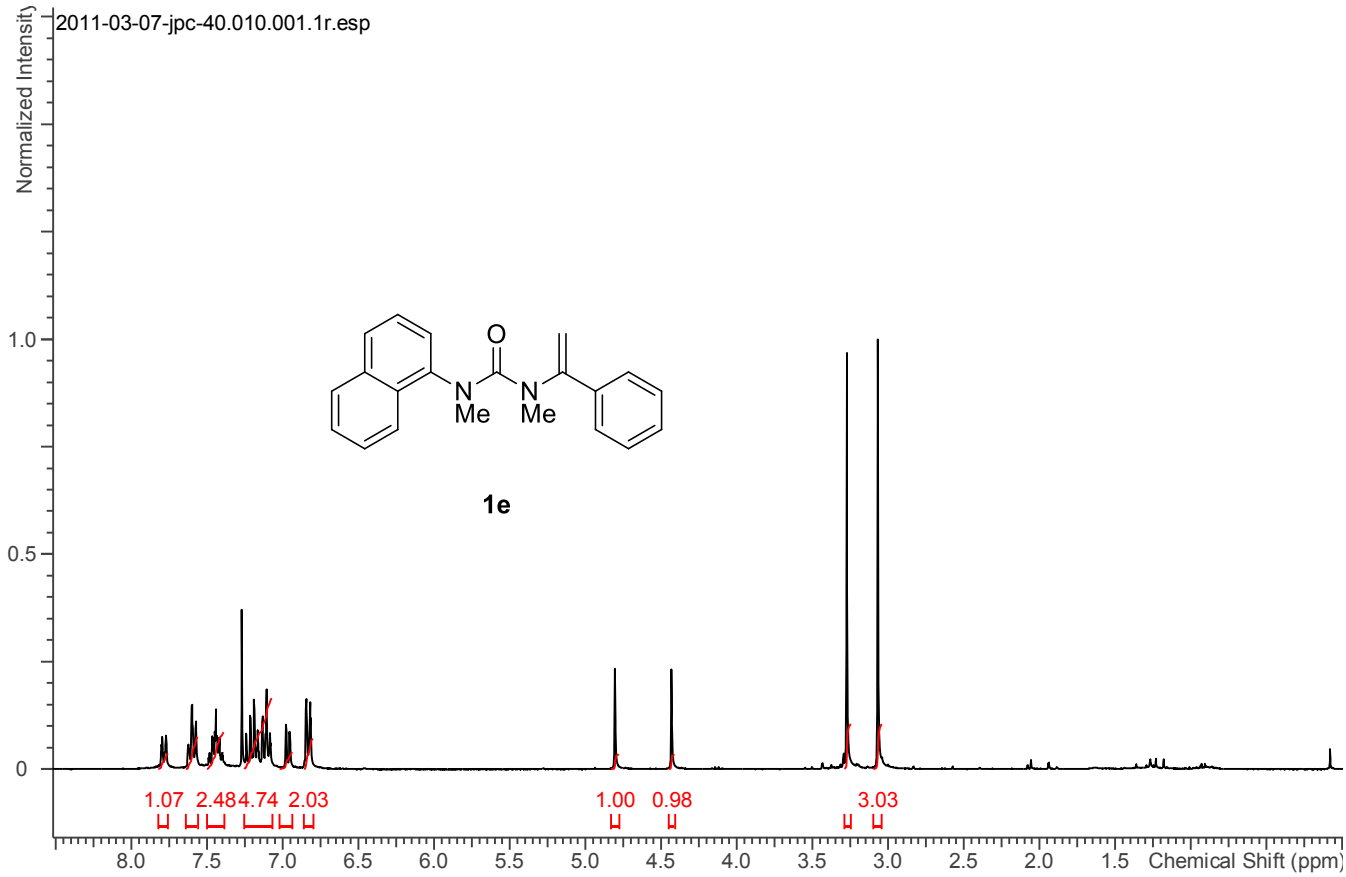
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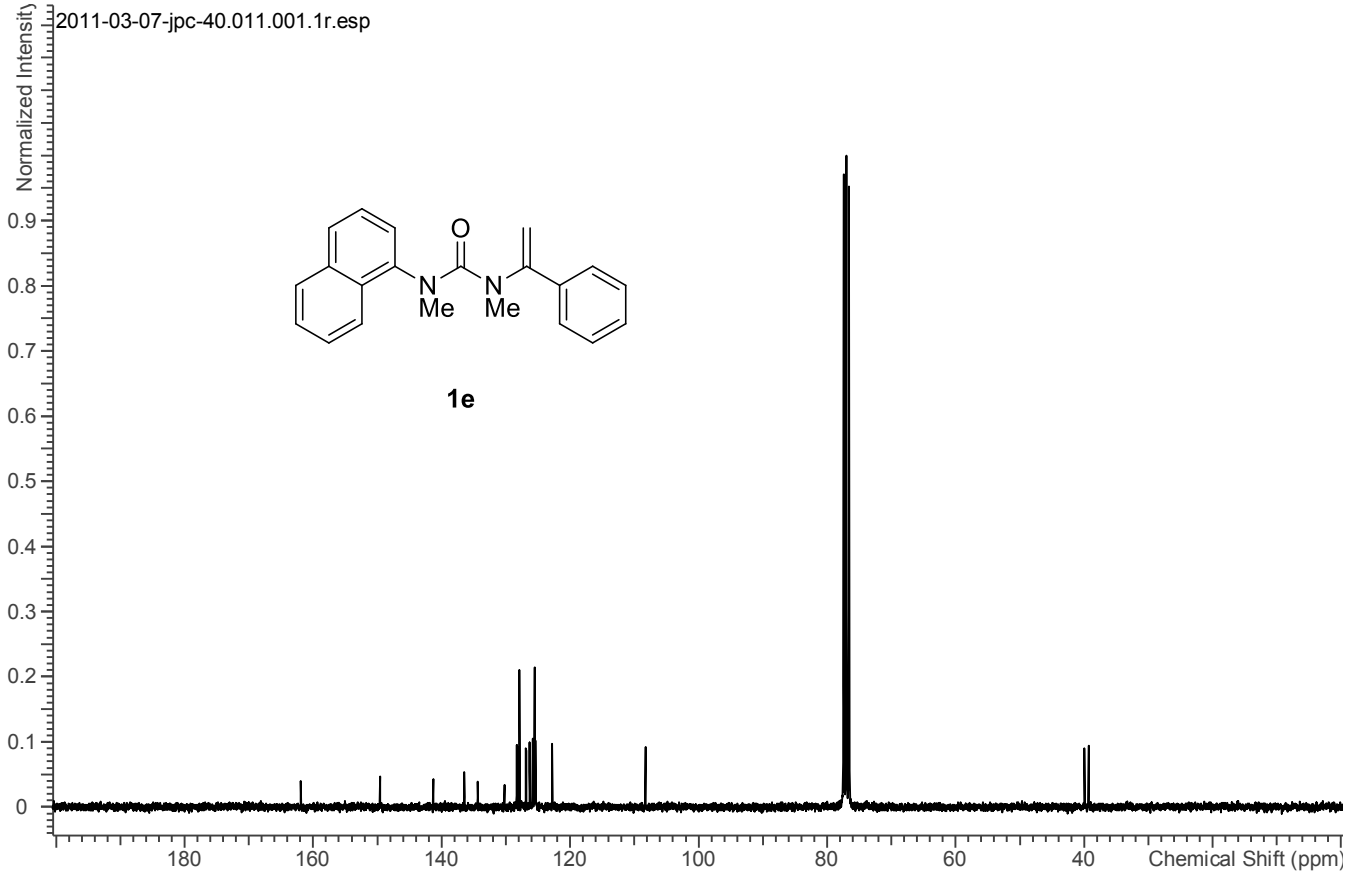
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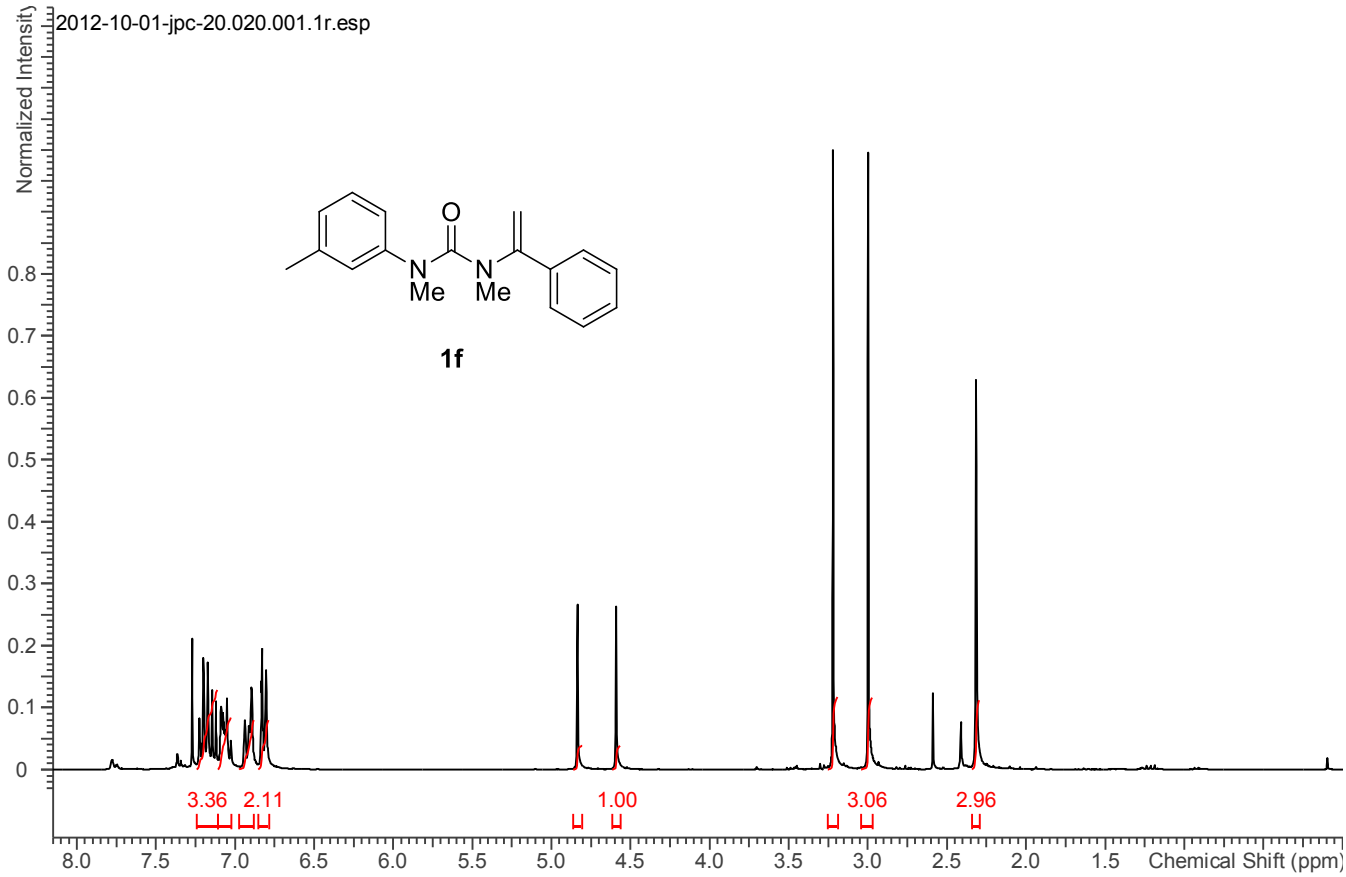
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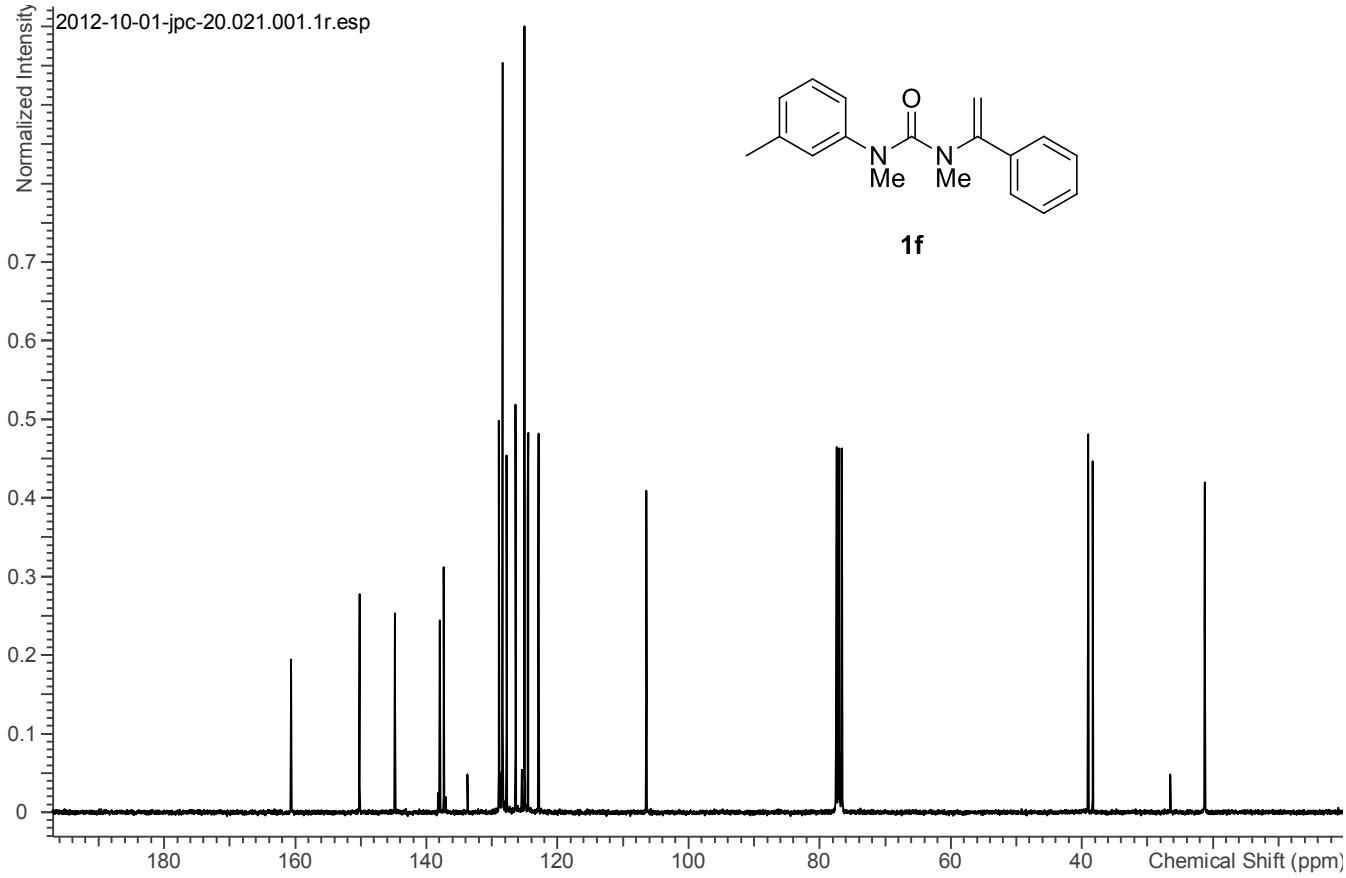
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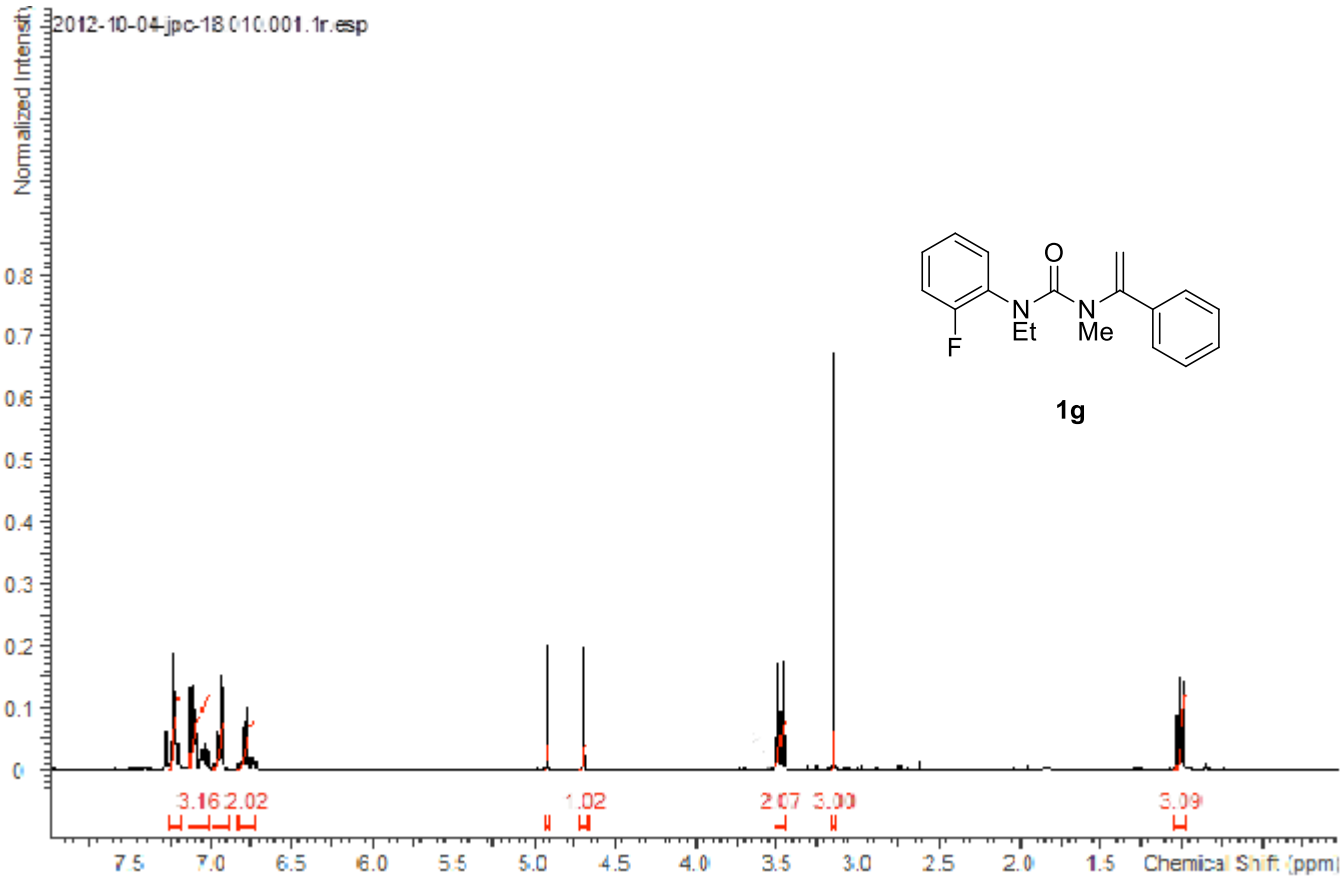
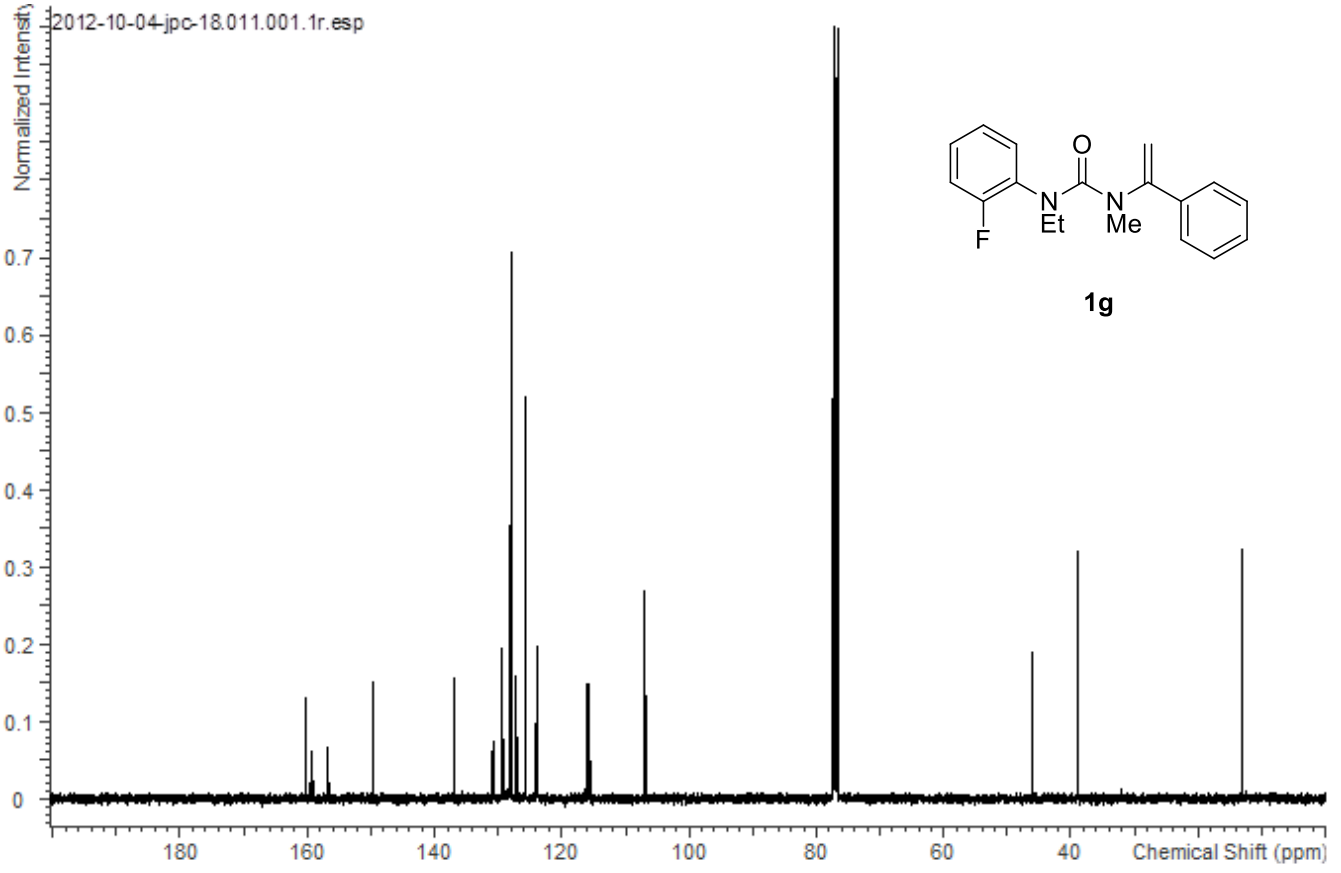
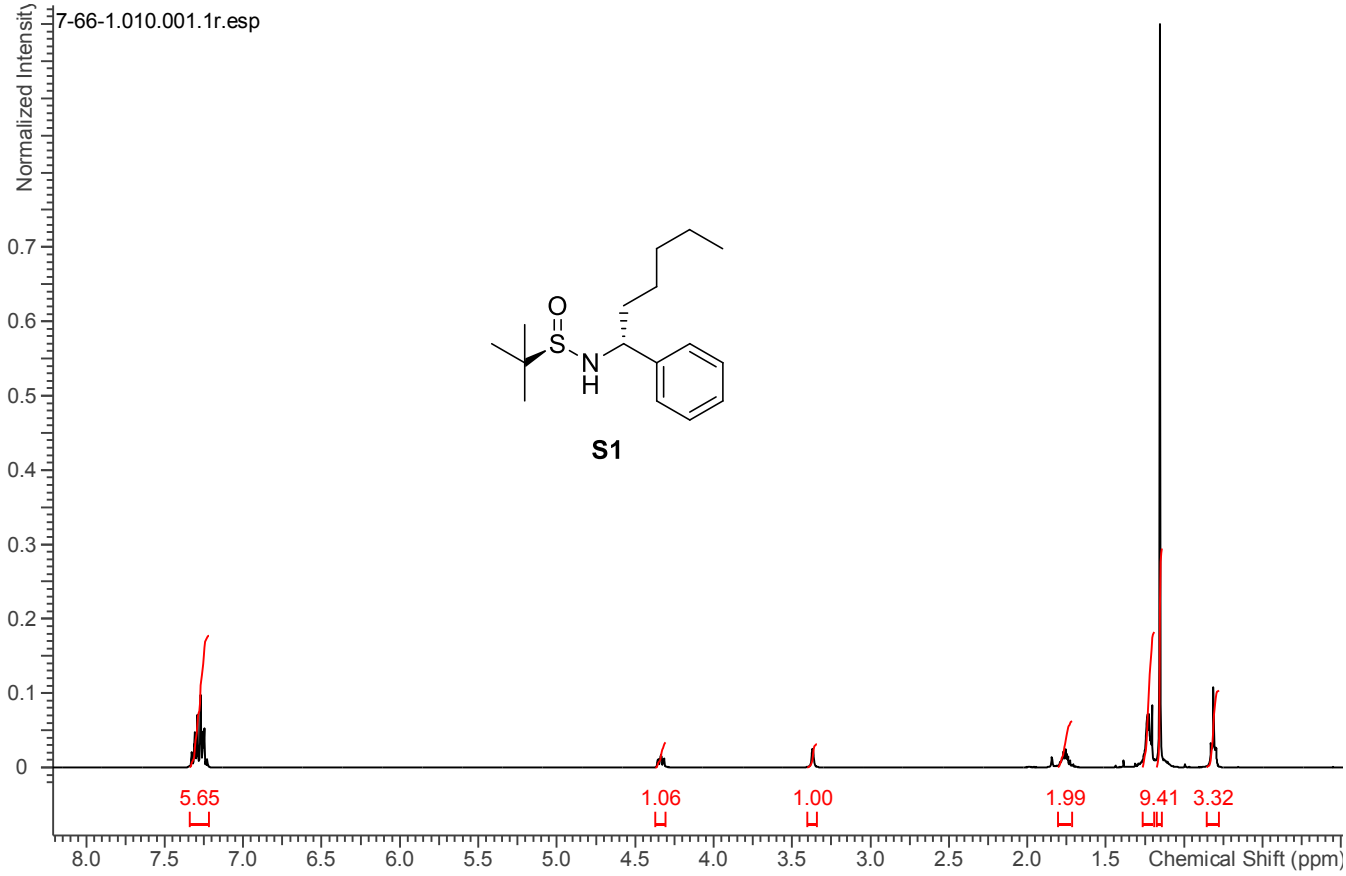
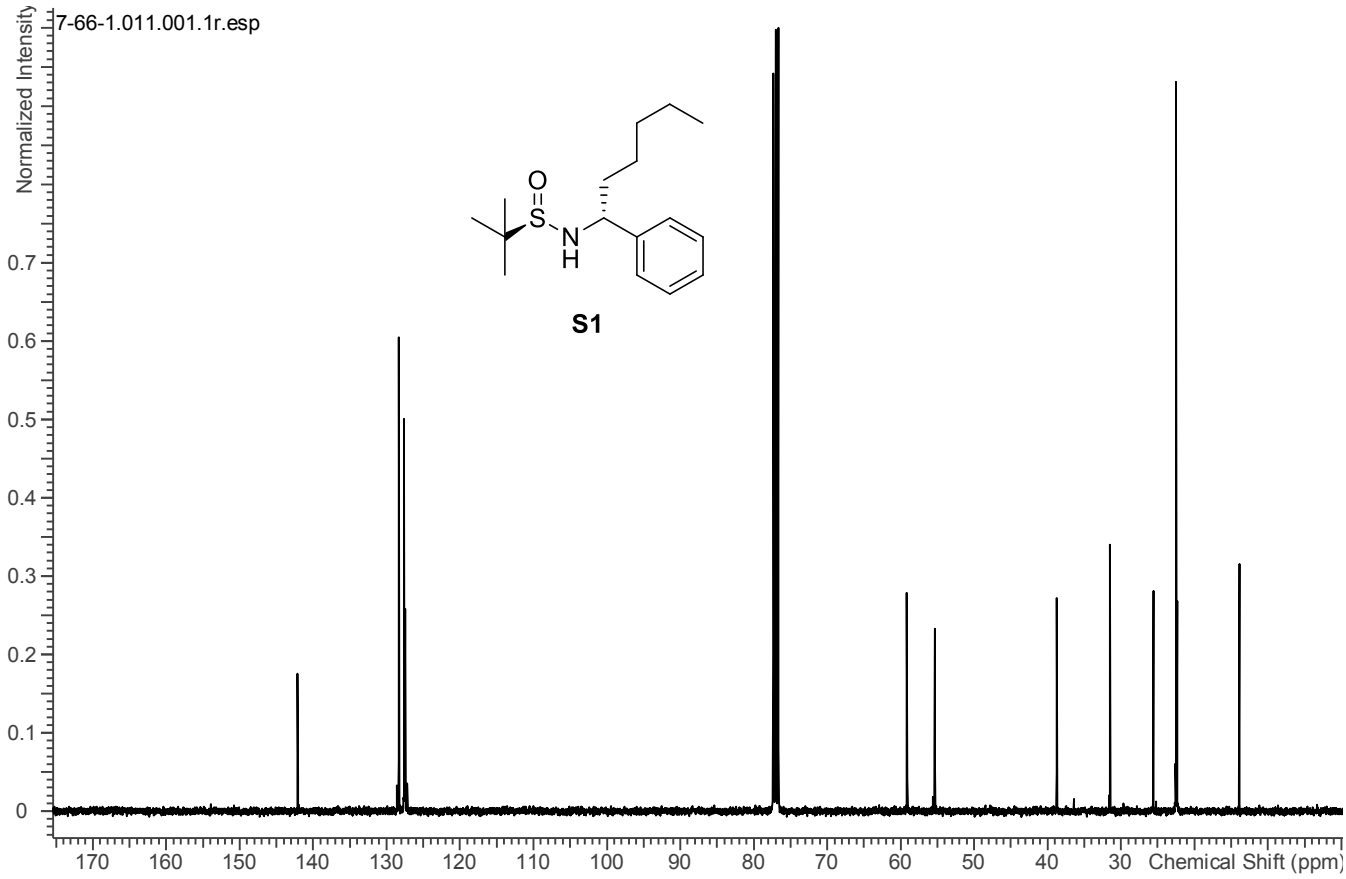
80
60
40
Chemical Shift (ppm)

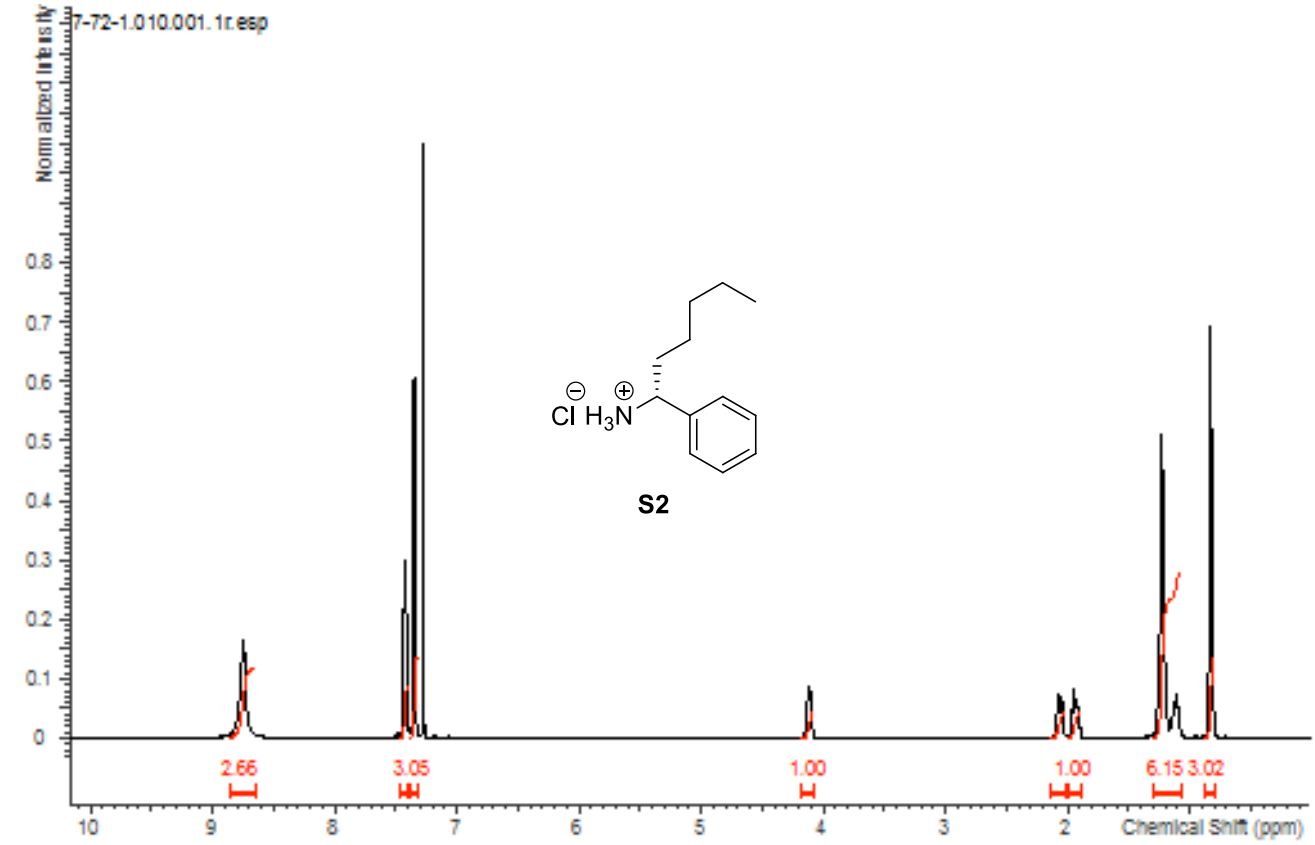

2012-10-04-jpc-18.010.001.1r.esp
Normalized Intensity
3.16
2.02
1.02
2.07
3.00
3.09
Chemical Shift (ppm)
O
N
Et
N
Me
F
1g


2012-10-04-jpc-18.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
O
N
Et
N
Me
F
1g

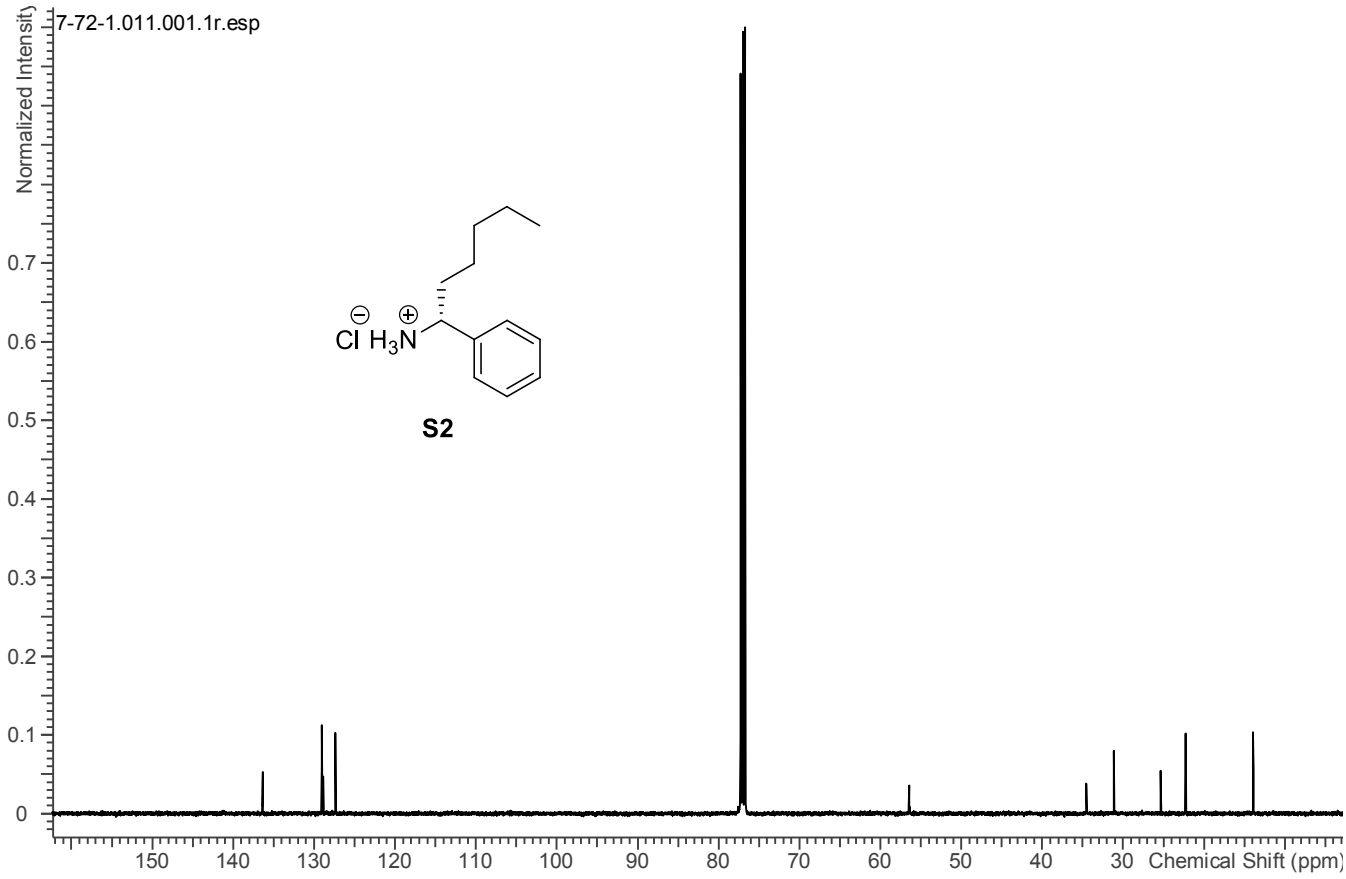

7-66-1.010.001.1r.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
O
S
N
H
S1
5.65
1.06
1.00
1.99
9.41
3.32
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


7-66-1.011.001.1r.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
O
S
N
H
S1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

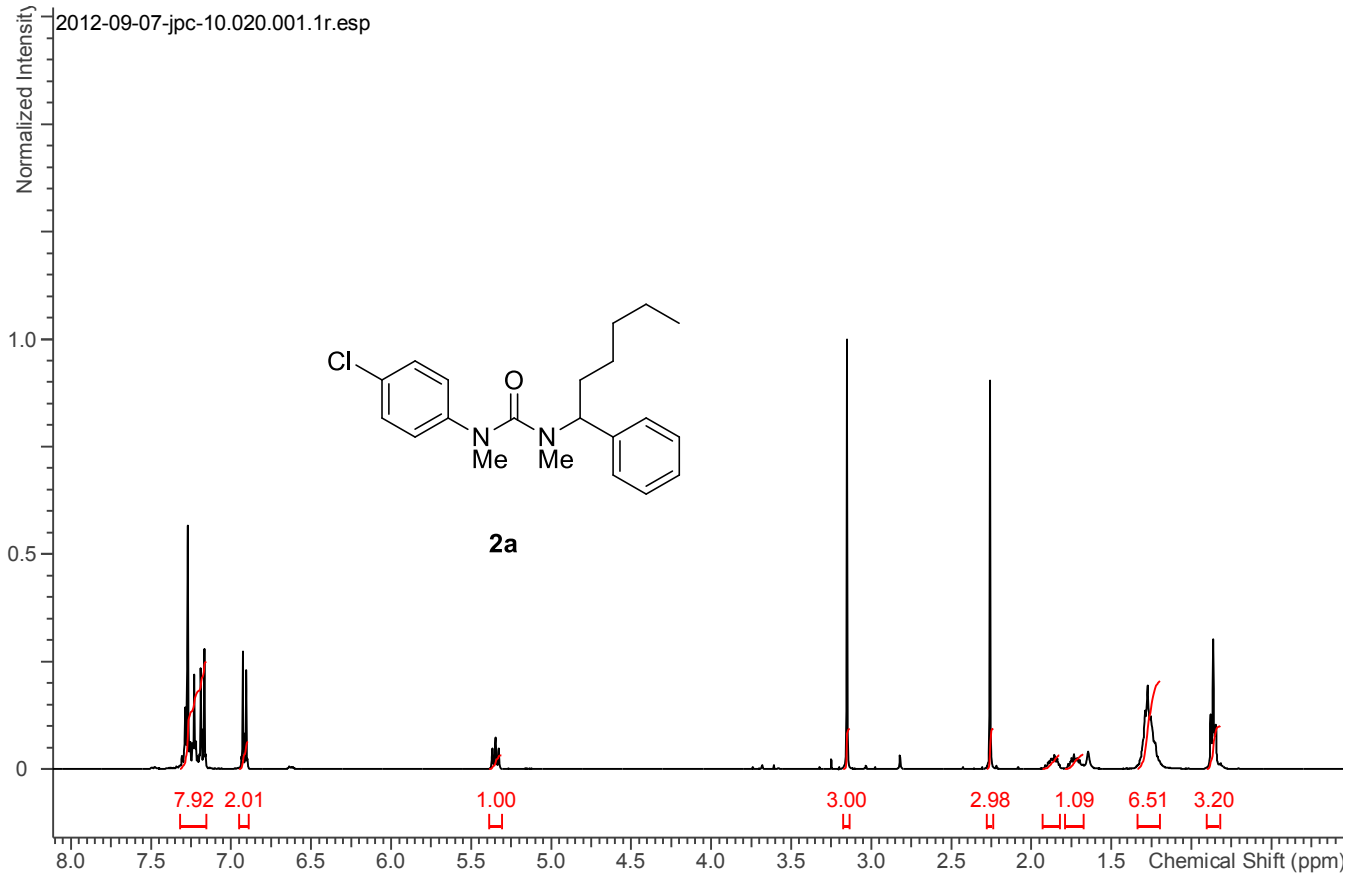
27

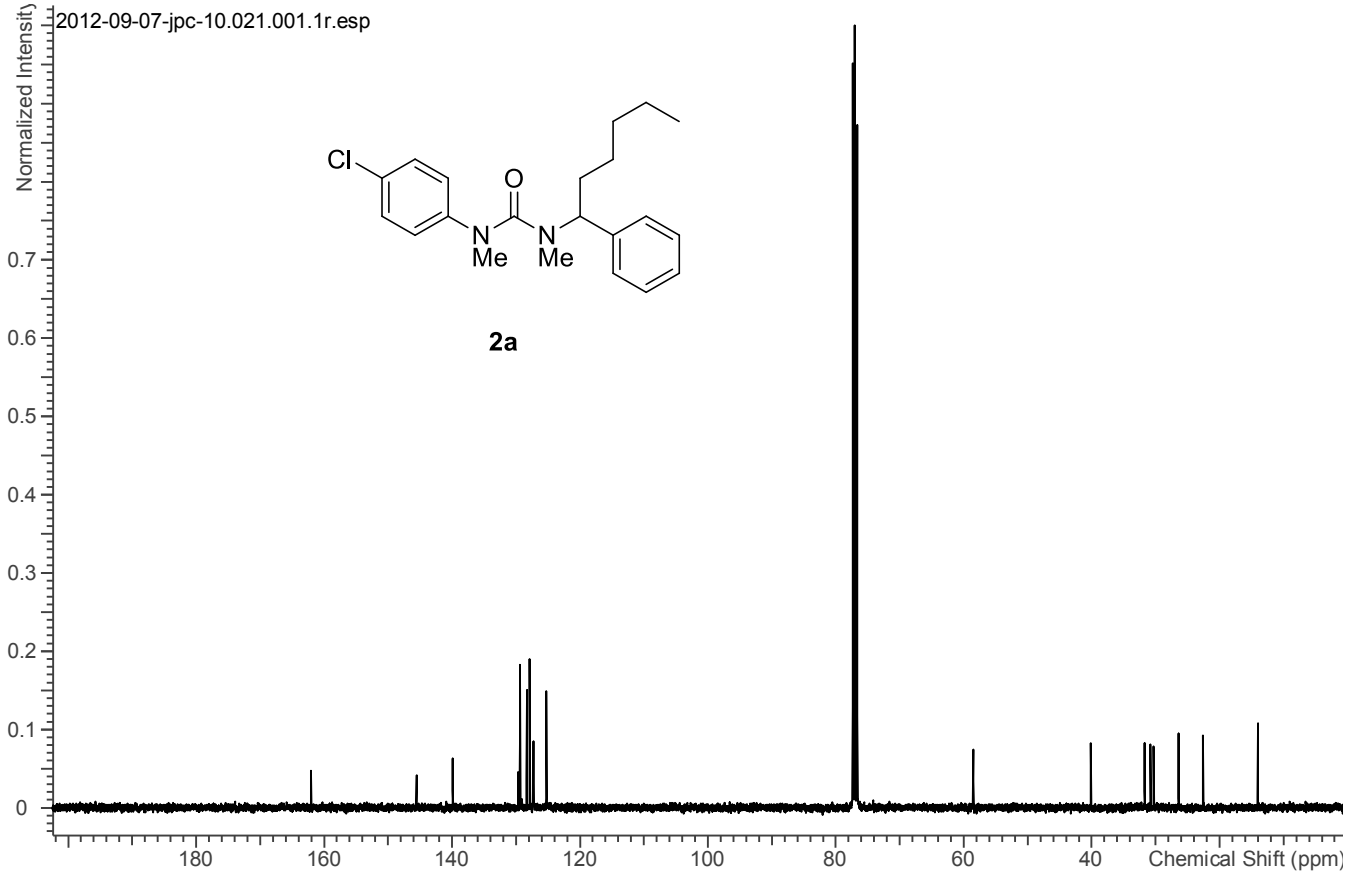

7-72-1.010.001.1r.esp
Normalized Intensity
2.66
3.05
1.00
1.00
6.15
3.02
Chemical Shift (ppm)

S2

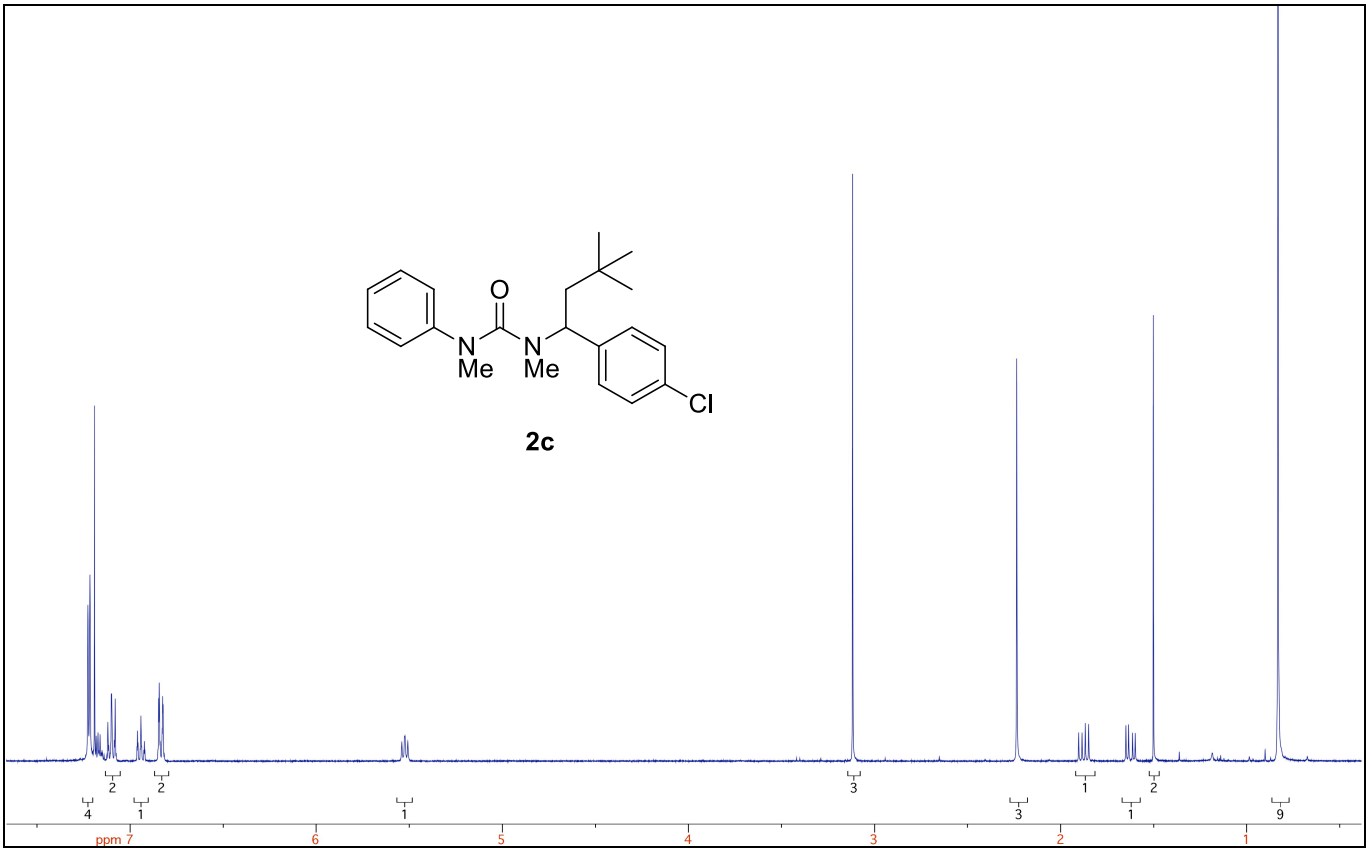

7-72-1.011.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)

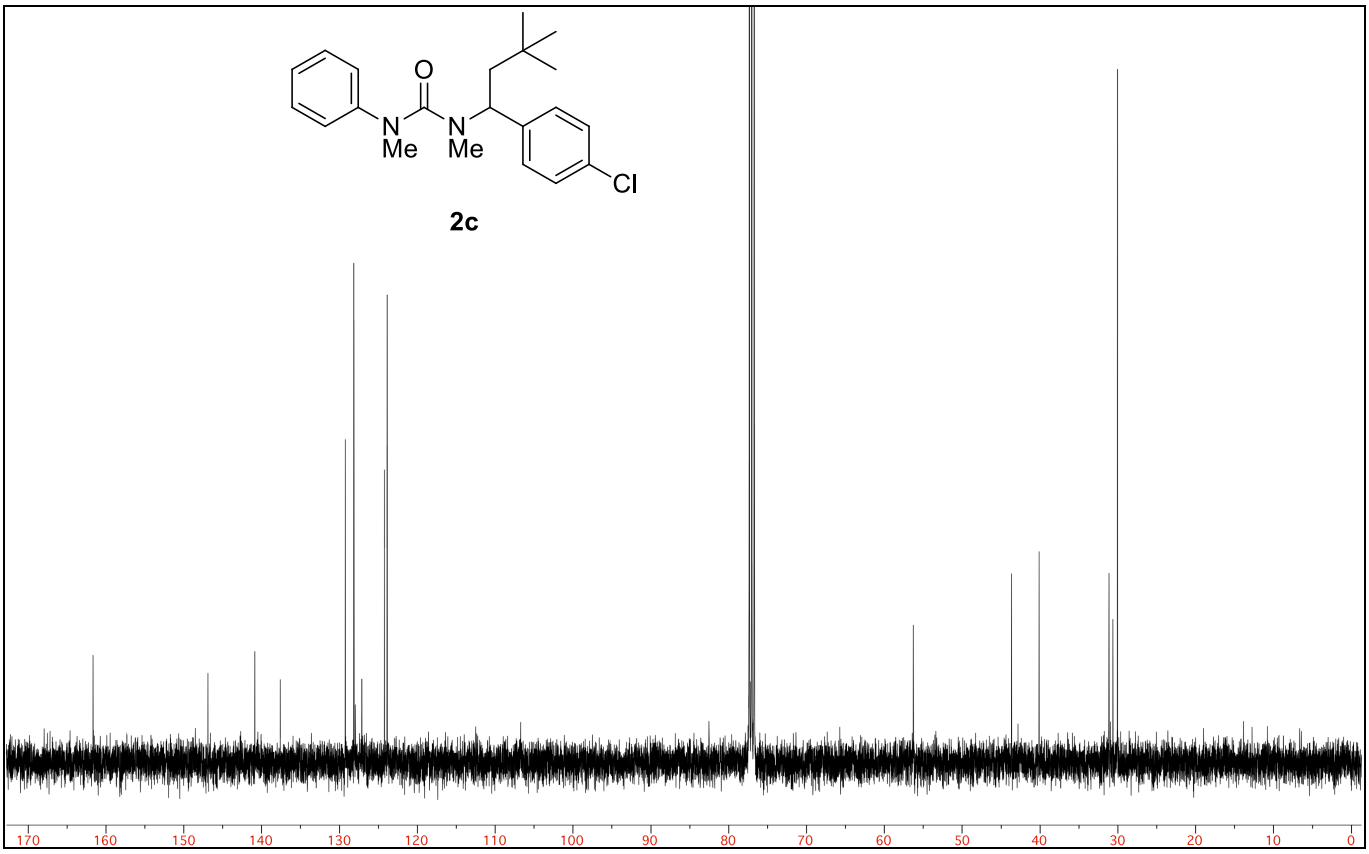
S2

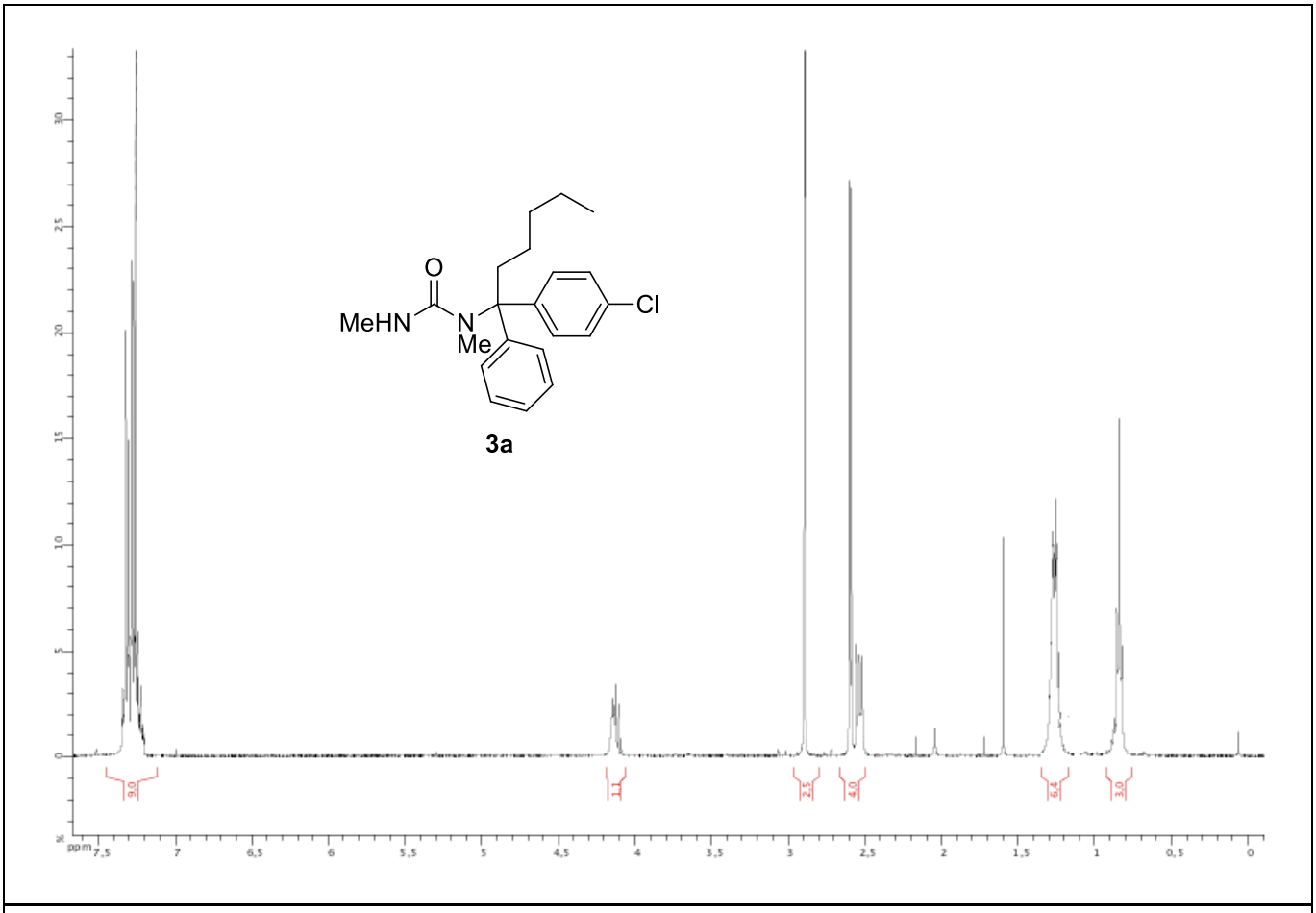

2012-09-07-jpc-10.020.001.1r.esp
Normalized Intensity
1.0
0.5
0
Cl
O
N
Me
N
Me
2a
7.92
2.01
1.00
3.00
2.98
1.09
6.51
3.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

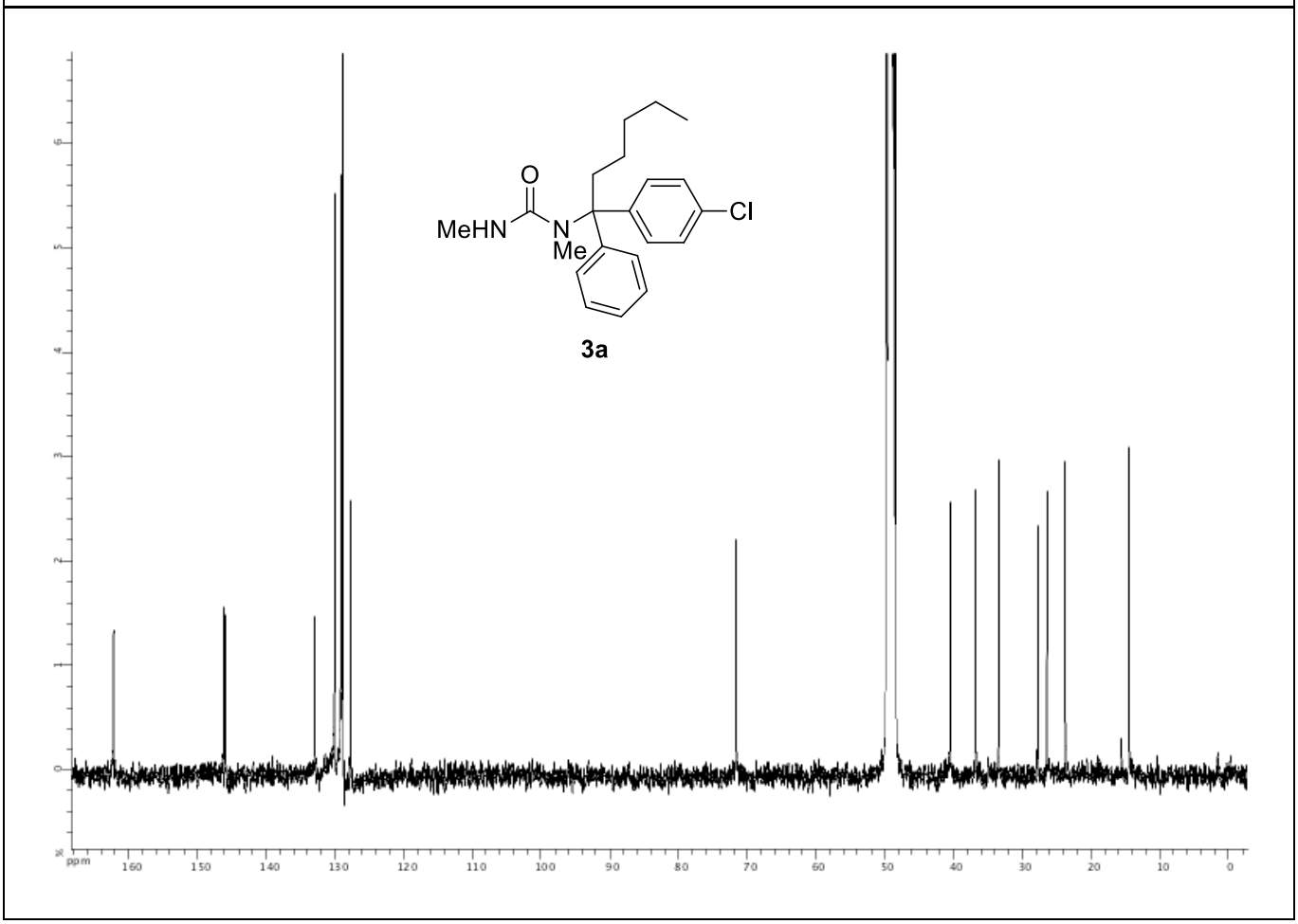

2012-09-07-jpc-10.021.001.1r.esp
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Cl
O
N
Me
N
Me
2a
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

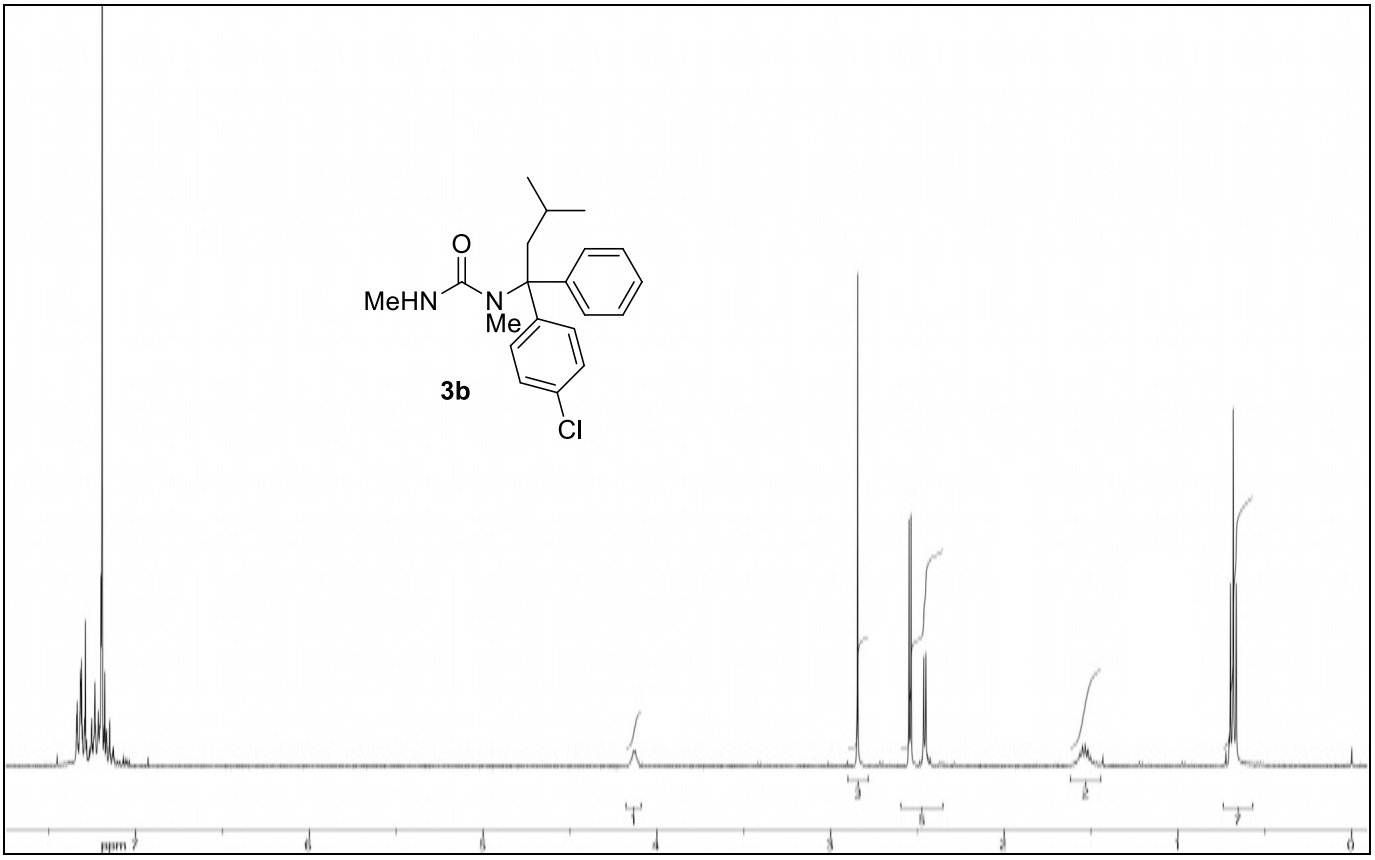
29

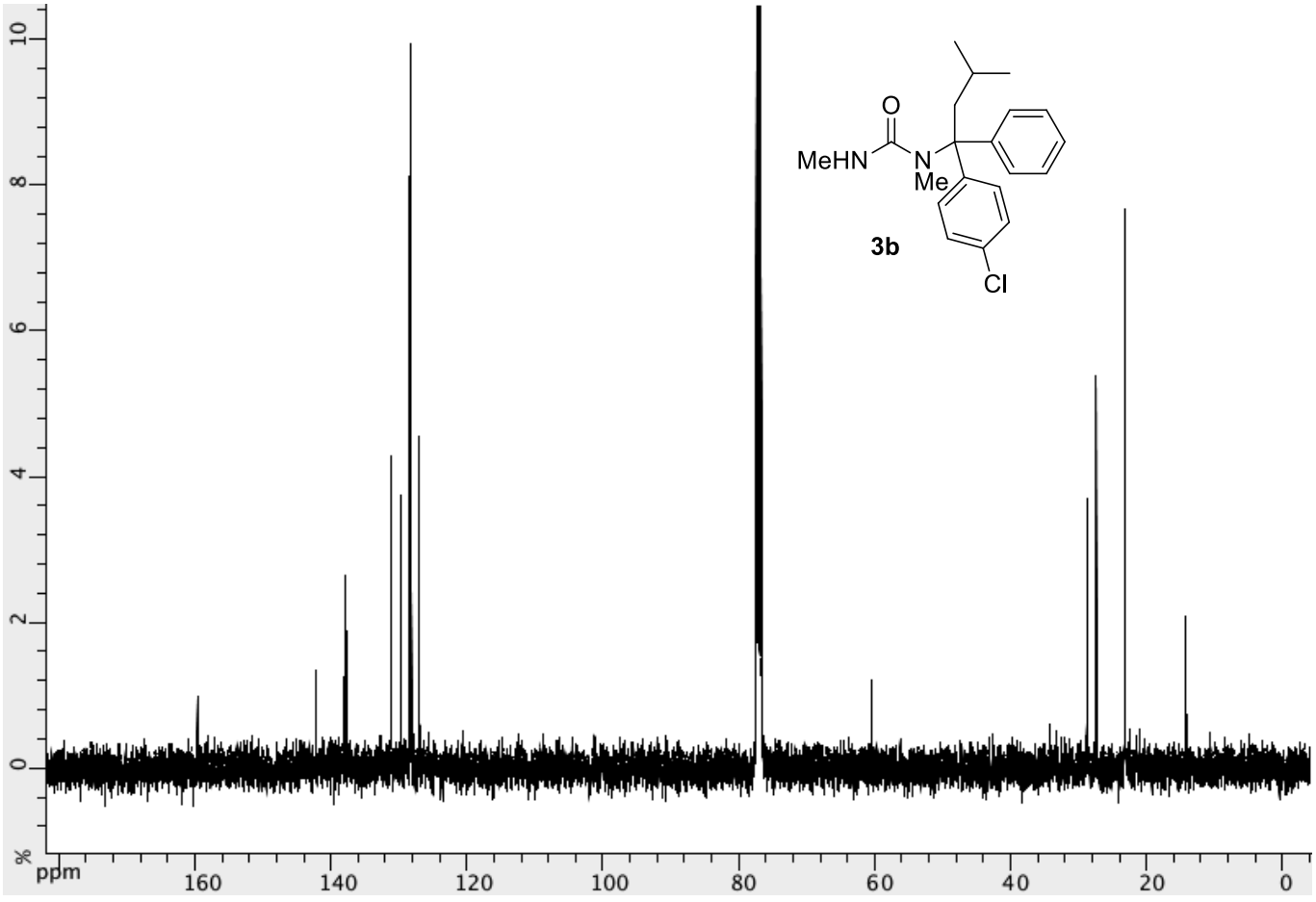

O
N
Me
N
Me
Cl
2c
4
2
1
2
1
3
3
1
1
2
9
ppm 7
6
5
4
3
2
1

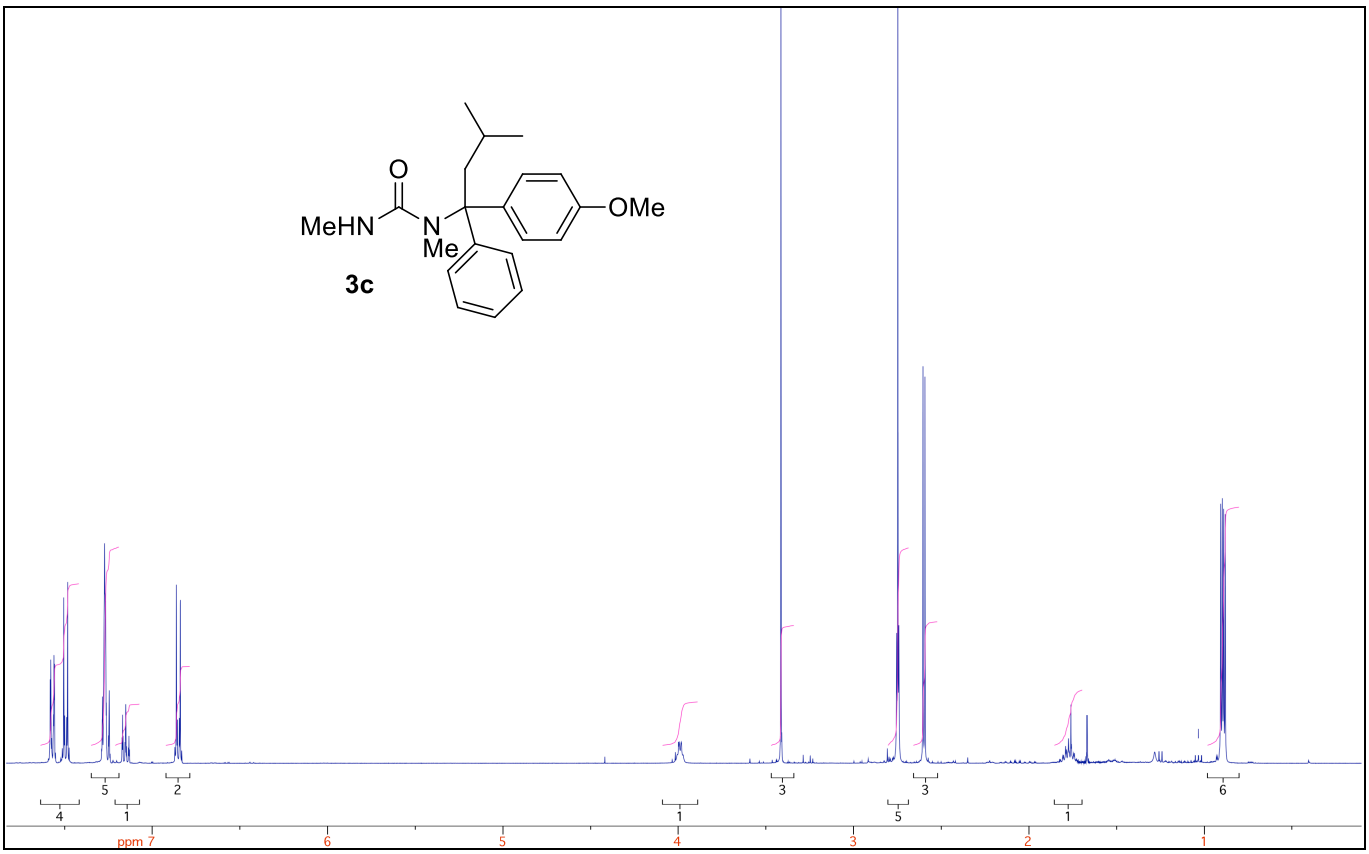

O
N
Me
N
Me
Cl
2c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

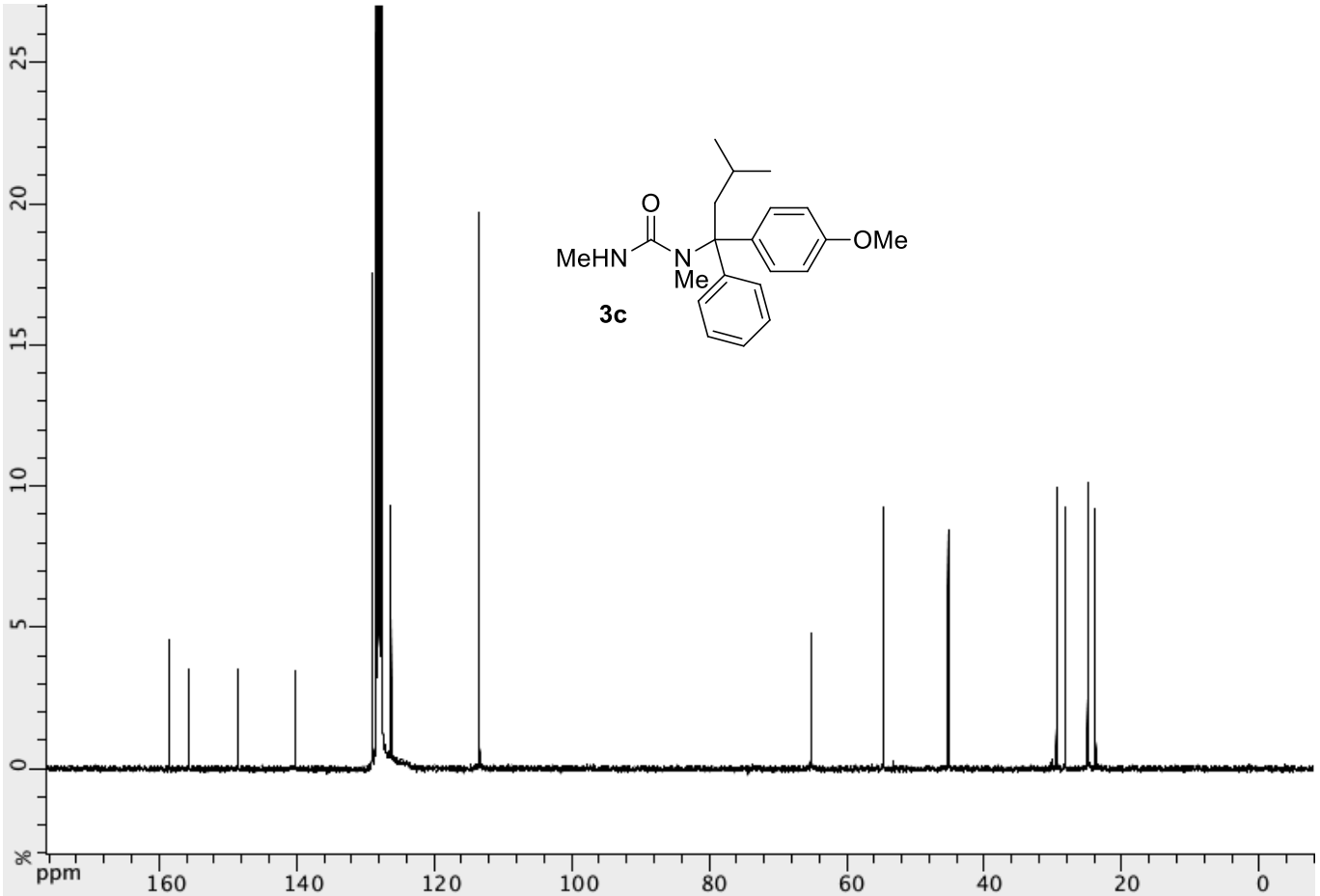

MeHN
O
N
Me
Cl
3a
9.0
1.1
2.5
4.0
6.4
3.0
ppm

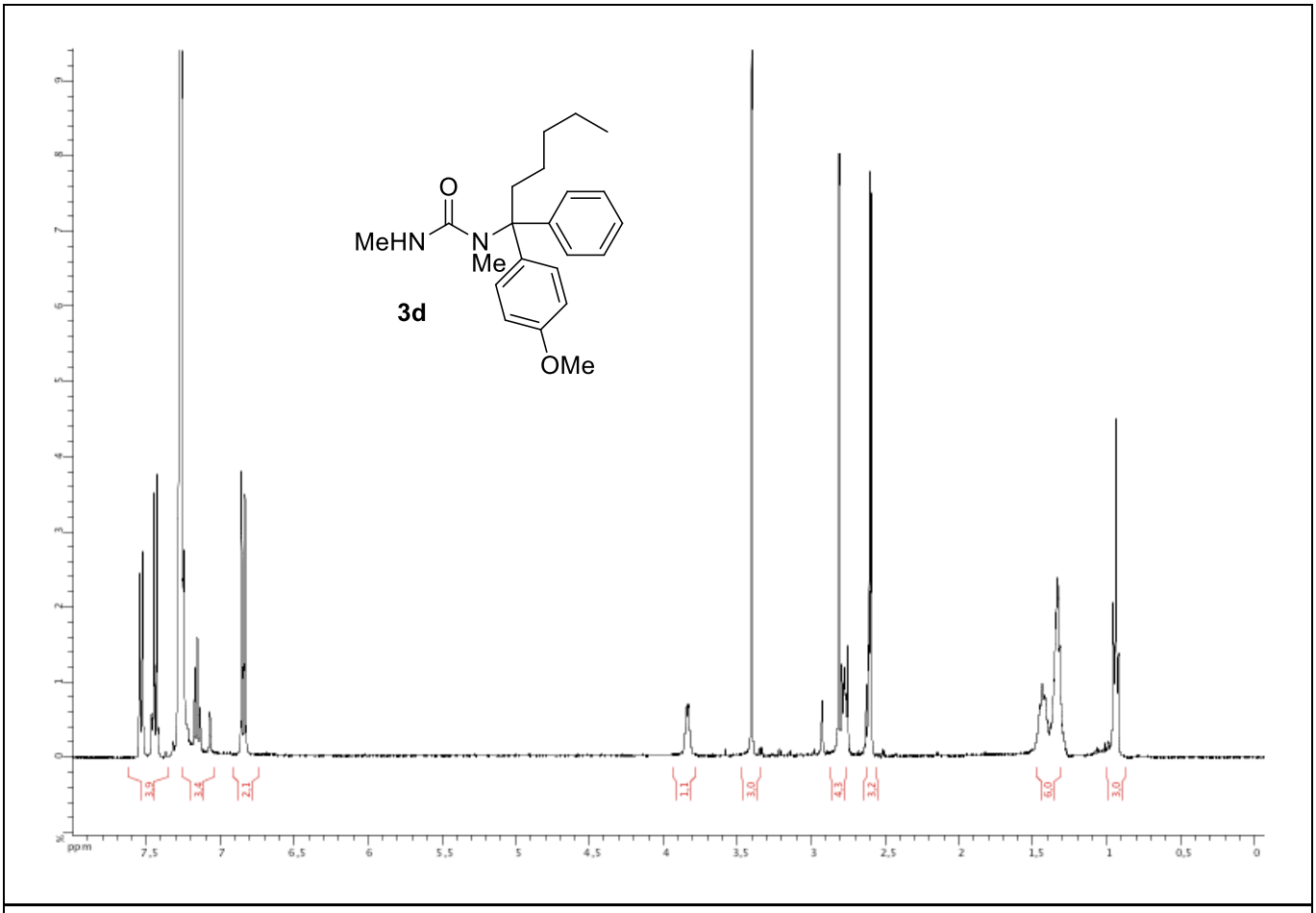

MeHN
O
N
Me
Cl
3a
ppm

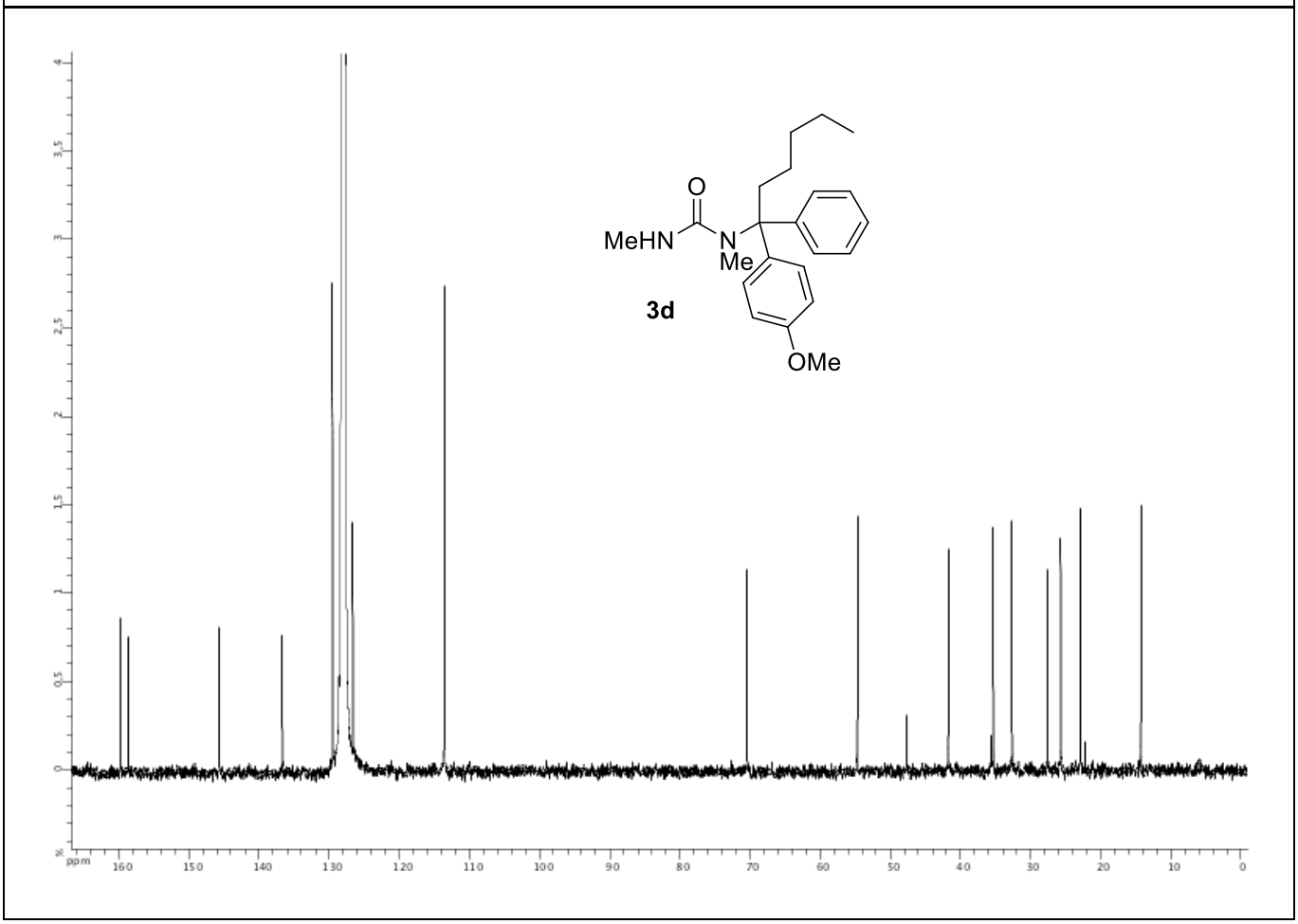

O
MeHN
N
Me
3b
Cl

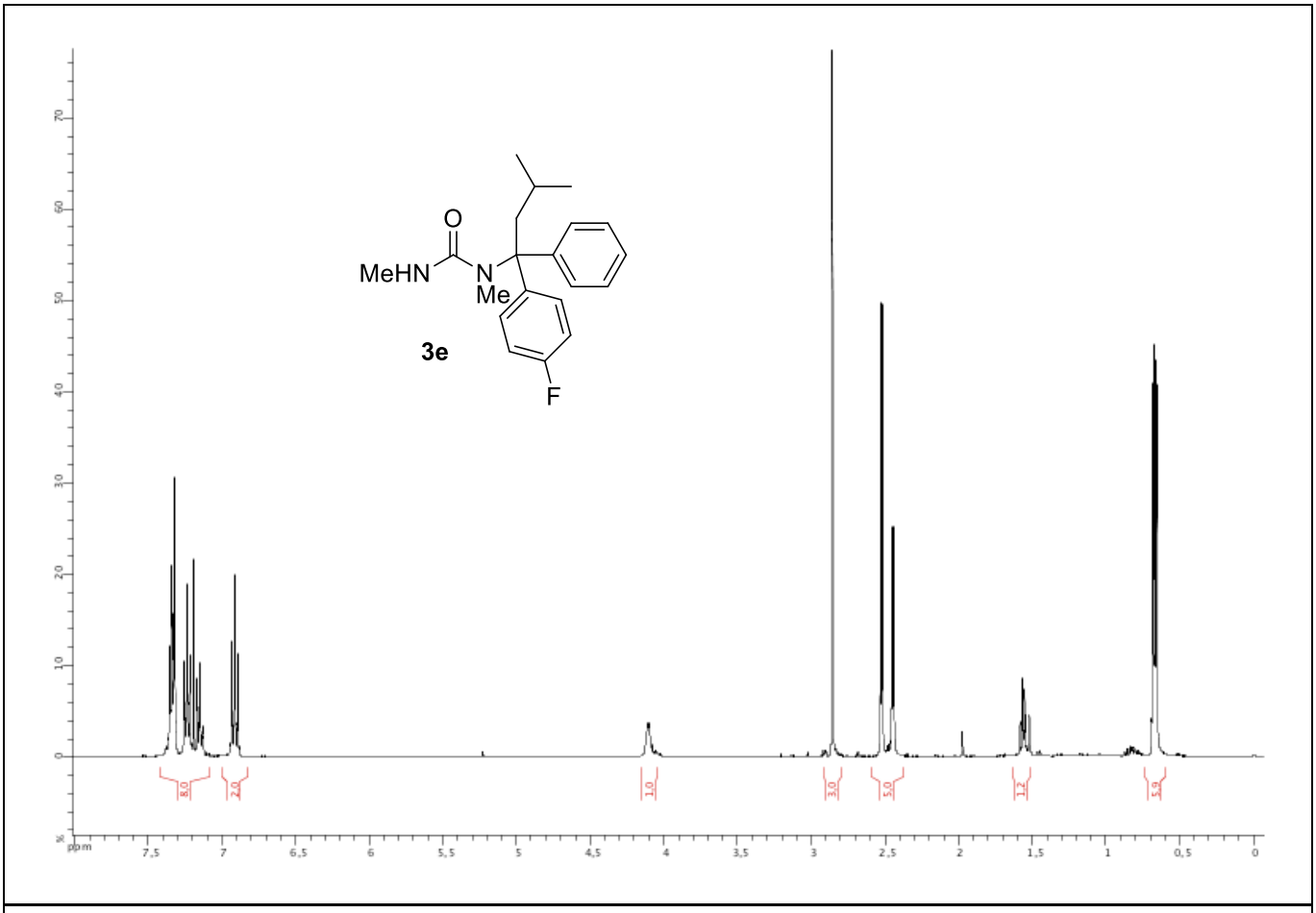

O
MeHN
N
Me
3b
Cl
10
8
6
4
2
0
%
ppm
160
140
120
100
80
60
40
20
0

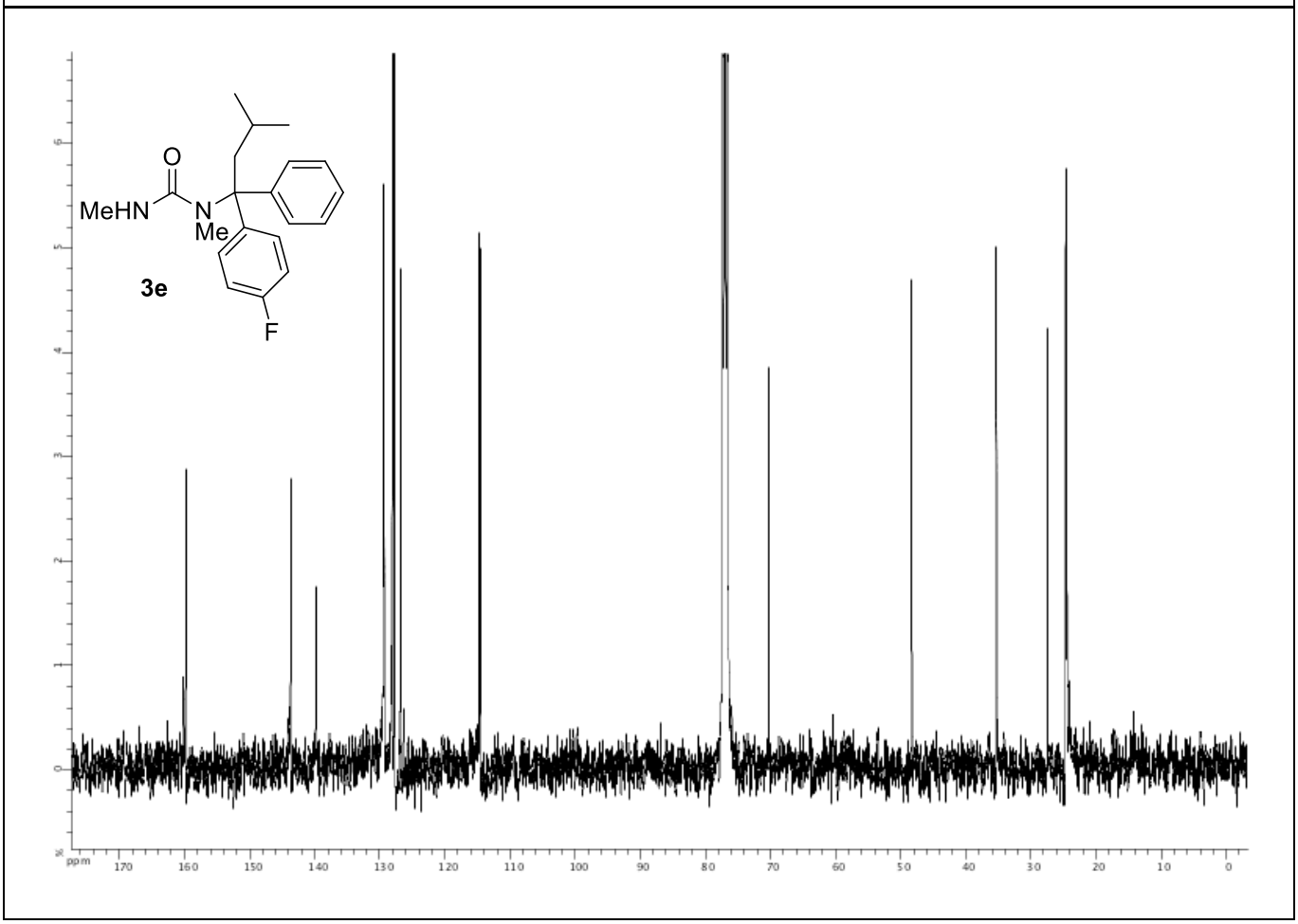

O
MeHN
N
Me
OMe
3c
4
5
1
2
1
3
5
3
1
6
ppm 7
6
5
4
3
2
1

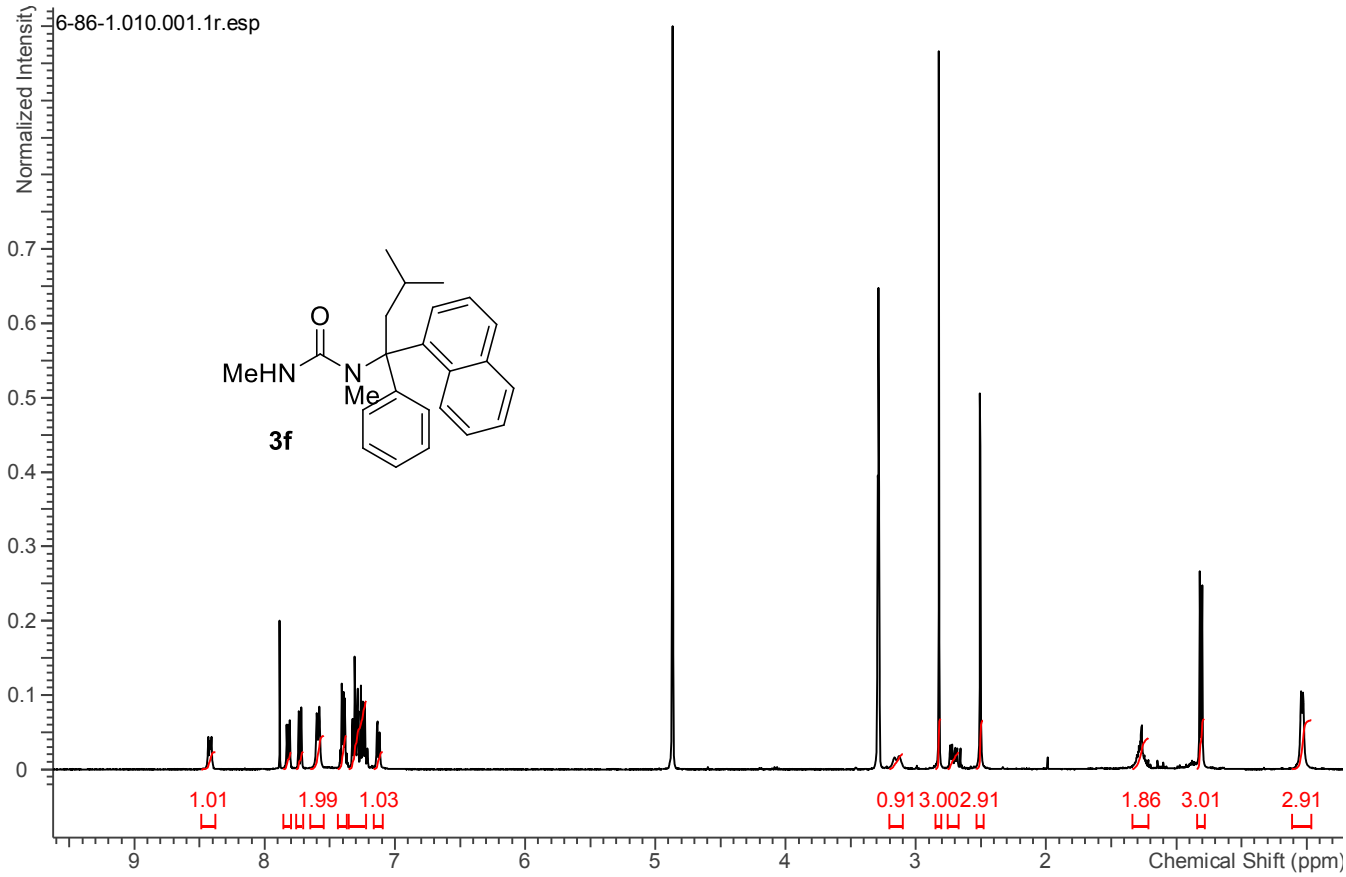

O
MeHN
N
Me
OMe
3c
25
20
15
10
5
0
%
ppm
160
140
120
100
80
60
40
20
0

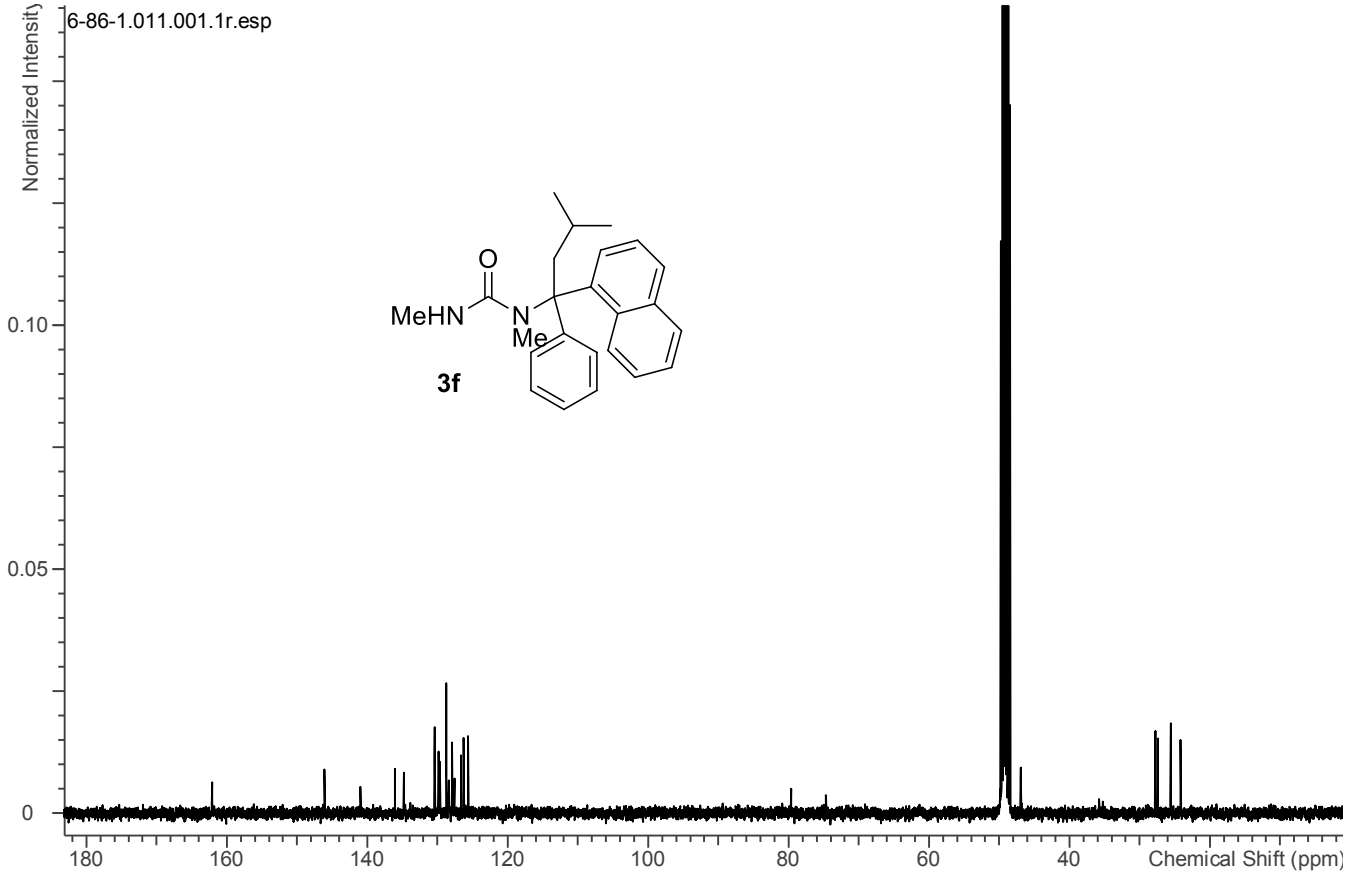

MeHN
O
N
Me
OMe
3d

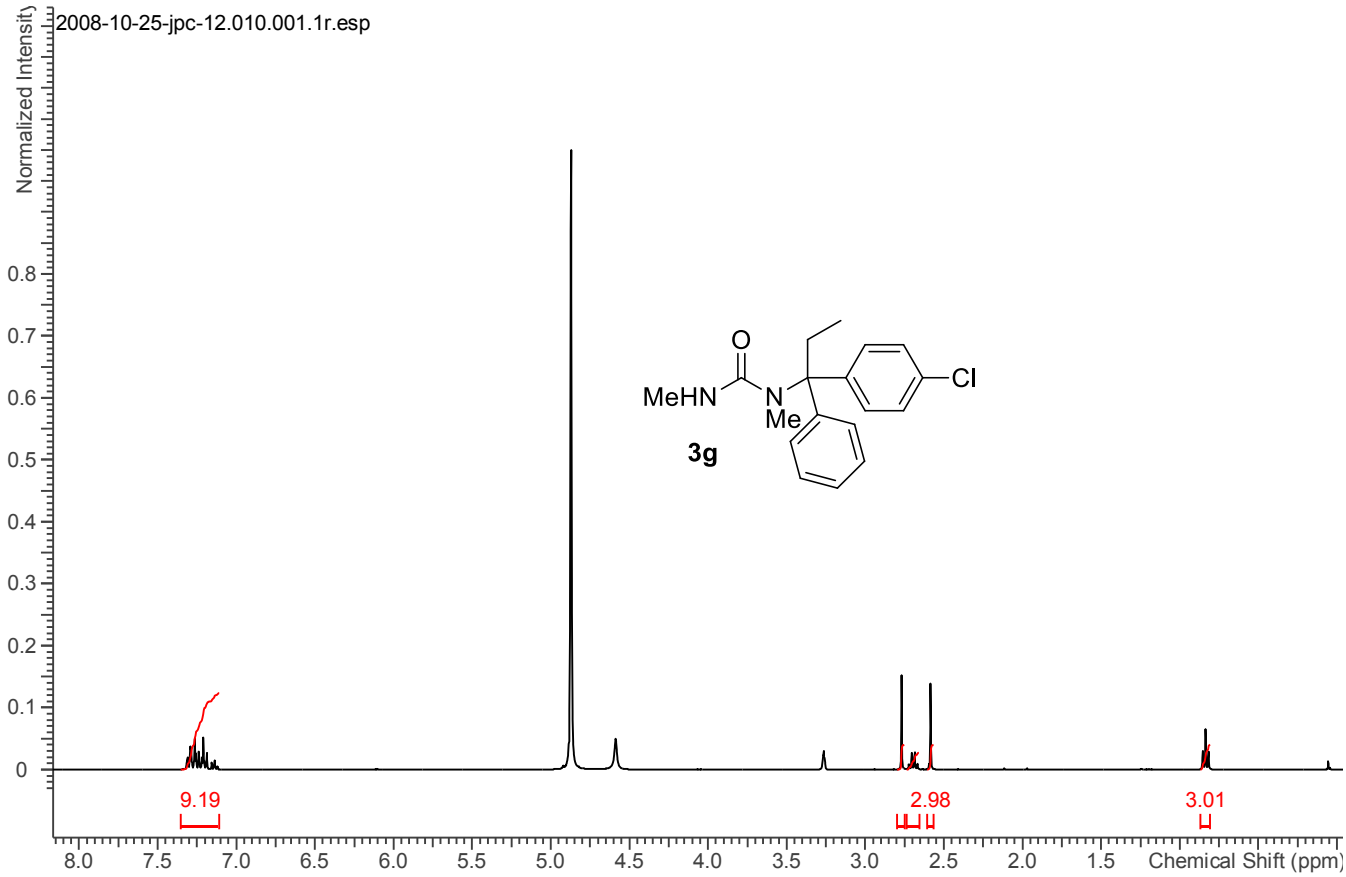

MeHN
O
N
Me
OMe
3d

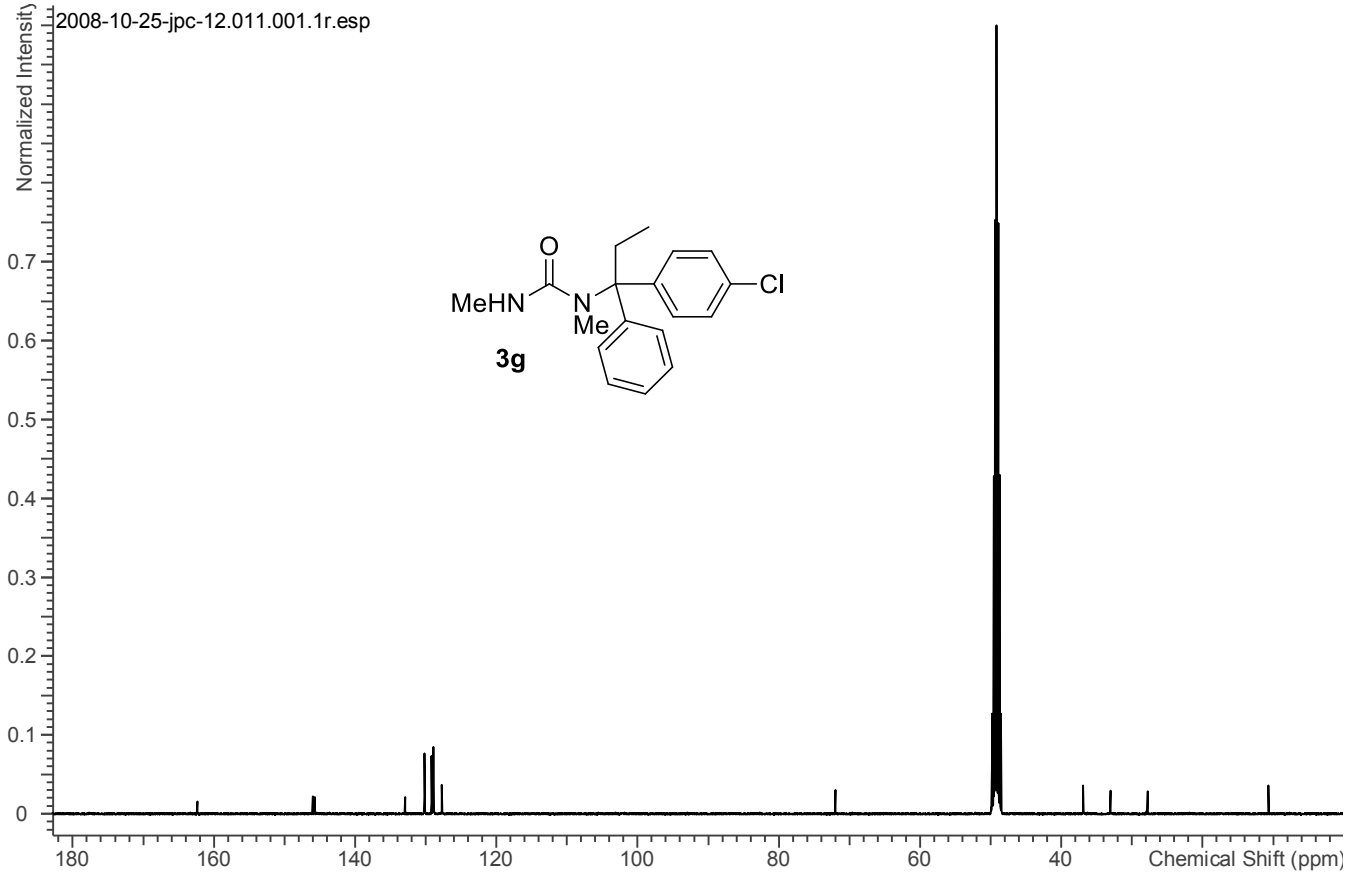

MeHN
O
N
Me
F
3e

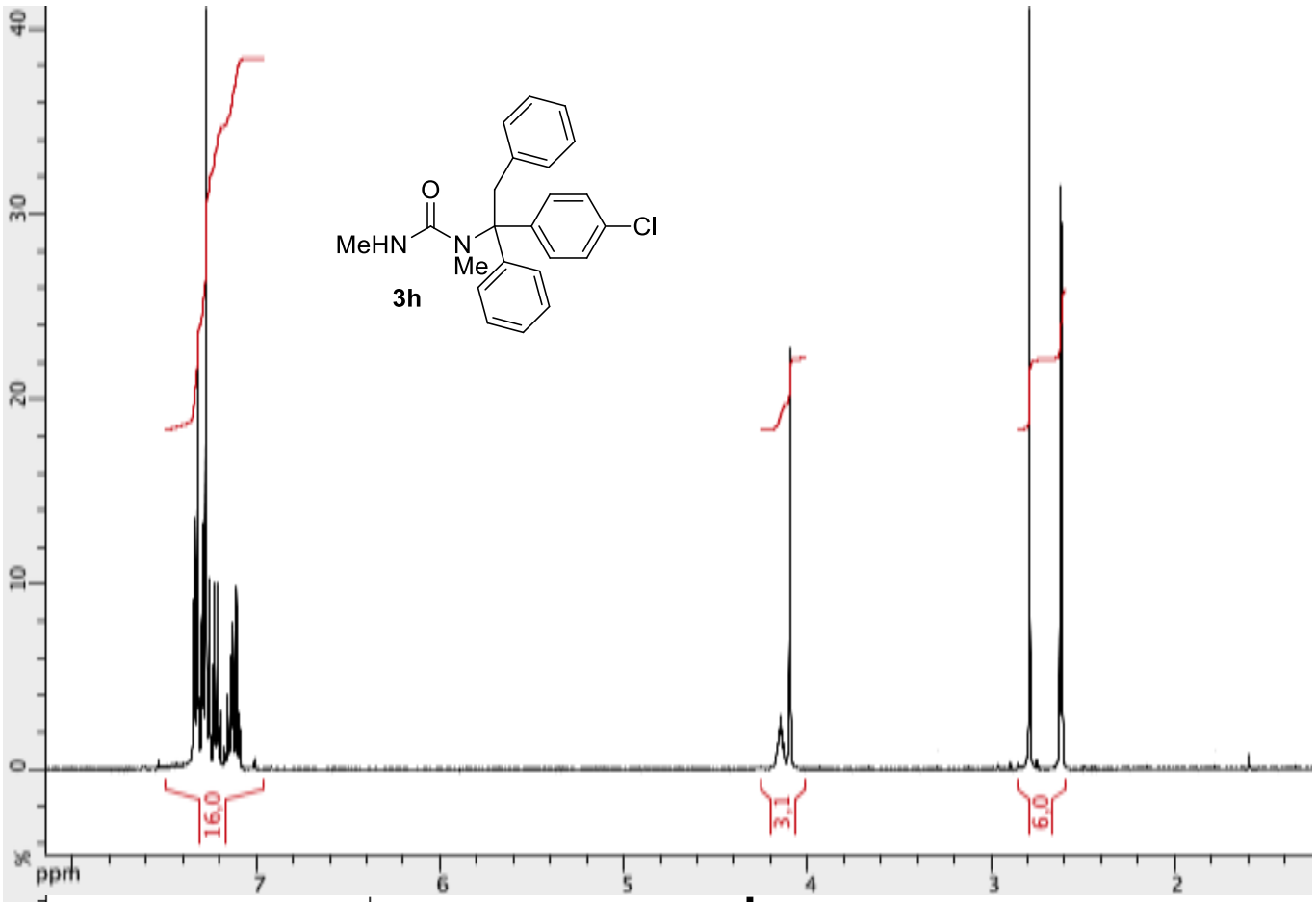

MeHN
O
N
Me
F
3e

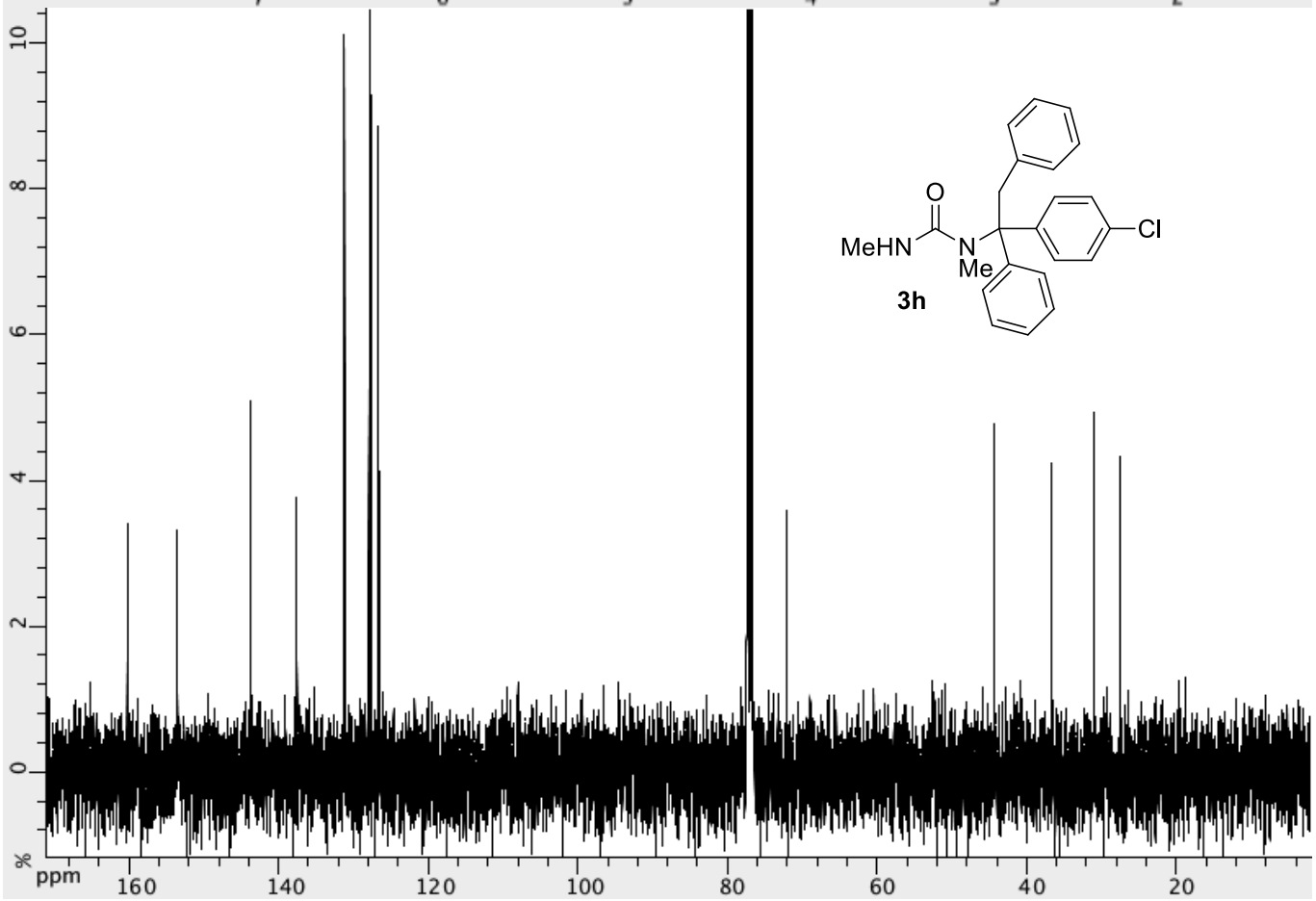

6-86-1.010.001.1r.esp
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
O
MeHN
N
Me
3f
1.01
1.99
1.03
0.91
3.00
2.91
1.86
3.01
2.91
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

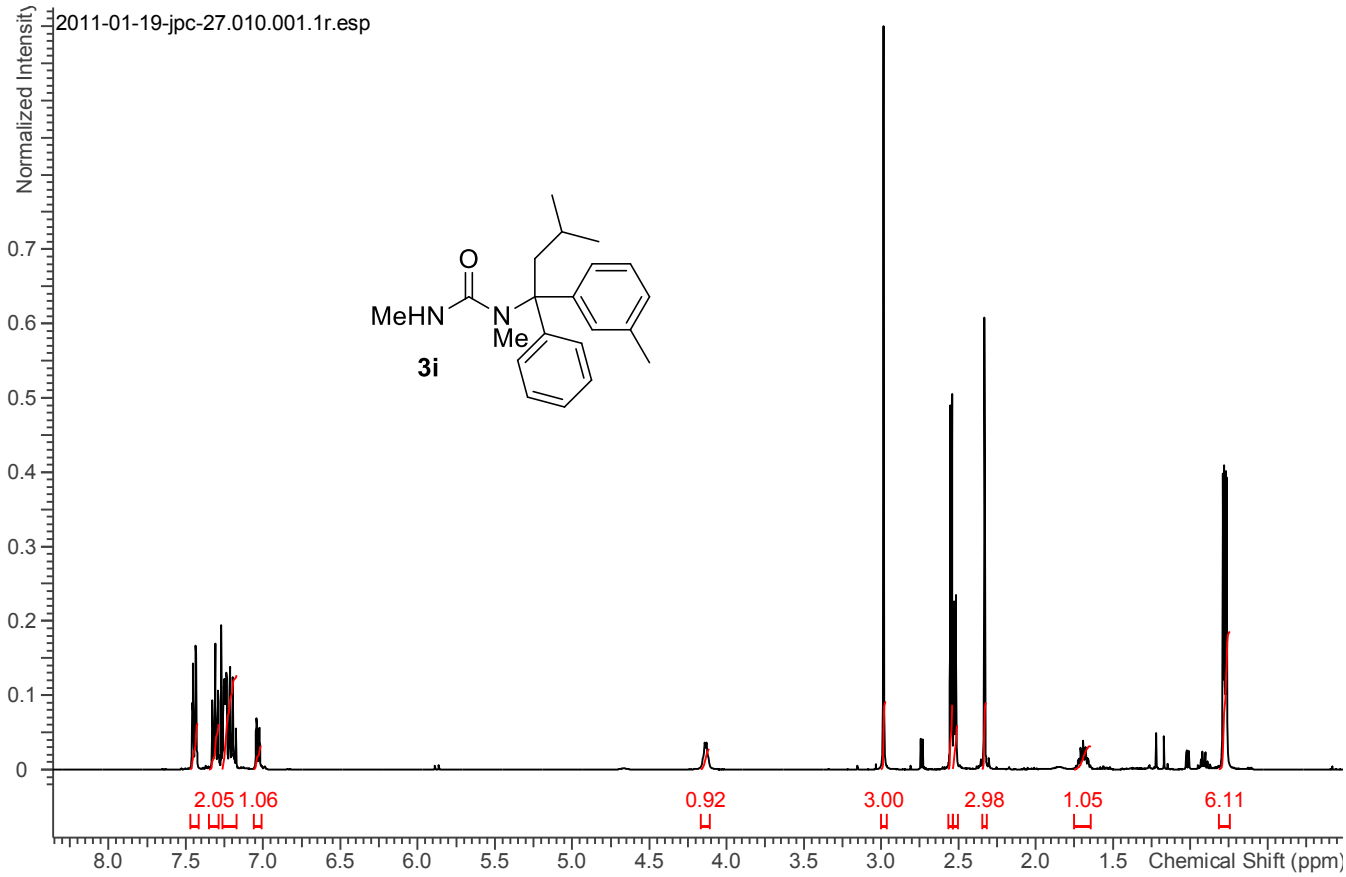

6-86-1.011.001.1r.esp
Normalized Intensity
0.10
0.05
0
O
MeHN
N
Me
3f
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

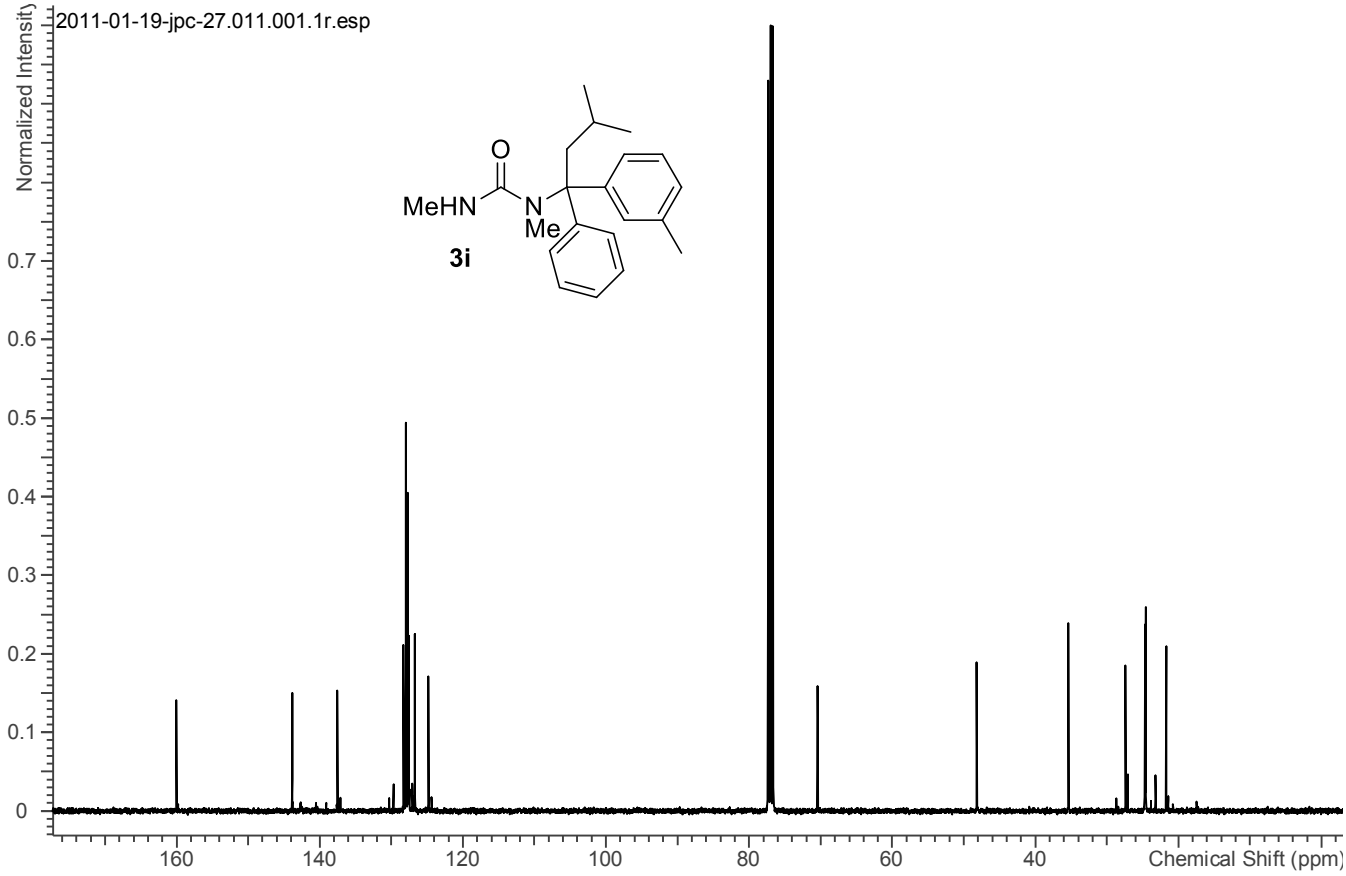

2008-10-25-jpc-12.010.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
Cl
3g
9.19
2.98
3.01
Chemical Shift (ppm)

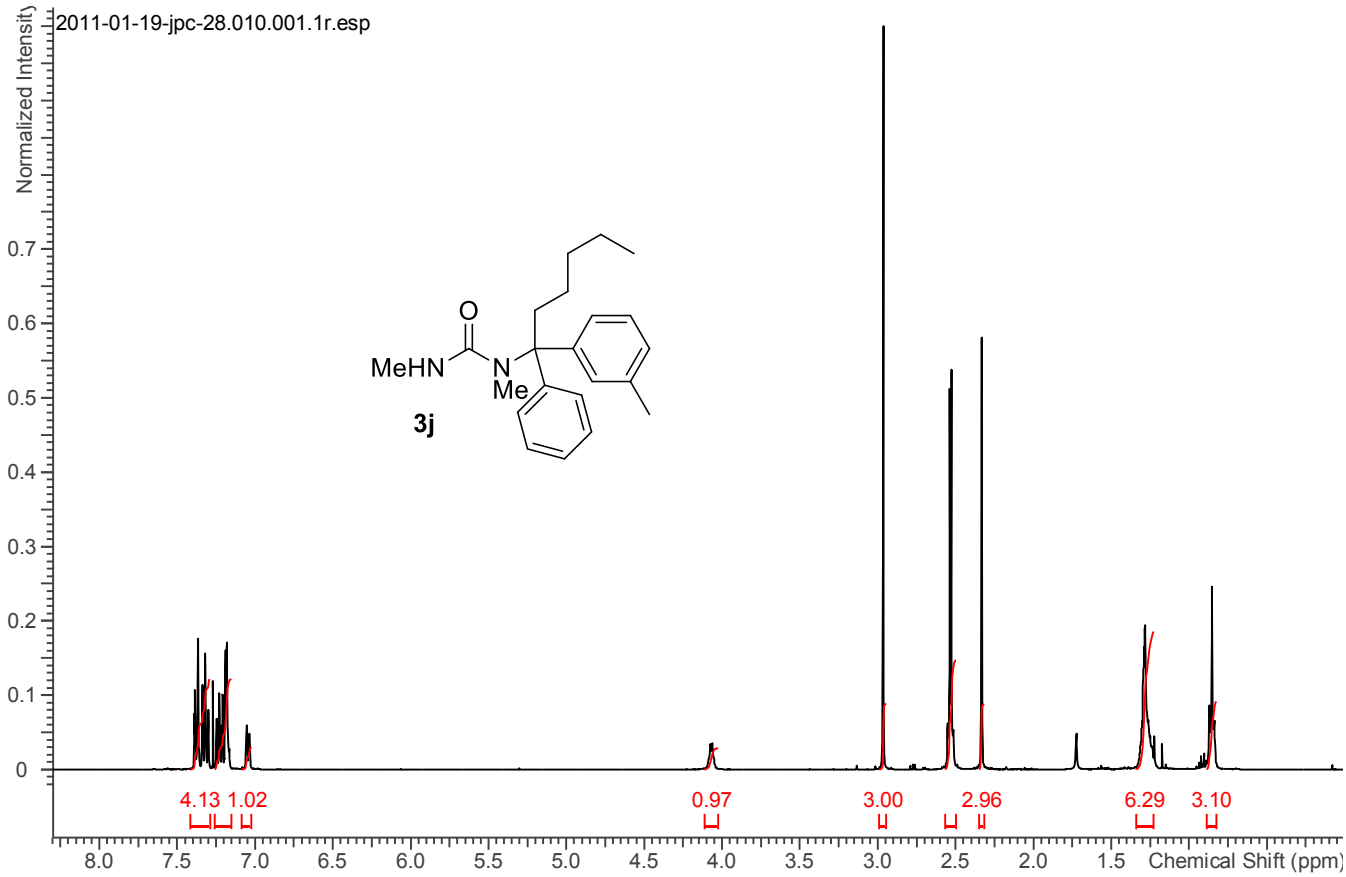

2008-10-25-jpc-12.011.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
Cl
3g
Chemical Shift (ppm)

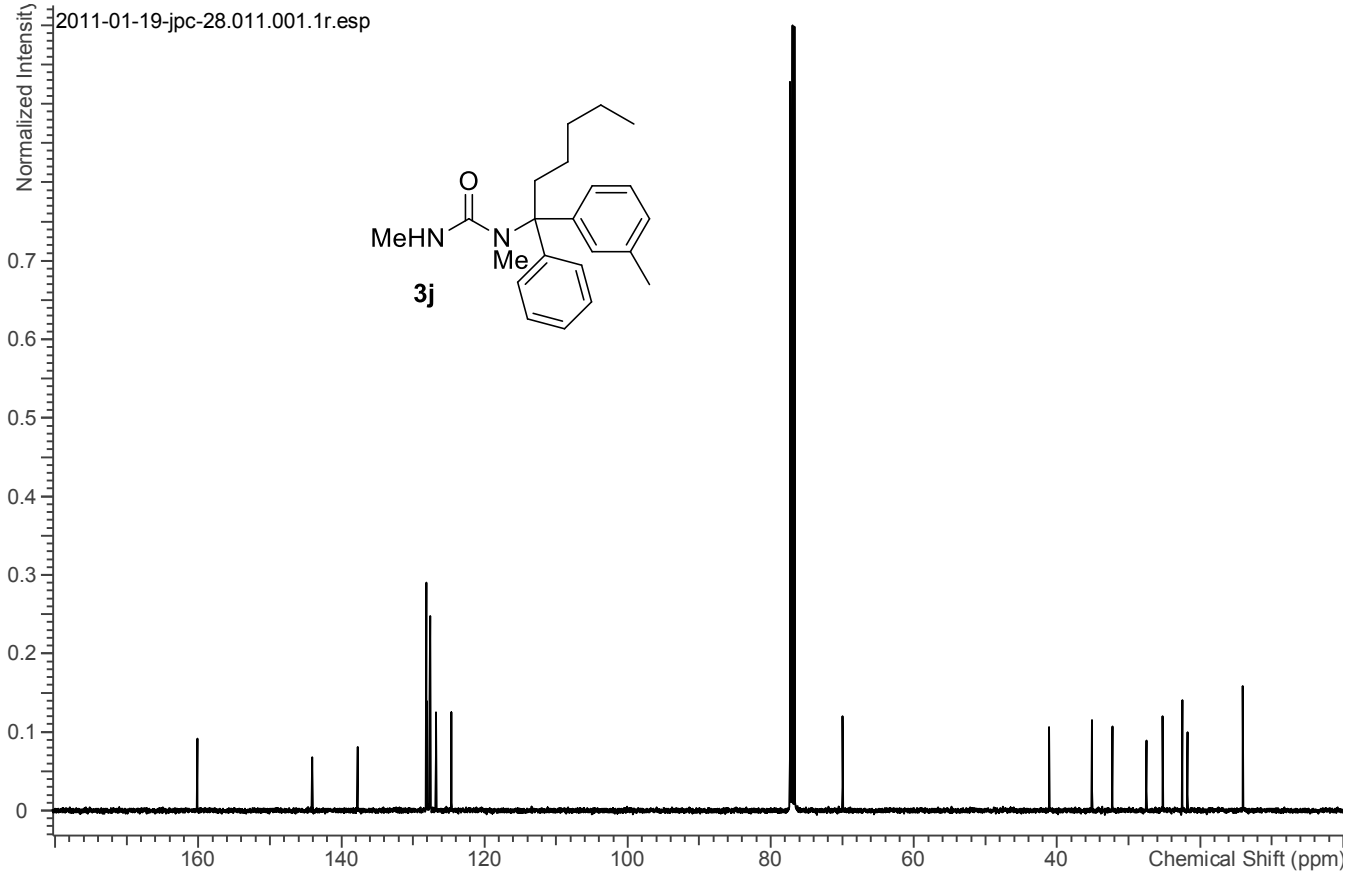

MeHN
O
N
Me
Cl
3h
16.0
3.1
6.0
ppm

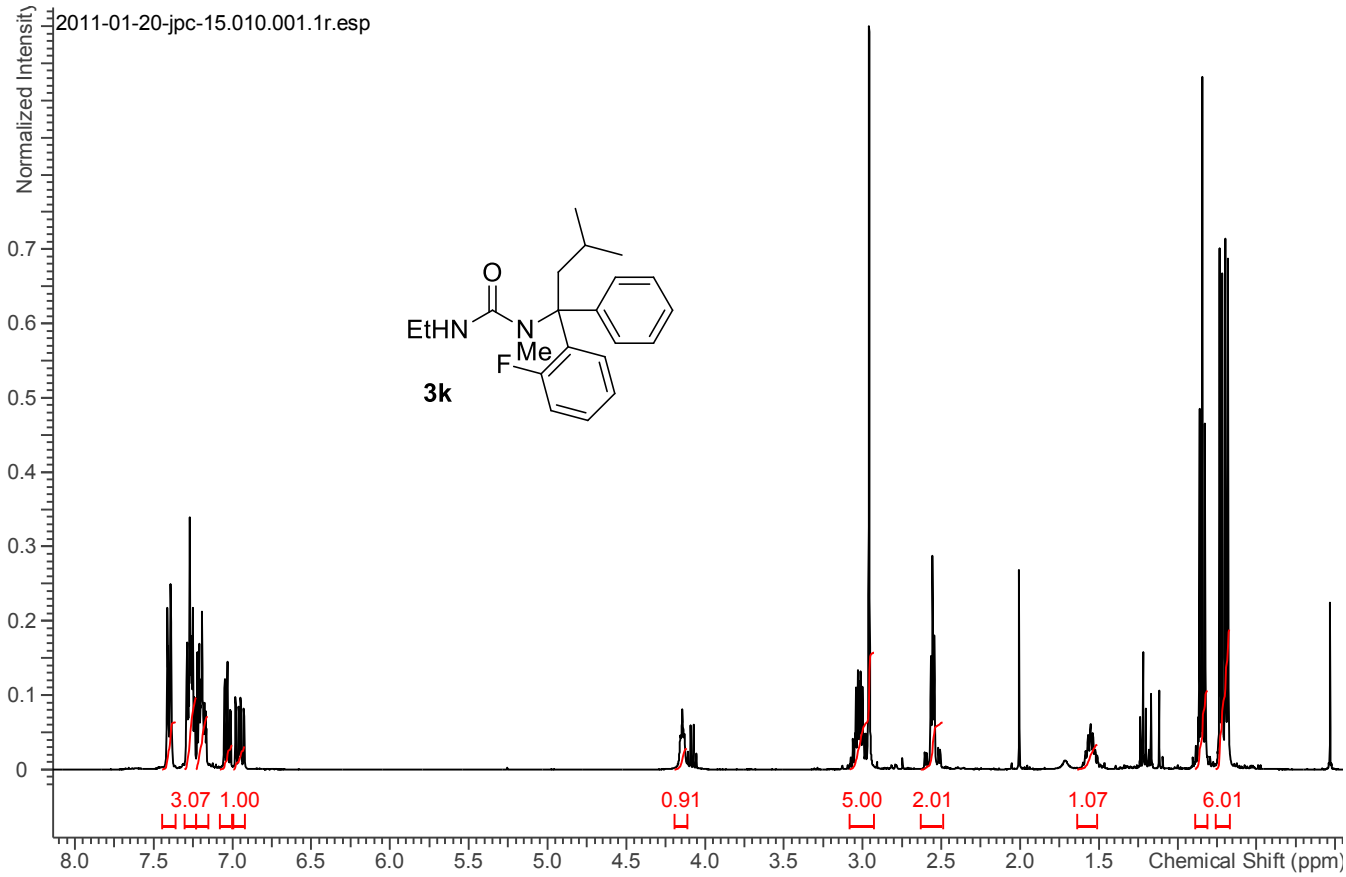

MeHN
O
N
Me
Cl
3h
ppm

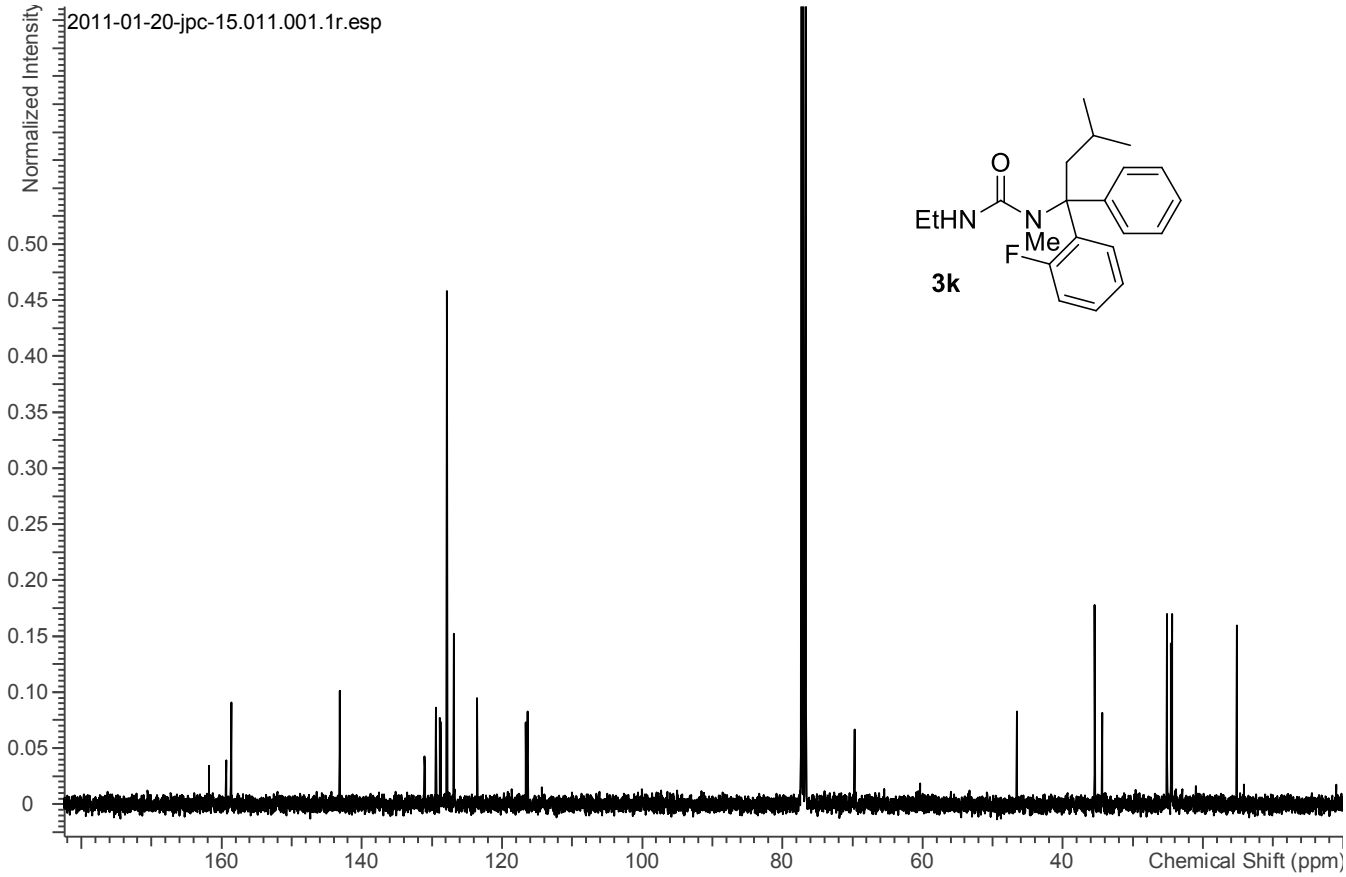

2011-01-19-jpc-27.010.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
3i
2.05
1.06
0.92
3.00
2.98
1.05
6.11
Chemical Shift (ppm)

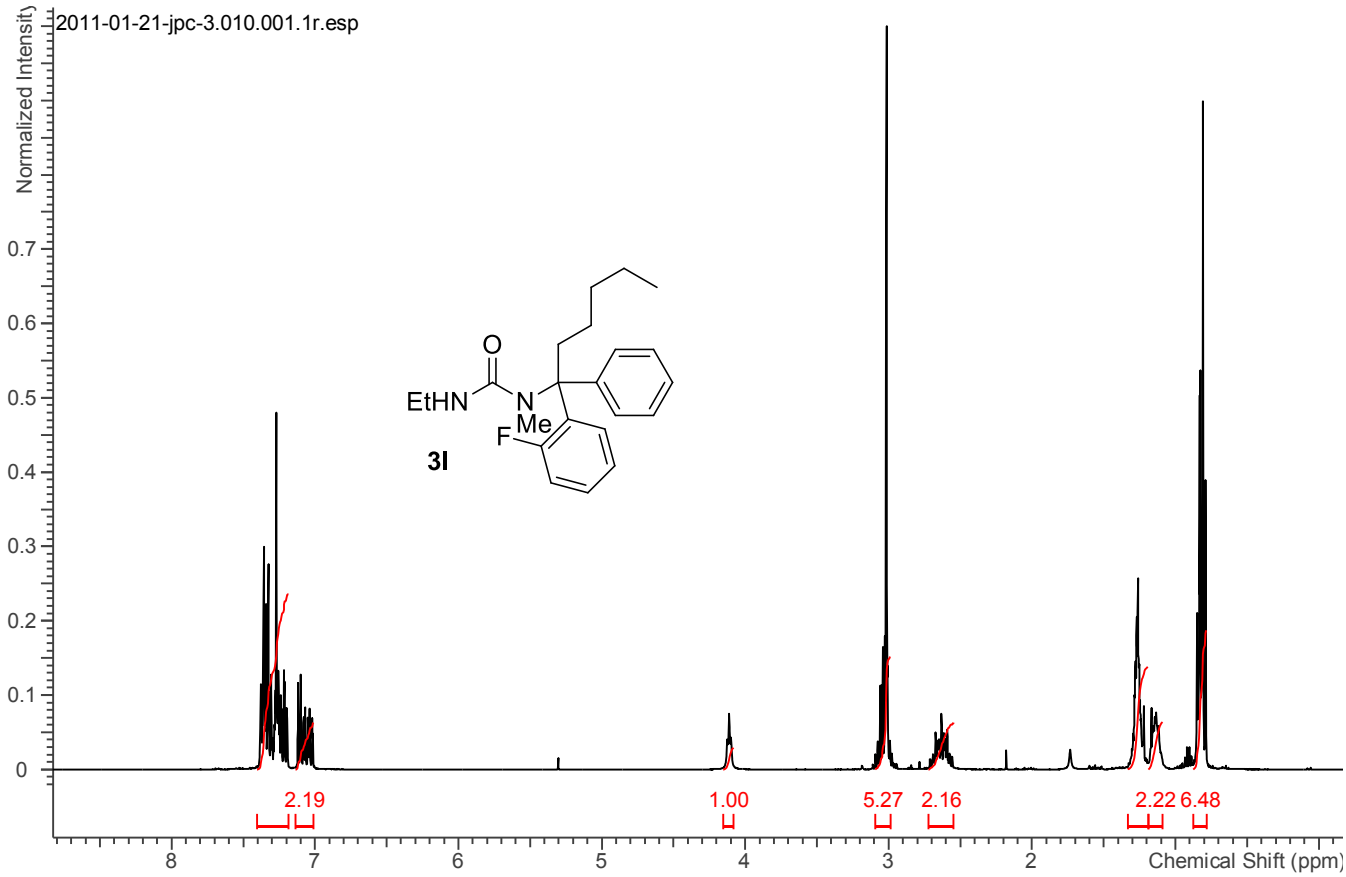

2011-01-19-jpc-27.011.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
3i
Chemical Shift (ppm)

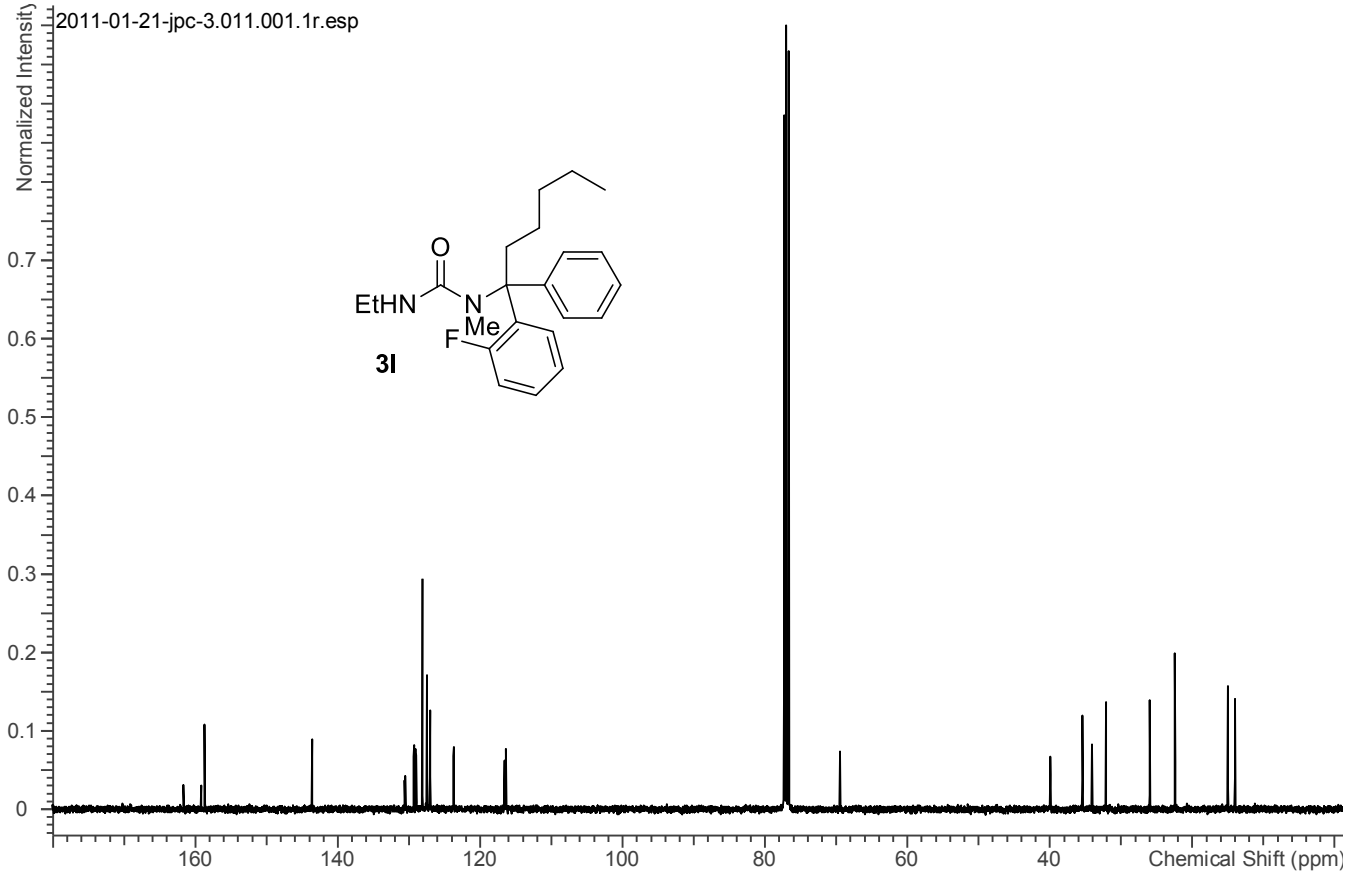

2011-01-19-jpc-28.010.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
3j
4.13
1.02
0.97
3.00
2.96
6.29
3.10
Chemical Shift (ppm)

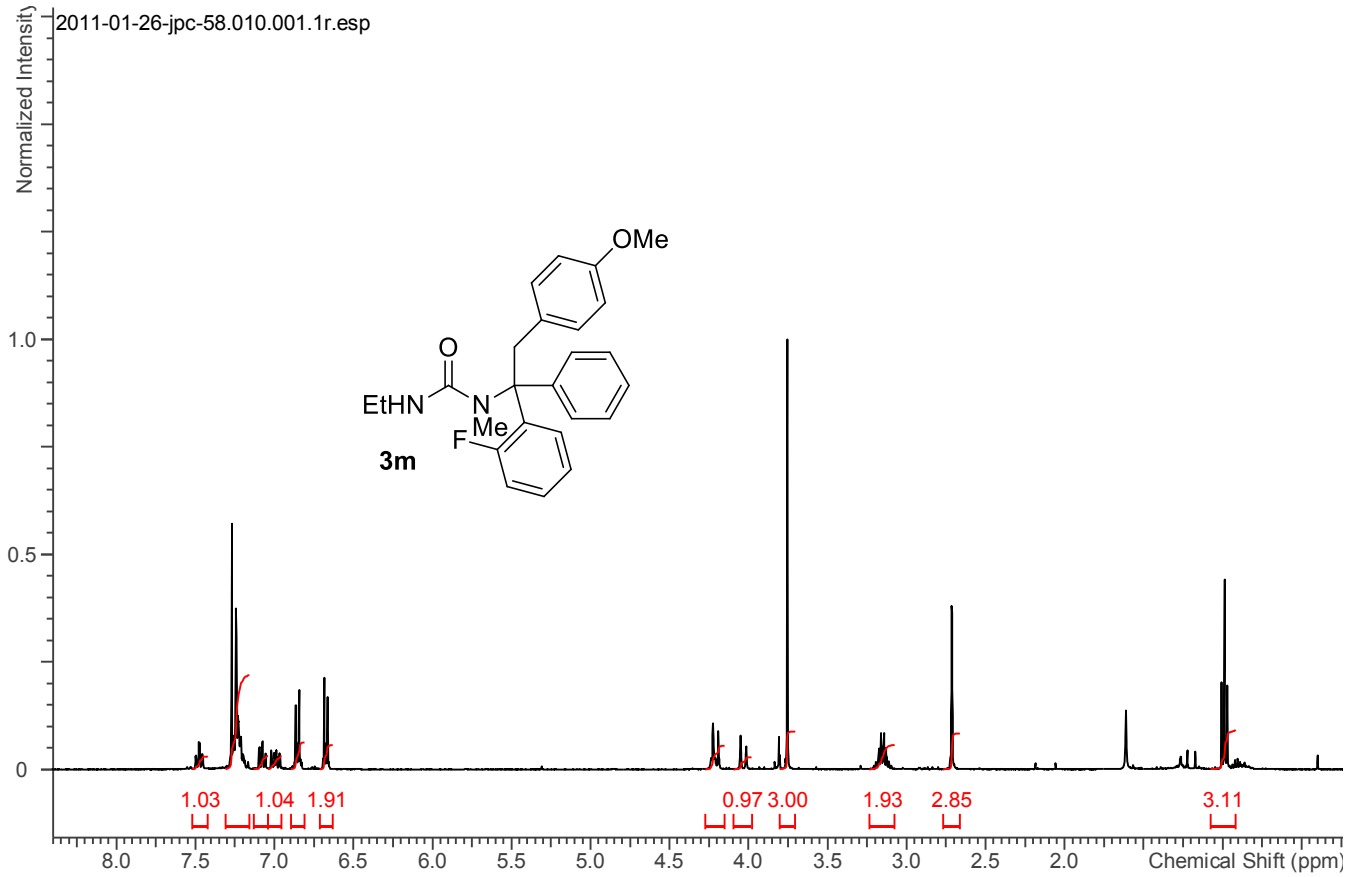

2011-01-19-jpc-28.011.001.1r.esp
Normalized Intensity
MeHN
O
N
Me
3j
Chemical Shift (ppm)

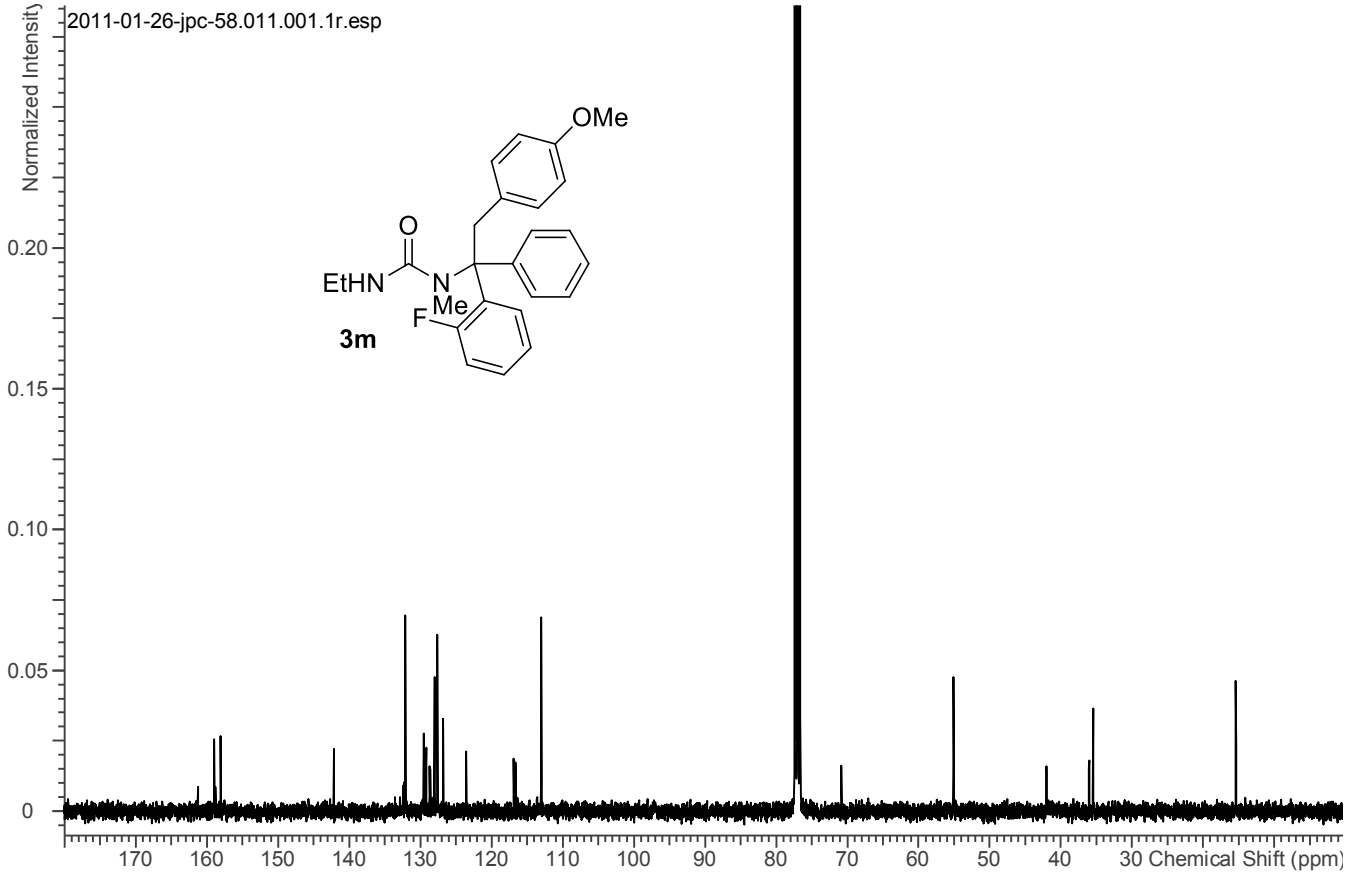

2011-01-20-jpc-15.010.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3k
3.07
1.00
0.91
5.00
2.01
1.07
6.01
Chemical Shift (ppm)

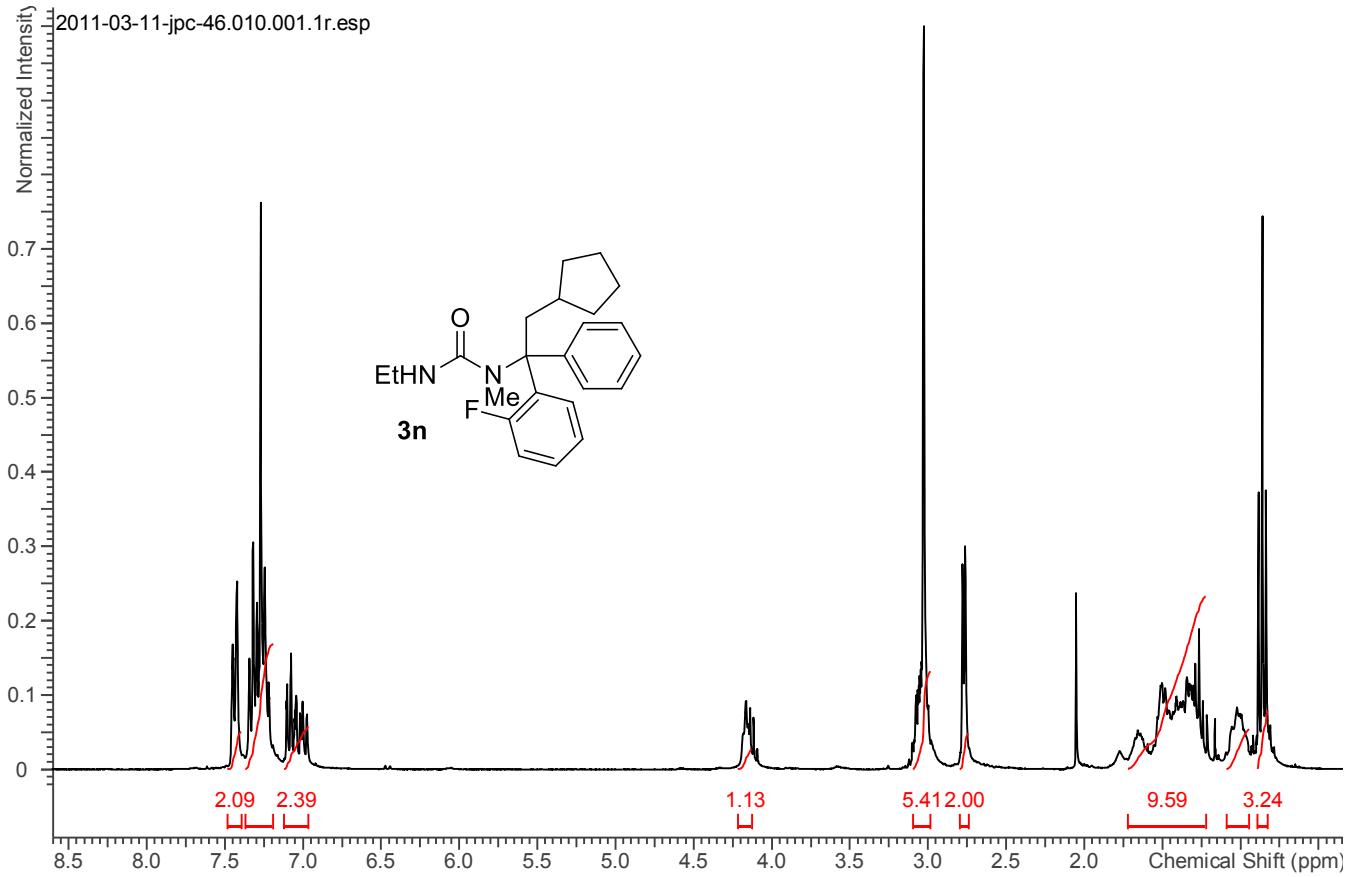

2011-01-20-jpc-15.011.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3k
Chemical Shift (ppm)

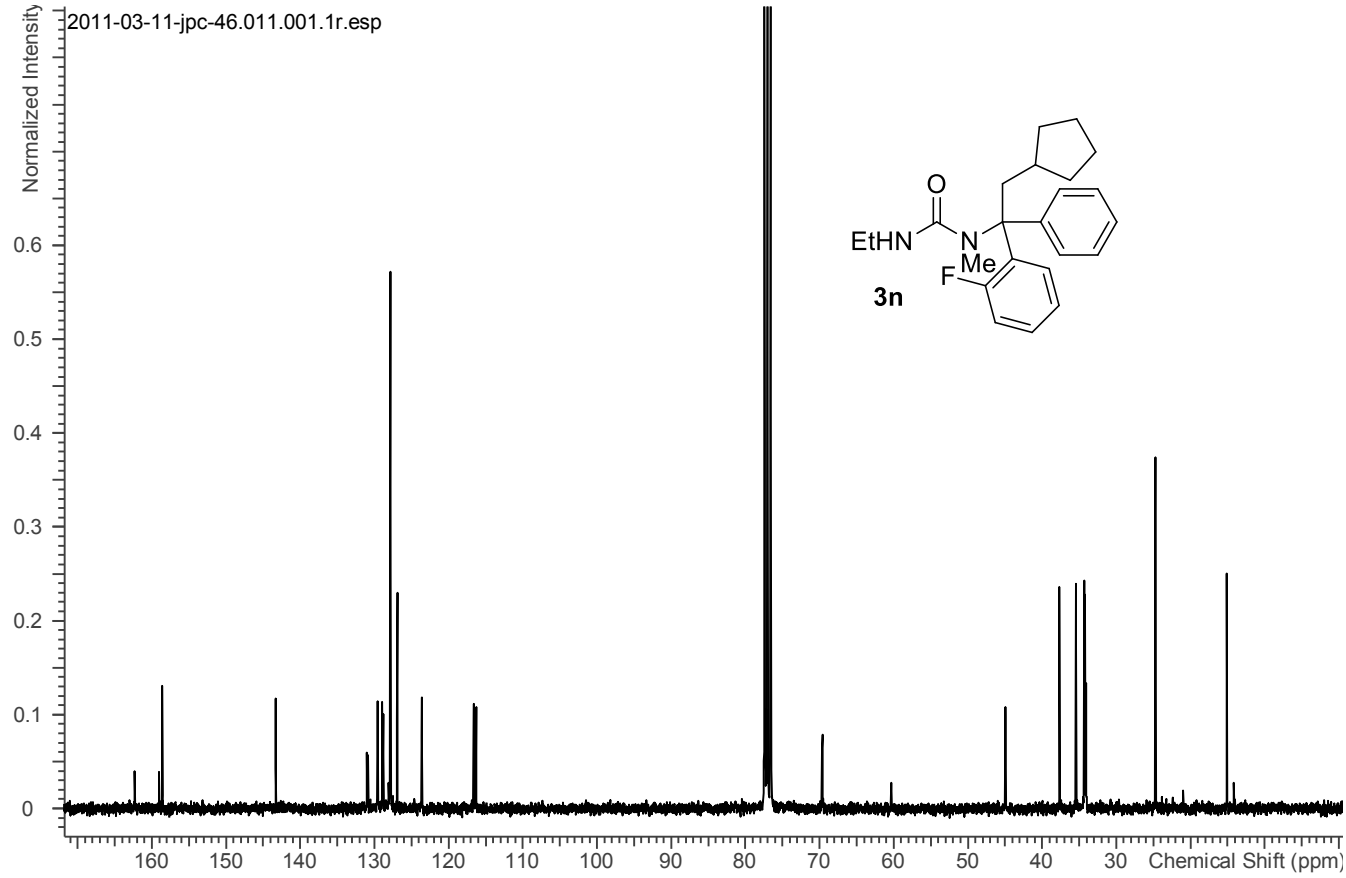

2011-01-21-jpc-3.010.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3l
2.19
1.00
5.27
2.16
2.22
6.48
Chemical Shift (ppm)

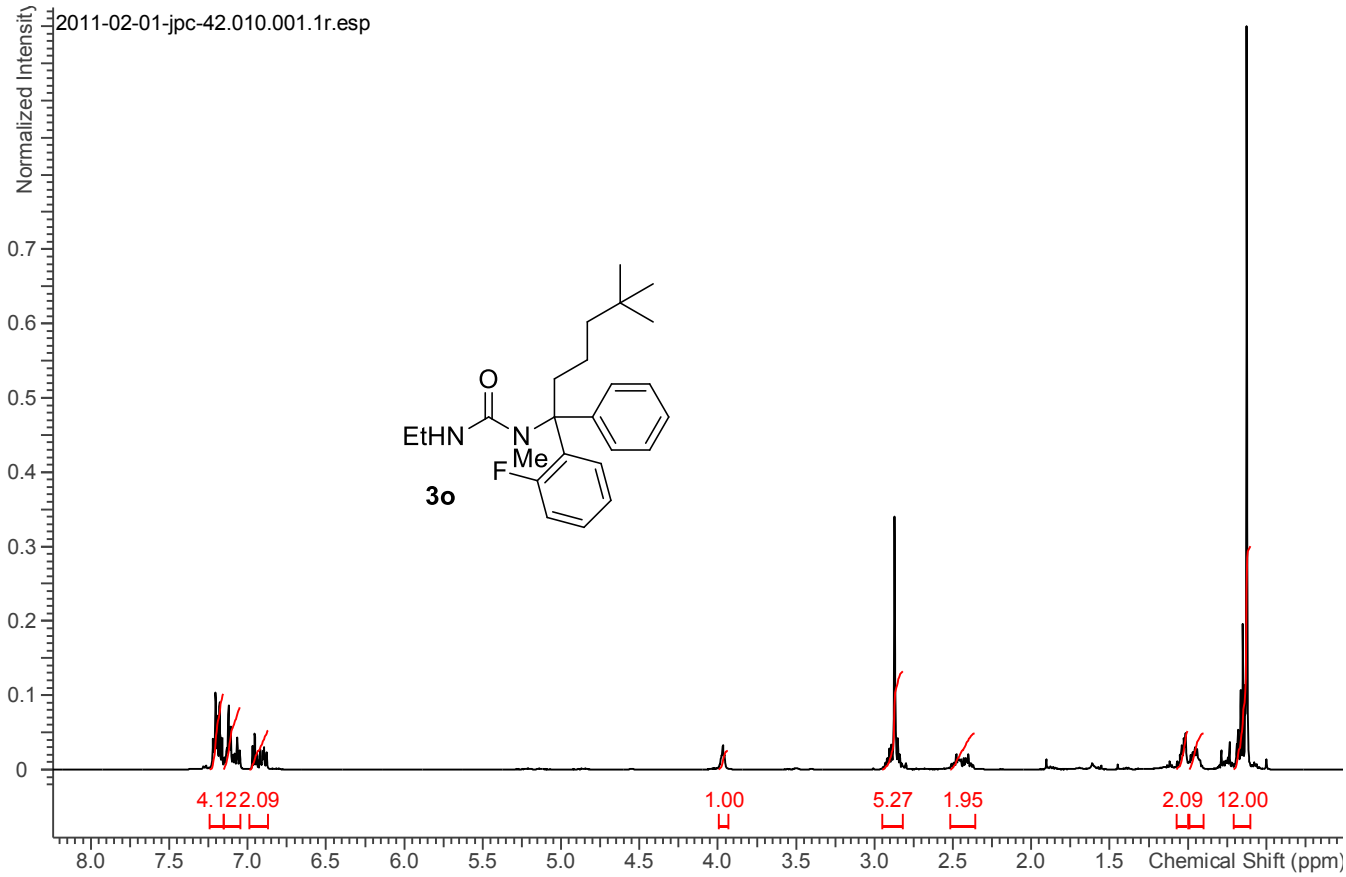

2011-01-21-jpc-3.011.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3l
Chemical Shift (ppm)

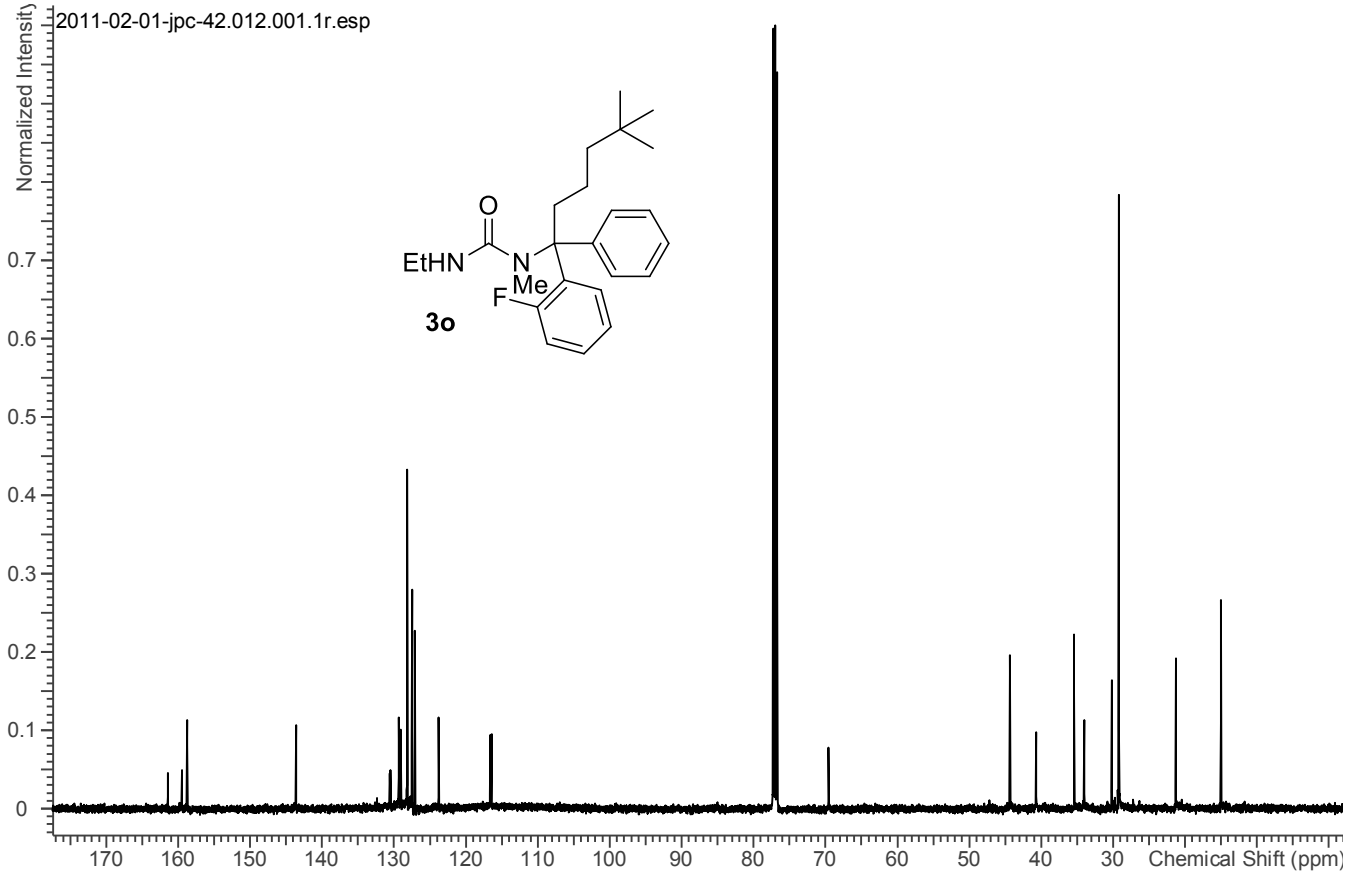

2011-01-26-jpc-58.010.001.1r.esp
Normalized Intensity
1.0
0.5
0
OMe
O
EtHN
N
Me
F
3m
1.03
1.04
1.91
0.97
3.00
1.93
2.85
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

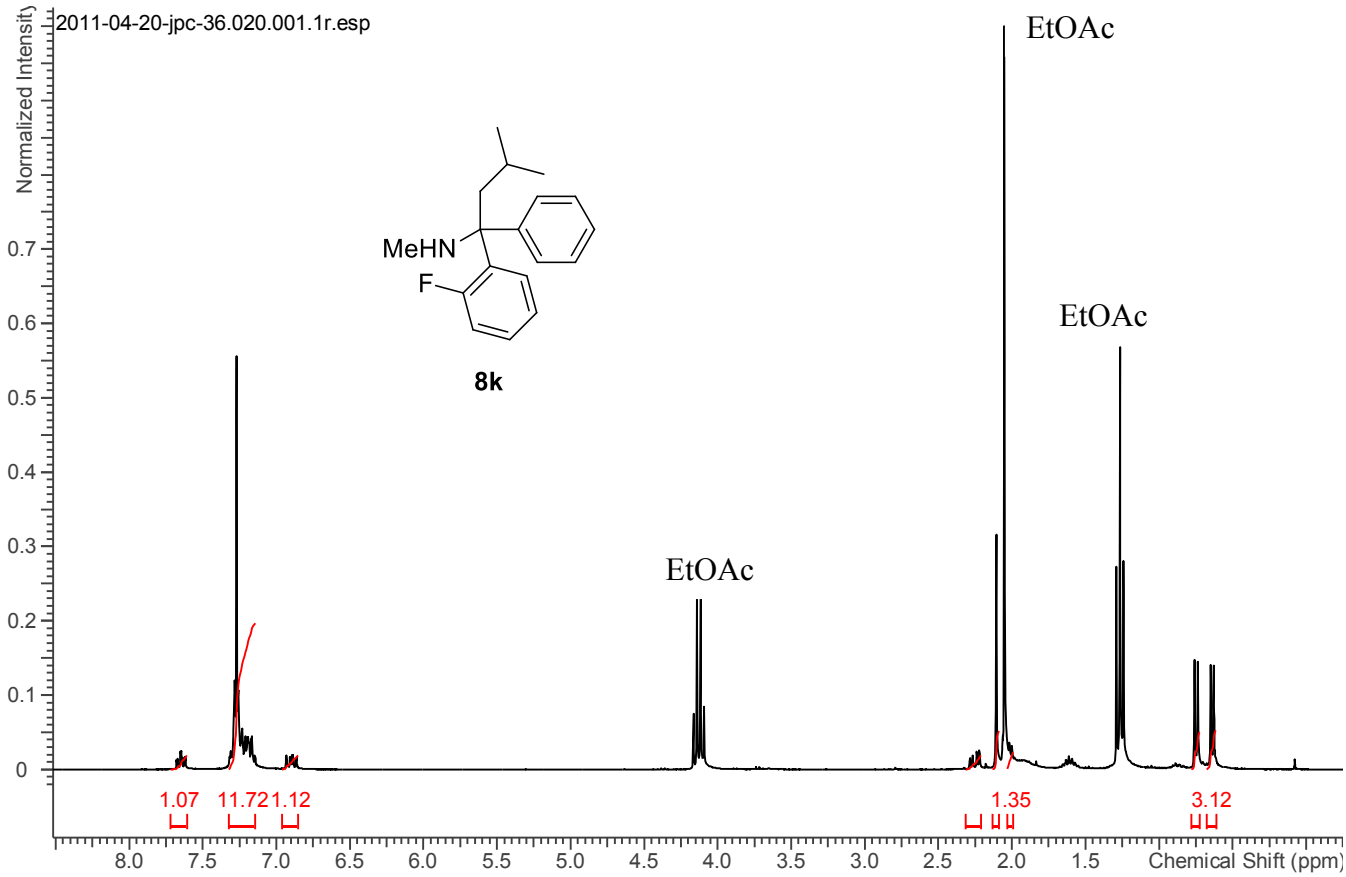

2011-01-26-jpc-58.011.001.1r.esp
Normalized Intensity
0.20
0.15
0.10
0.05
0
OMe
O
EtHN
N
Me
F
3m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30 Chemical Shift (ppm)

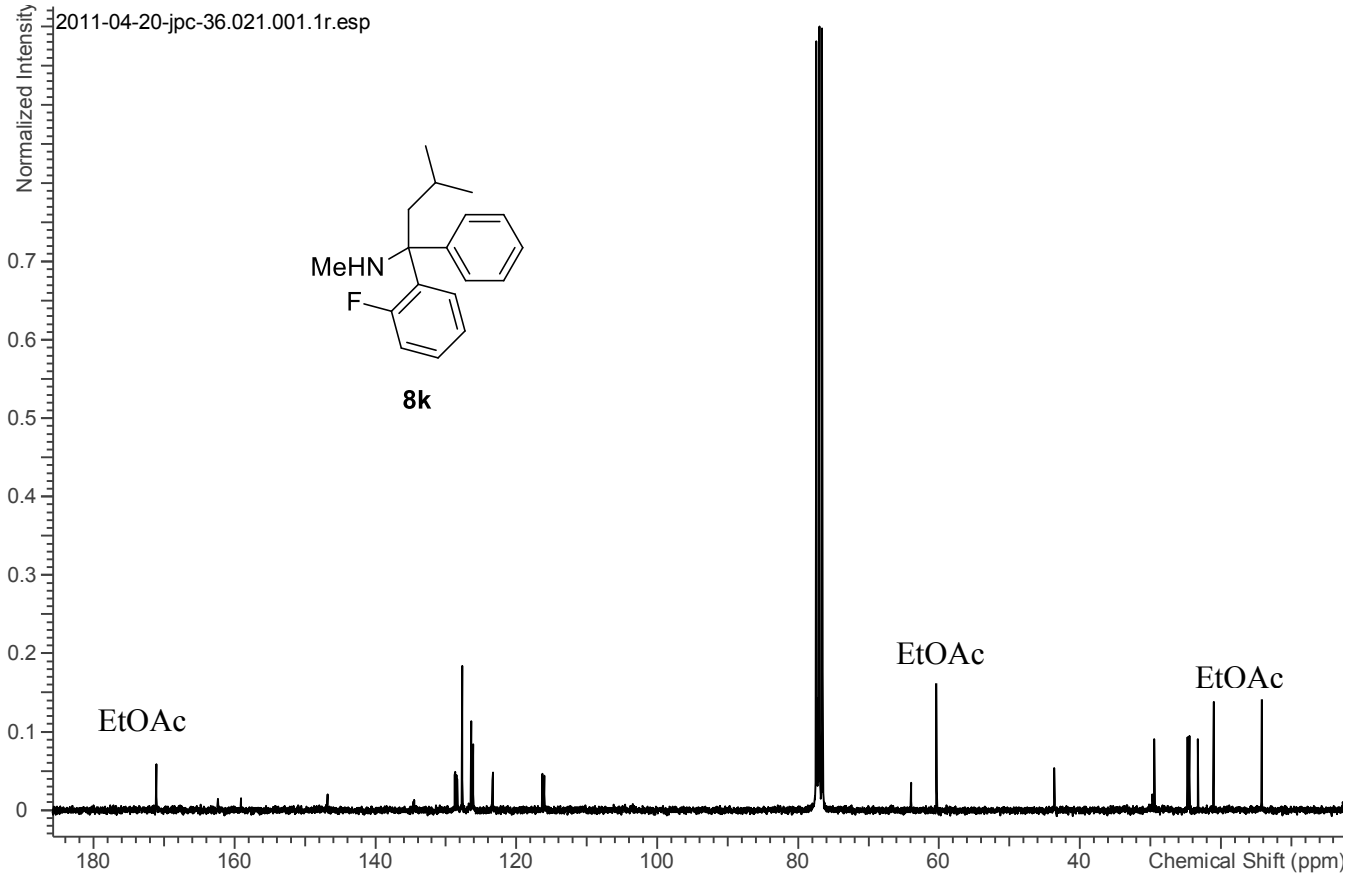

2011-03-11-jpc-46.010.001.1r.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
O
EtHN
N
Me
F
3n
2.09
2.39
1.13
5.41
2.00
9.59
3.24
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

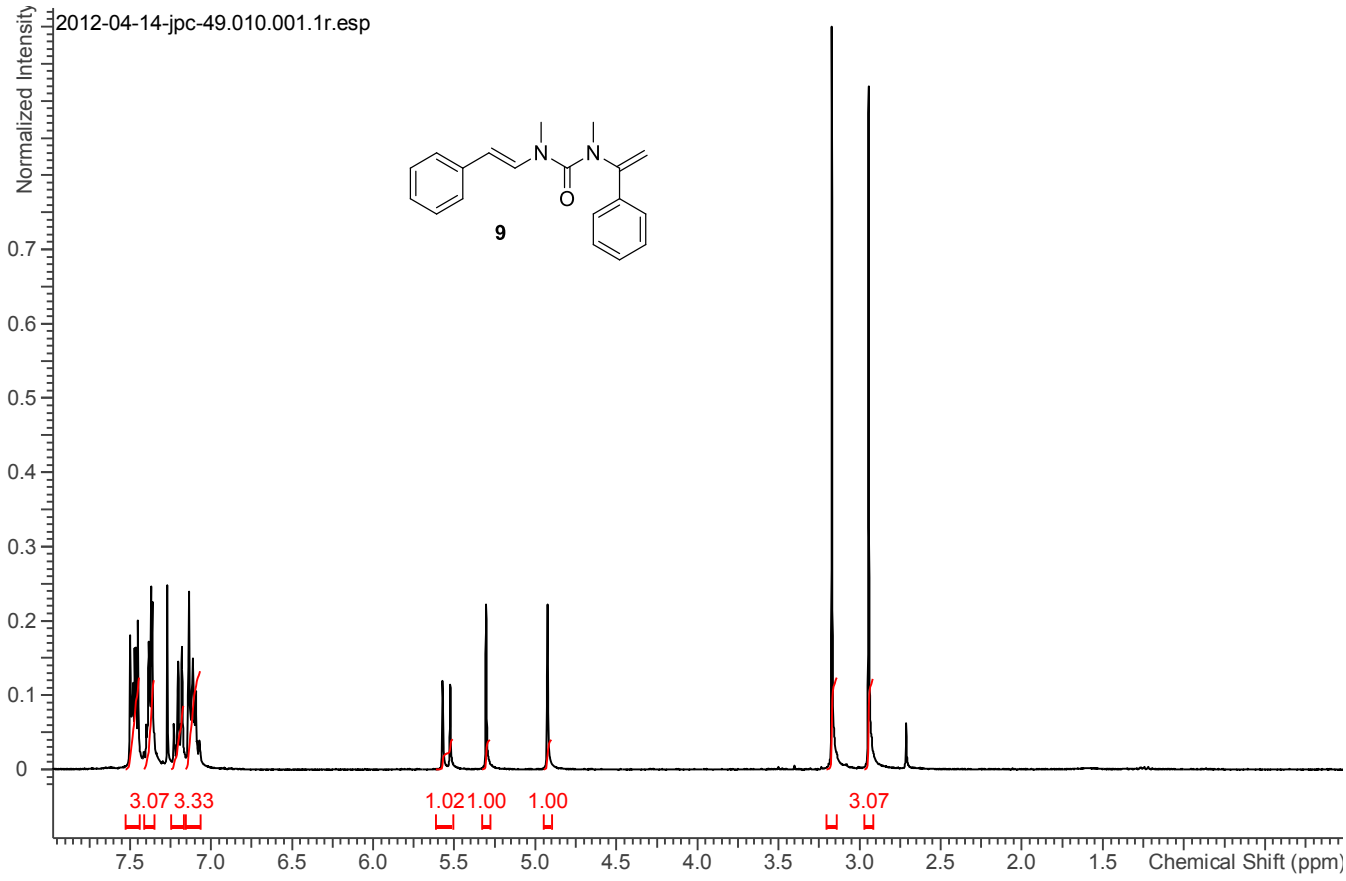

2011-03-11-jpc-46.011.001.1r.esp
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
O
EtHN
N
Me
F
3n
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

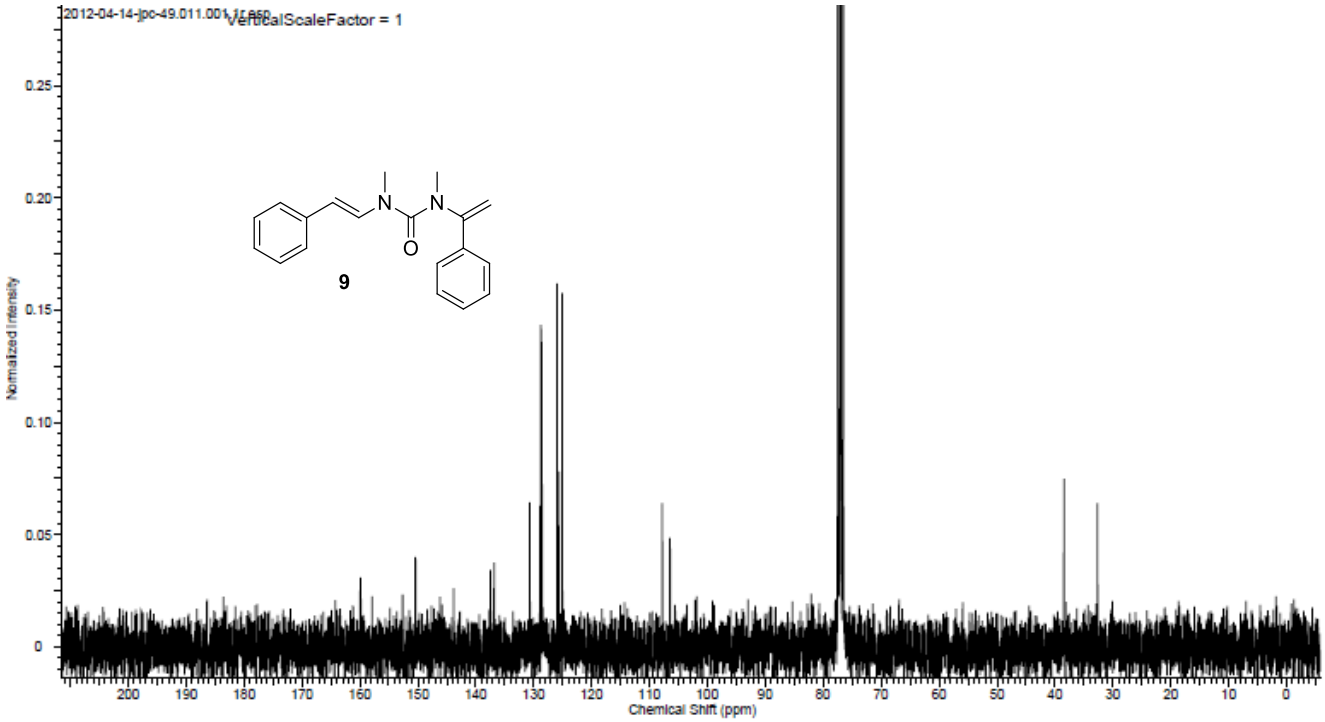

2011-02-01-jpc-42.010.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3o
4.12
2.09
1.00
5.27
1.95
2.09
12.00
Chemical Shift (ppm)


2011-02-01-jpc-42.012.001.1r.esp
Normalized Intensity
EtHN
O
N
Me
F
3o
Chemical Shift (ppm)

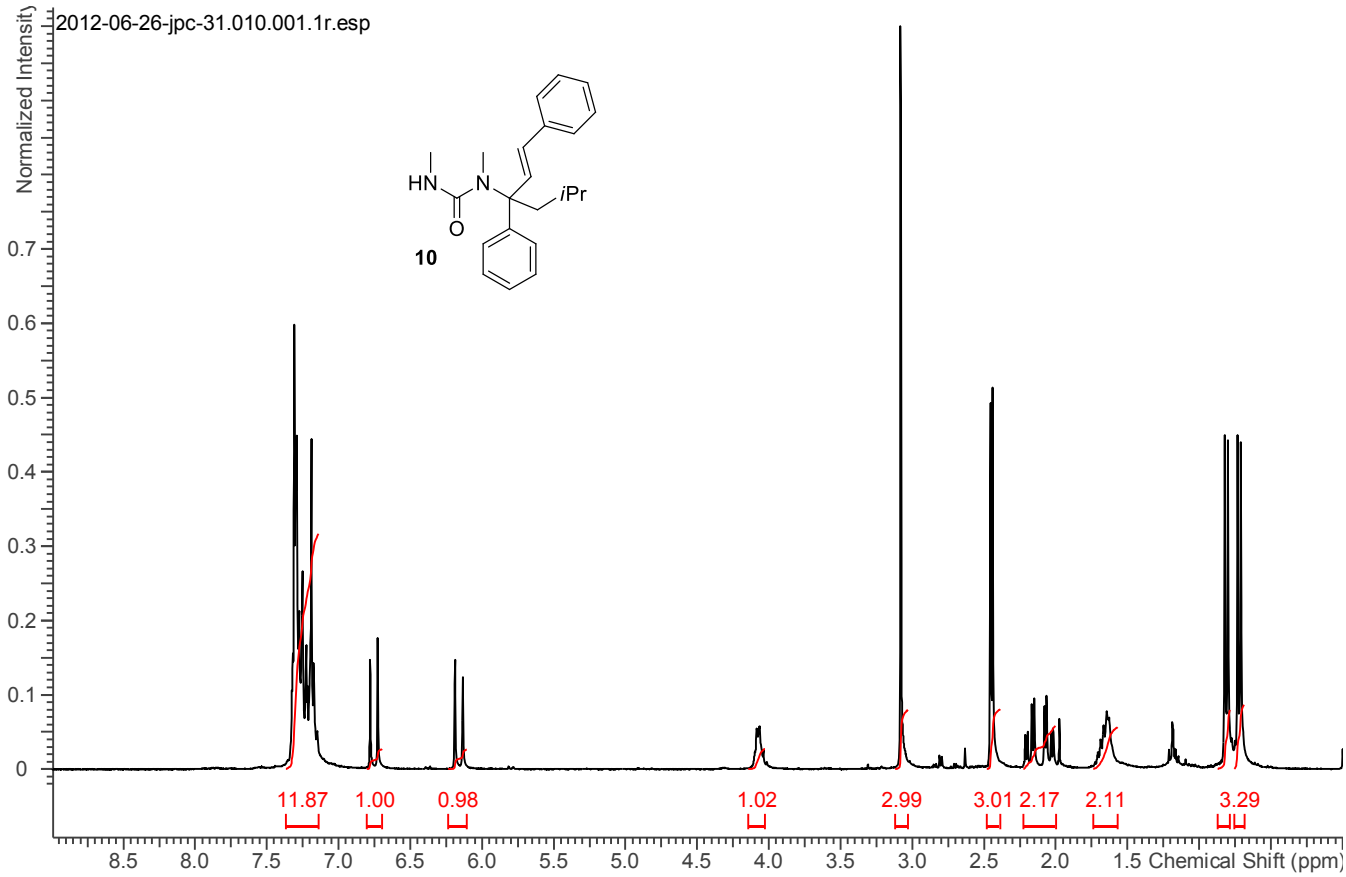

2011-04-20-jpc-36.020.001.1r.esp
Normalized Intensity
MeHN
F
8k
EtOAc
EtOAc
EtOAc
1.07
11.72
1.12
1.35
3.12
Chemical Shift (ppm)

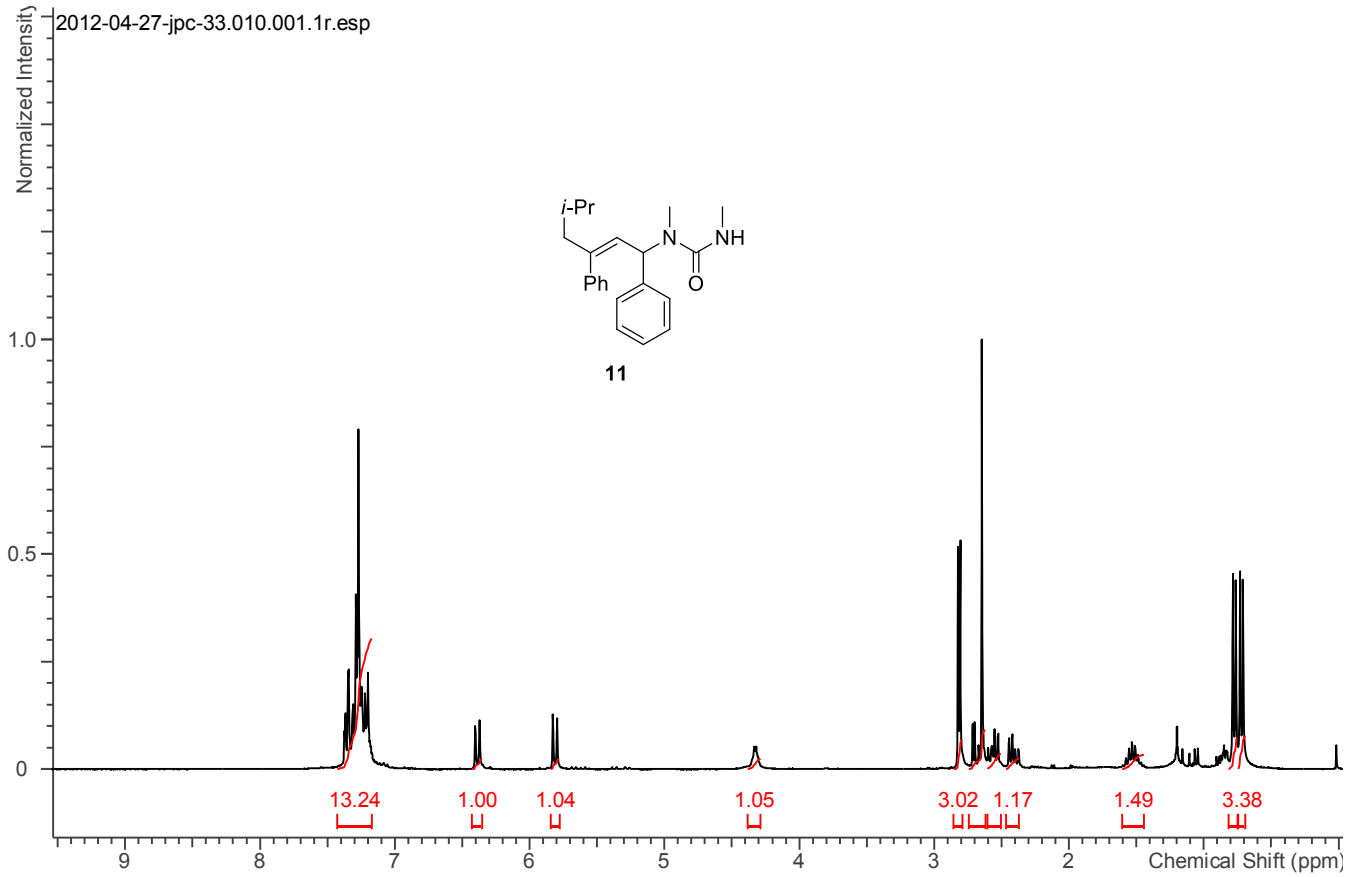

2011-04-20-jpc-36.021.001.1r.esp
Normalized Intensity
MeHN
F
8k
EtOAc
EtOAc
EtOAc
Chemical Shift (ppm)

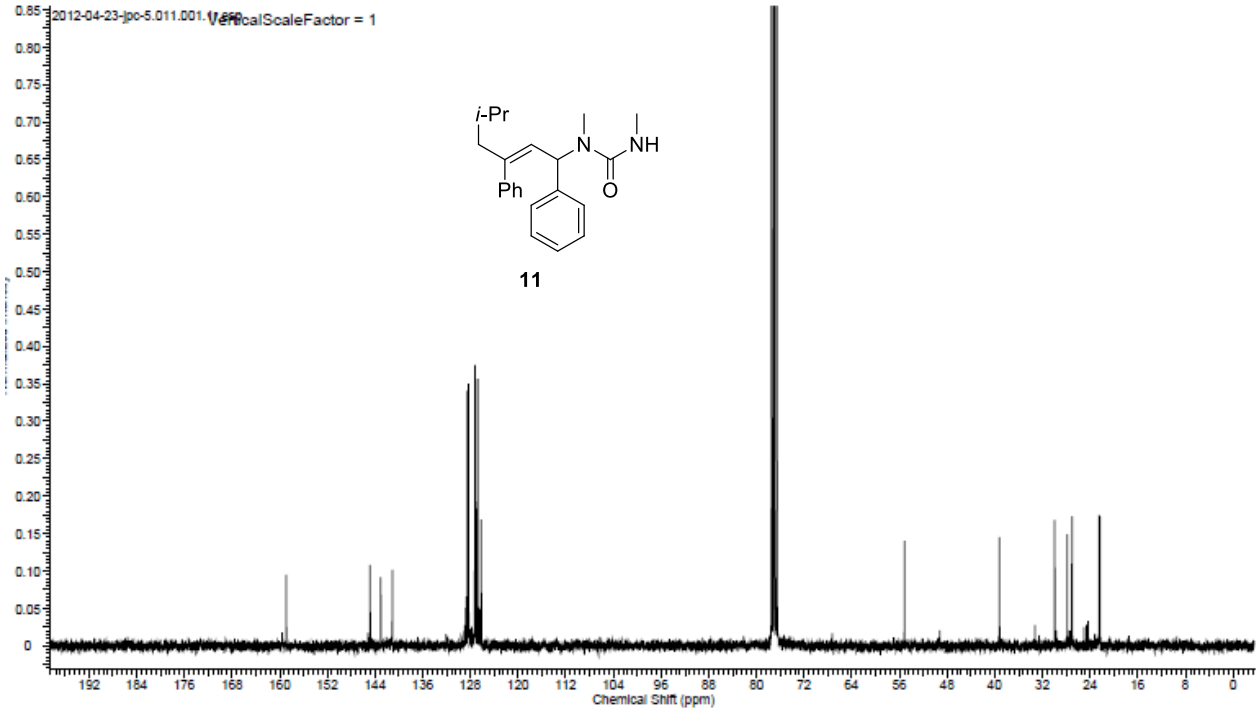

2012-04-14-jpc-49.010.001.1r.esp
Normalized Intensity
9
3.07 3.33
1.02 1.00
1.00
3.07
Chemical Shift (ppm)

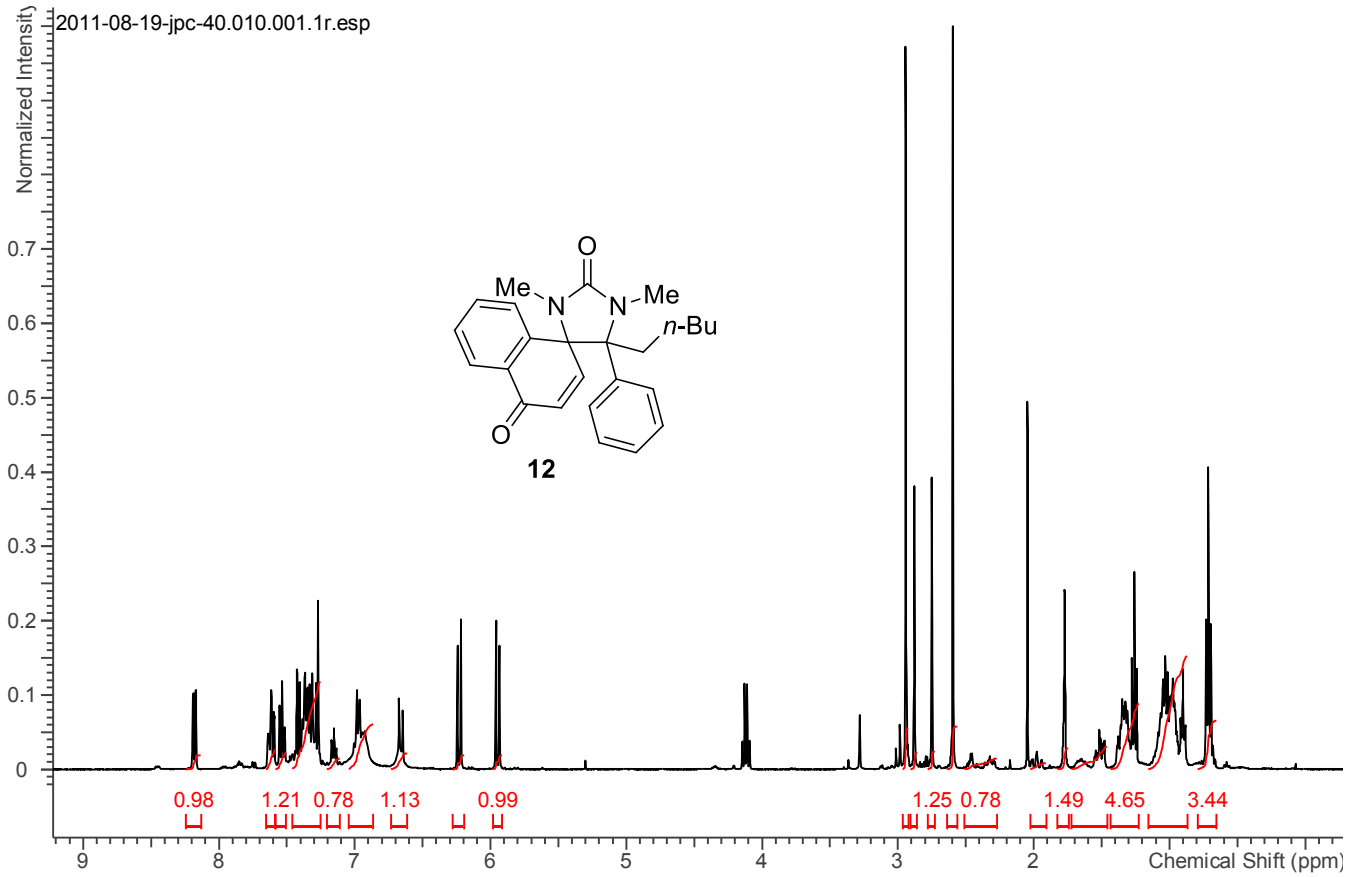

VerticalScaleFactor = 1
9
Chemical Shift (ppm)

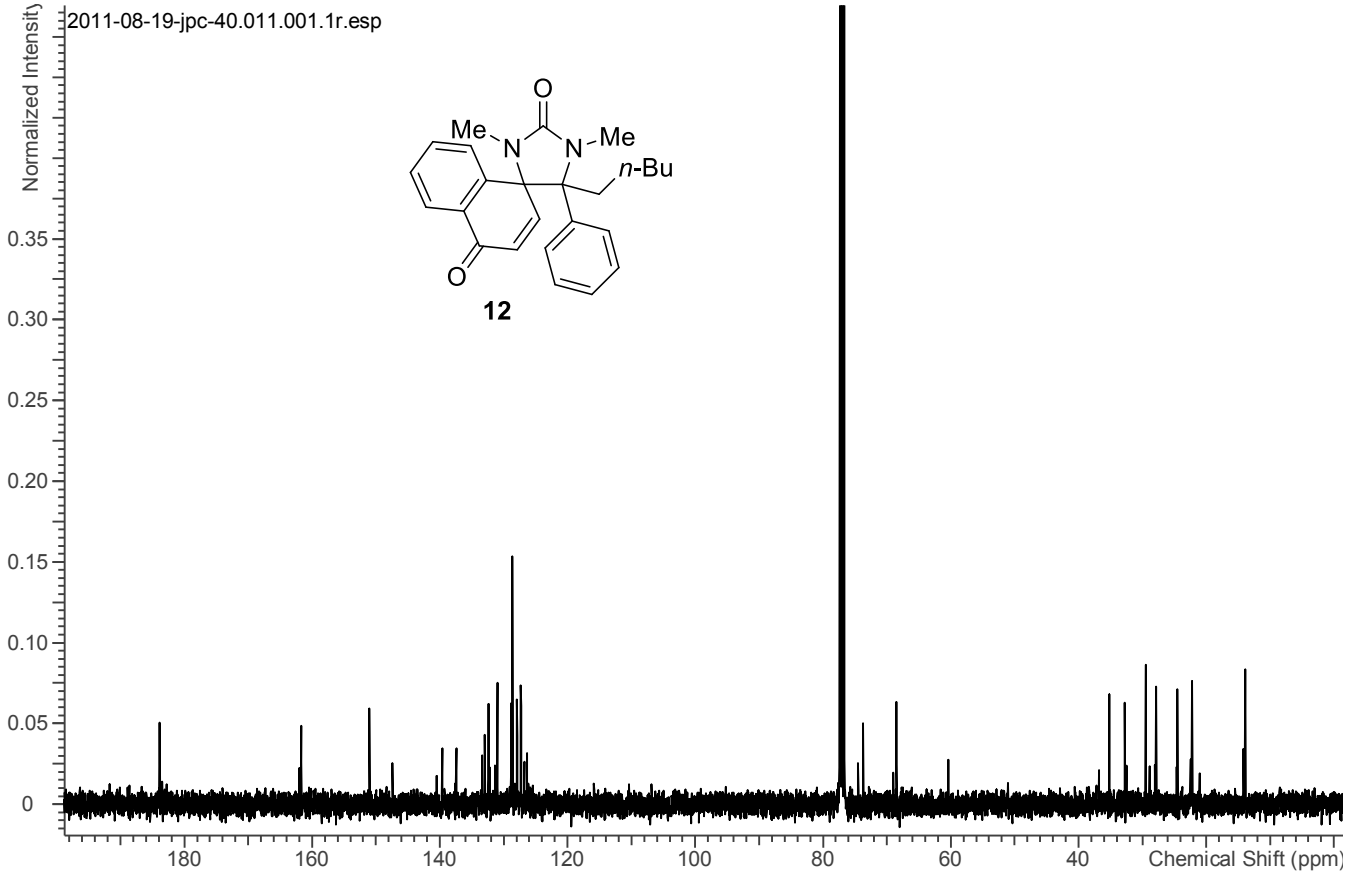
47


2012-06-26-jpc-31.010.001.1r.esp
Normalized Intensity
HN
N
O
iPr
10
11.87
1.00
0.98
1.02
2.99
3.01
2.17
2.11
3.29
Chemical Shift (ppm)


2012-04-27-jpc-33.010.001.1r.esp
Normalized Intensity
i-Pr
N
NH
O
Ph
11
1.0
0.5
0
13.24
1.00
1.04
1.05
3.02
1.17
1.49
3.38
9
8
7
6
5
4
3
2
Chemical Shift (ppm)


2012-04-23-jpc-5.011.001.1r.esp
VerticalScaleFactor = 1
i-Pr
N
NH
O
Ph
11
Chemical Shift (ppm)


2011-08-19-jpc-40.010.001.1r.esp
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Me
N
O
N
Me
n-Bu
O
12
0.98
1.21
0.78
1.13
0.99
1.25
0.78
1.49
4.65
3.44
9
8
7
6
5
4
3
2
Chemical Shift (ppm)


2011-08-19-jpc-40.011.001.1r.esp
Normalized Intensity
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
Me
N
O
N
Me
n-Bu
O
12
180
160
140
120
100
80
60
40
Chemical Shift (ppm)