Intermolecular Cope-Type Hydroamination of Alkynes Using Hydrazines

Pamela H. Cebrowski, Jean-Grégoire Roveda, Joseph Moran, Serge I. Gorelsky[‡] and André M. Beauchemin*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada, K1N 6N5

andre.beauchemin@uottawa.ca

Supporting Information

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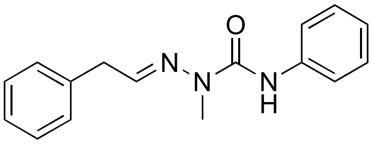
General Information. All reactions were performed in flame-dried or oven-dried glass round-bottomed flasks. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with UV light and an aqueous $KMnO_4$ or vanillin solution followed by heating.

^1H NMR spectra were recorded on a 300 or 400 MHz spectrometer at ambient temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded at 75 or 100 MHz. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained from the Ottawa-Carleton Mass Spectrometry Centre.

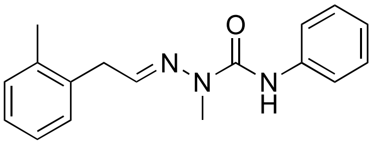
Materials. Dichloromethane, isopropanol, and toluene were dried by distillation over calcium hydride. Tetrahydrofuran and diethyl ether were dried by distillation over sodium/benzophenone ketyl. Methyl hydrazine was dried by distillation over barium oxide and phenyl isocyanate was dried by distillation over phosphorus pentoxide. Unless otherwise noted, all commercial materials were used without further purification.

General Procedure for Alkyne Hydroamination (Tables 1 and 2). An oven-dried sealed tube equipped with a magnetic stir bar and a rubber septum was purged with an argon balloon and an outlet for 10 minutes. Isopropanol (1.0 mL) was added, followed by methyl hydrazine (266 μL, 5.0 mmol) and the alkyne (1.0 mmol). The sealed tube was then closed and heated to 113 or 140 °C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for crude NMR analysis. ^1H NMR spectra of these solutions were recorded, and the % conversion calculated based on the ratio of the styrene alkene (1H) resonance at 5.78 ppm to the resonance corresponding to the product's hydrazone CH proton resonance (1H) at approximately 7.00 ppm or the product's CH_2 proton resonance (2H) at approximately 3.75 ppm. The method is estimated to have an error of approximately ±5%.[1] The crude reaction mixture was then concentrated and subjected to the following derivatization procedure without further purification.

General Procedure for Derivitization to Semicarbazide (Table 2). Prepared from a modified procedure by Bailey.[2] A flame-dried round bottomed flask charged with a magnetic stir bar and the hydrazone (0.60 mmol) was purged with argon for 15 minutes. Methylene chloride (6.0 mL) was added and the solution was cooled to 0˚C. Triethylamine (209 μL, 1.20 mmol) was added, followed by phenyl isocyanate (130 μL, 1.50 mmol). The reaction was allowed to warm to room temperature, and stirred for another 3 hours. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the semicarbazide.



2-Methyl-4-phenyl-1-(2-phenylethylidene)semicarbazide (4a, Table 2, Entry 1). The crude yellow oil was purified by column chromatography (40% Et_2O/hexanes) and isolated as a colourless oil (777 mg, 58% yield). TLC R_f 0.27 (40% Et_2O/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.66 (br, 1H), 7.54 (ap dd, *J* = 8.61, 1.03 Hz, 2H), 7.46-7.27 (m, 8H), 7.08 (td, *J* = 14.77, 1.13 Hz, 1H), 7.03 (t, *J* = 5.26, 5.26 Hz, 1H), 3.75 (d, *J* = 5.23 Hz, 2H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 138.6, 138.5, 136.8, 129.1, 128.9, 128.8, 126.9, 122.9, 119.2, 39.5, 27.7; IR (film): 3378, 1690, 1591, 1524, 1442, 1124, 1014, 754, 693 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{17}N_3O$ $[M]^+$: 267.1372. Found: 267.1392.



2-Methyl-4-phenyl-1-(2-o-tolylethylidene)semicarbazide (4c, Table 2, Entry 2). Procedure as indicated above except used 1.5 equivalents of triethylamine (421 μL, 3.02 mmol) and 1.2 equivalents of phenylisocyanate (264 μL, 2.42 mmol). The crude yellow oil was purified by column chromatography (20% EtOAc/hexanes) and isolated as a colourless oil (370 mg, 50% yield). TLC R_f 0.50 (30% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.53 (br, 1H), 7.44 (dd, *J* = 8.8, 1.2 Hz, 2H), 7.32-7.27 (m, 2H), 7.25-7.18 (m, 4H), 7.04 (tt, *J* = 7.6, 1.2 Hz, 1H), 6.97 (t, *J* = 5.2 Hz, 1H), 3.71 (d, *J* = 4.8 Hz, 2H), 3.25 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 138.6, 137.7, 136.6, 135.2, 130.5, 129.6, 128.8, 127.1, 126.3, 122.8, 119.0, 37.2, 27.5, 19.6; IR (film): 3381, 3351, 1692, 1591, 1526, 1442, 1123, 1014, 751, 693 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ $[M]^+$: 281.1528. Found: 281.1531.

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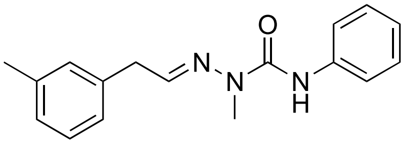
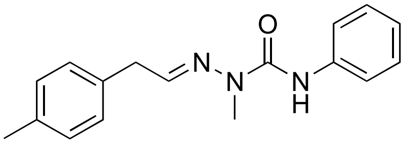
[1] Control experiments have been performed to ensure that styrene is a suitable standard due to the apparent possibility of overestimation of conversion due to slower relaxation times of olefinic protons compared to aliphatic protons. Increased T1 relaxation times led to similar conversion values and, most importantly, isolated yields (see reference 4 of the manuscript) have always been in very good agreement with conversions calculated using styrene.

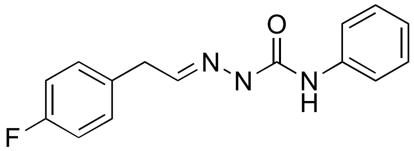
[2] M. D. Bailey, T. Halmos, N. Goudreau, E. Lescop, M. Llinas-Brunet, *J. Med. Chem.* **2004**, *47*, 3788.



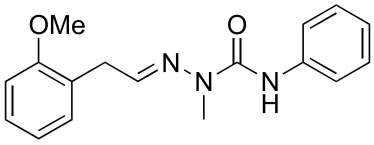
2-Methyl-4-phenyl-1-(2-m-tolylethylidene)semicarbazide (4d, Table 2, Entry 3). The crude yellow oil was purified by column chromatography (10-30% EtOAc/hexanes) and isolated as a pale yellow oil (339 mg, 49% yield). TLC R_f 0.39 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (br, 1H), 7.50 (ap dd, J = 8.8, 1.2 Hz, 2H), 7.31 (dd, J = 10.0, 8.4 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.12-7.02 (m, 4H), 6.99 (t, J = 5.6 Hz, 1H), 3.68 (d, J = 5.2 Hz, 2H), 3.26 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 138.6, 138.6, 138.5, 136.7, 129.7, 128.9, 128.7, 127.6, 126.0, 122.9, 119.1, 39.4, 27.6, 21.4; IR (film): 3366, 2925, 1686, 1593, 1522, 1443, 1310, 1231, 1123, 1009, 753, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ $[M]^+$: 281.1528. Found: 281.1530.



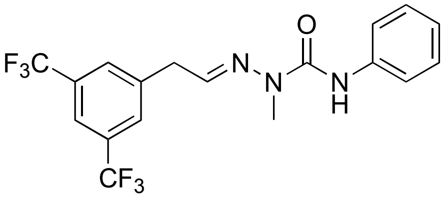
2-Methyl-4-phenyl-1-(2-p-tolylethylidene)semicarbazide (4b, Table 2, Entry 4). The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a colourless oil (104 mg, 37% yield). TLC R_f 0.49 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.63 (br, 1H), 7.49 (ap dd, J = 8.7, 1.2 Hz, 2H), 7.34-7.29 (m, 2H), 7.21-7.14 (m, 4H), 7.05 (tt, J = 14.7, 1.2 Hz, 1H), 6.96 (t, J = 5.1 Hz, 1H), 3.68 (d, J = 5.1 Hz, 2H), 3.25 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 138.7, 138.6, 136.5, 133.7, 129.4, 128.9, 128.8, 122.8, 119.0, 39.0, 27.5, 21.0; IR (film): 3381, 3340, 1690, 1591, 1526, 1442, 1123, 1014, 753, 693 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ $[M]^+$: 281.1528. Found: 281.1514.



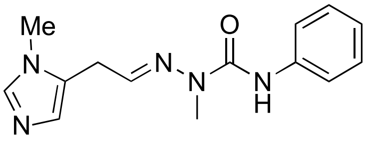
1-(2-(4-Fluorophenyl)ethylidene)-2-methyl-4-phenylsemicarbazide (4e, Table 2, Entry 5). The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a white solid (528 mg, 44% yield). TLC R_f 0.45 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.61 (br, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.27-7.17 (m, 2H), 7.10-7.01 (m, 3H), 6.96 (t, J = 7.7 Hz, 1H), 3.67 (d, J = 5.2 Hz, 2H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7 (d, J = 248.9 Hz), 152.7, 138.4, 138.1, 132.4 (d, J = 3.3 Hz), 130.4 (d, J = 7.9 Hz), 128.8, 122.8, 119.0, 115.4 (d, J = 21.4 Hz), 38.4, 27.4; IR (film): 3376, 1688, 1591, 1527, 1509, 1443, 1221, 1125, 1015, 753, 693 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}FN_3O$ $[M]^+$: 285.1277. Found: 285.1265.



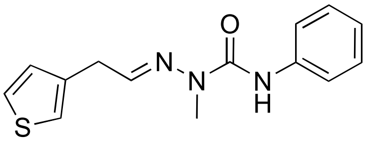
2-Methyl-4-phenyl-1-(2-(2-methoxyphenyl)ethylidene)semicarbazide (4f, Table 2, Entry 6). Procedure as indicated above except used 1.5 equivalents of triethylamine (318 μL, 2.28 mmol) and 1.2 equivalents of phenylisocyanate (218 μL, 1.83 mmol). The crude yellow oil was purified by column chromatography (20% EtOAc/hexanes) and isolated as a yellow oil (276 mg, 40% yield). TLC *R*$_f$ 0.47 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.62 (br, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.32-7.28 (m, 3H), 7.21 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.06-7.01 (m, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.71 (d, *J* = 5.2 Hz, 2H), 3.86 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 157.3, 153.0, 138.7, 138.5, 130.4, 128.8, 128.2, 125.4, 122.7, 120.6, 119.0, 110.5, 55.4, 34.0, 27.5; IR (film): 3375, 2941, 1690, 1591, 1526, 1442, 1244, 1122, 1015, 753, 695 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ [M]$^+$: 294.1477. Found: 297.1483.



1-(2-(3,5-bis(Trifluoromethyl)phenyl)ethylidene)-2-methyl-4-phenylsemicarbazide (4h, Table 2, Entry 8). The crude yellow oil was purified by column chromatography (20-45% EtOAc/hexanes) and isolated as a yellow solid (260 mg, 31% yield). TLC *R*$_f$ 0.38 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.46 (br, 1H), 7.83 (s, 1H), 7.73 (s, 2H), 7.46 (ap d, *J* = 8.1, 2H), 7.30 (ap t, J = 7.5, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (t, J = 5.1, 1H), 3.84 (d, *J* = 5.1, 2H), 3.27 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 152.6, 139.4, 138.3, 135.8, 132.2 (q, *J* = 33.4 Hz), 129.3 (ap d, *J* = 2.7 Hz), 129.0, 123.24, 123.22 (q, J = 272.8 Hz), 121.2-121.0 (m), 119.3, 39.0, 27.9; IR (film): 3383, 3058, 2948, 1694, 1593, 1528, 1444, 1378, 1279, 1172, 1131, 1016, 892, 754, 684 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{18}H_{15}F_6N_3O$ [M]$^+$: 403.1119. Found: 403.1123.



2-Methyl-1-(2-(1-methyl-1H-imidazol-5-yl)ethylidene)-4-phenylsemicarbazide (4i, Table 2, Entry 9). The crude yellow oil was purified by column chromatography (5% MeOH/CH$_2$Cl$_2$) and isolated as a colourless oil (421 mg, 55% yield). TLC *R*$_f$ 0.17 (5% MeOH/CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.45 (br, 1H), 7.47-7.40 (m, 3H), 7.28 (t, *J* = 7.9, Hz, 2H), 7.02 (ap t, *J* = 7.4 Hz, 1H), 6.91-6.84 (m, 2H), 3.66 (d, *J* = 4.8 Hz, 2H), 3.55 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 152.5, 138.3, 138.2, 135.2, 128.8, 127.7, 126.6, 122.9, 118.9, 31.4, 28.0, 27.6; IR (film): 3374, 1686, 1591, 1526, 1443, 1234, 1123, 1013, 755, 694 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{17}N_5O$ [M]$^+$: 271.1433. Found: 271.1459.



2-Methyl-4-phenyl-1-(2-(thiophen-3-yl)ethylidene)semicarbazide (4j, Table 2, Entry 10). The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a colourless oil (341 mg, 45% yield). TLC *R*f 0.46 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (br, 1H), 7.51 (ap dd, *J* = 8.4, 1.2 Hz, 2H), 7.36-7.92 (m, 3H), 7.10-7.01 (m, 3H), 6.98 (t, *J* = 5.2 Hz, 1H), 3.72 (d, *J* = 5.2 Hz, 2H), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 138.4, 137.7, 136.7, 128.7, 128.2, 126.0, 122.8, 121.9, 119.0, 33.8, 27.5; IR (film): 3378, 1686, 1590, 1523, 1442, 1313, 1230, 1123, 1014, 752, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{15}N_3OS$ $[M]^+$: 273.0936. Found: 273.0935.

Computational Details

Density functional theory (DFT) calculations have been performed using the *Gaussian 03* program.[3] Optimized molecular geometries were calculated using the B3LYP[4] exchange-correlation functional.

The triple-zeta TZVP[5] basis set and tight SCF convergence criteria were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate free energies of the species. Reaction coordinate scans[6] were performed to verify that the calculated TSs connects the correct minima for a given reaction step. The unscaled vibrational frequencies were used for calculating Gibbs free energies of the species (at 298K and 1 atm). The basis set superposition errors (BSSE) were evaluated using the Boys-Bernardi counterpoise method.[7] However, because all calculated corrections were sufficiently low (less than 0.6 kcal/mol) for the basis set employed, the correction were not included in the calculation of the energies of the species.

Solvation free energies of all species in methanol were calculated to probe the solvent effect for reaction barriers using the polarizable continuum model (PCM)[8] with the united atom topological radii (UAHF). The calculated solvation free energies were used to calculate the free energies of the species in solution. The results of these calculations summarized in Tables S1-S2.

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3. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.01*, Gaussian, Inc.: 2003.
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5. A. Schafer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829-5835.
6. (a) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154. (b) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523.
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8. M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43

Table S1. Free energies (kcal/mol) of the reaction species for the reactions of NH_2NH_2 with alkenes and alkynes (evaluated at 298K and 1 atm). The energies are relative to the free reactants. Free energies of the transition states in methanol are shown in parenthesis.

	Alkenes	Alkynes		
Species	C_2H_4	C_2H_2	C_8H_6 AM	C_8H_6 M
RC [a]	5.4	3.3	4.5	4.5
TS [b]	45.3 (43.4)	37.8 (33.6)	40.1 (34.9)	40.1 (42.4)

a) Reactants complex; b) see Figure S1 for the structures.

Table S2. Free energies (kcal/mol) of the reaction species for the reactions of NH_2NHCH_3 with C_8H_6 (evaluated at 298K and 1 atm). The energies are relative to the free reactants. Free energies of the transition states in methanol are shown in parenthesis.

Species	C_8H_6 AM_a	C_8H_6 AM_b	C_8H_6 AM_c	C_8H_6 M_a	C_8H_6 M_b	C_8H_6 M_c
RC [a]	4.5	5.5	5.5	4.5	5.5	5.5
TS [b]	41.5 (38.3)	39.1 (36.3)	39.1 (37.3)	40.5 (44.4)	40.6 (43.9)	40.7 (44.4)

a) Reactants complex; b) see Figure S2 for the structures.

Discussion on solvent effects.

Solvent effects are often important in organic transformations. As such, we decided to compare the values obtained in the gas phase with values for all species in methanol, which were calculated using the polarizable continuum model (PCM)[8] as discussed previously. We consider both values as extremes, with real values in *i*-PrOH being likely lying somewhere in this continuum. While both systems predict preference for the anti-Markovnikov, linear hydrazone products, the rationale and predicted regioselectivity are quite different. Our observed selectivities (varying from 5 to 17 : 1 in various solvents with C_8H_6 as substrate, see Table 1) are more consistent with the regioselectivity predicted in the gas phase (1.4 kcal/mol) than that predicted in MeOH (7.6 kcal/mol). In the latter case, the predicted, increased regioselectivity is a consequence of the preferential TS stabilization of the polar nature of the TS leading to the anti-Markovnikov (linear) hydrazones (6.1D for anti-Markovnikov TSs vs. ~2.5D for Markovnikov TSs, see Figure S2).

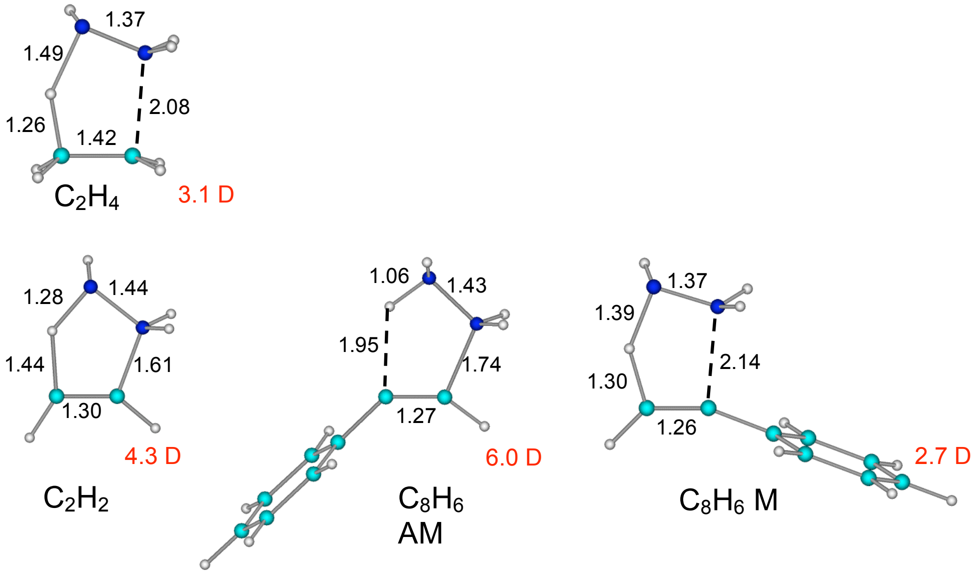


Figure S1. Transition state structures for the reaction of NH_2NH_2 with C_2H_4, C_2H_2 and C_8H_6. The internuclear distances (Å) are shown only for relevant chemical bonds. Calculated dipole moments (Debye) of the species in the gas phase are shown in red.

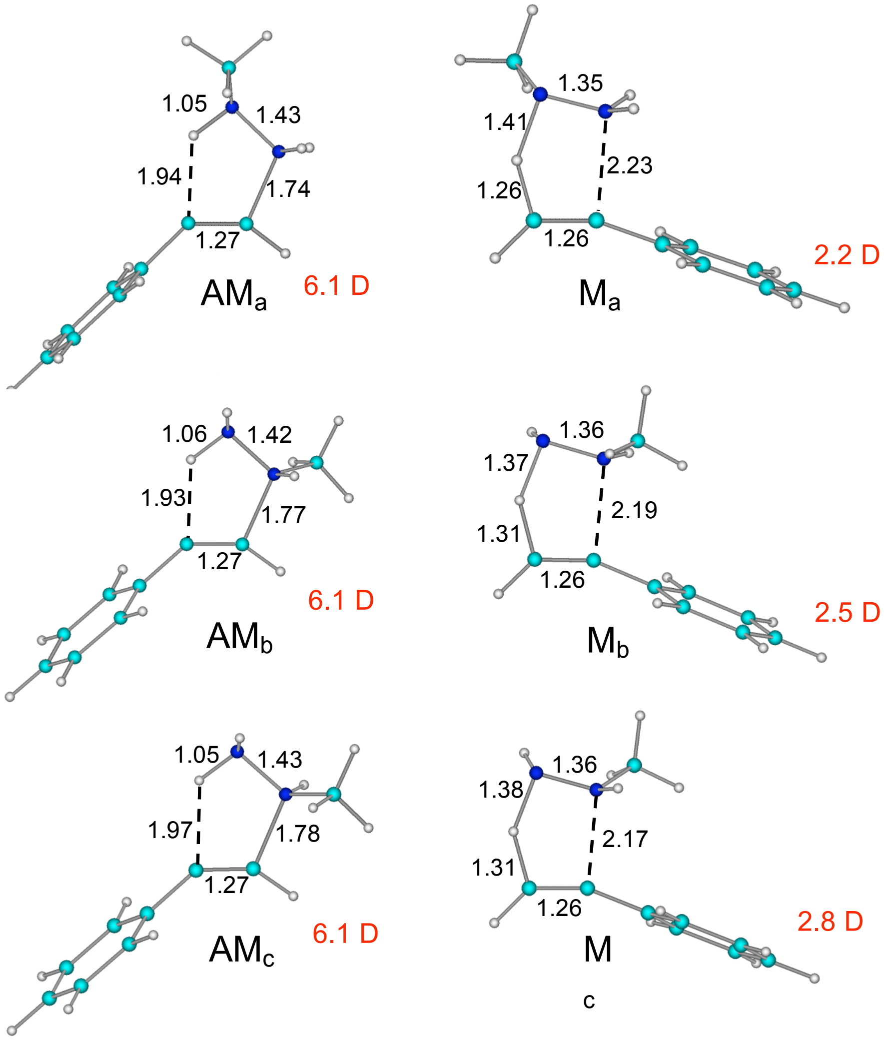


Figure S2. Transition state structures for the reaction of NH_2NHCH_3 with C_8H_6. The internuclear distances (Å) are shown only for relevant chemical bonds. Calculated dipole moments (Debye) of the species in the gas phase are shown in red.

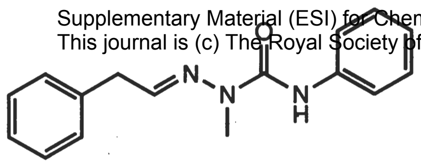
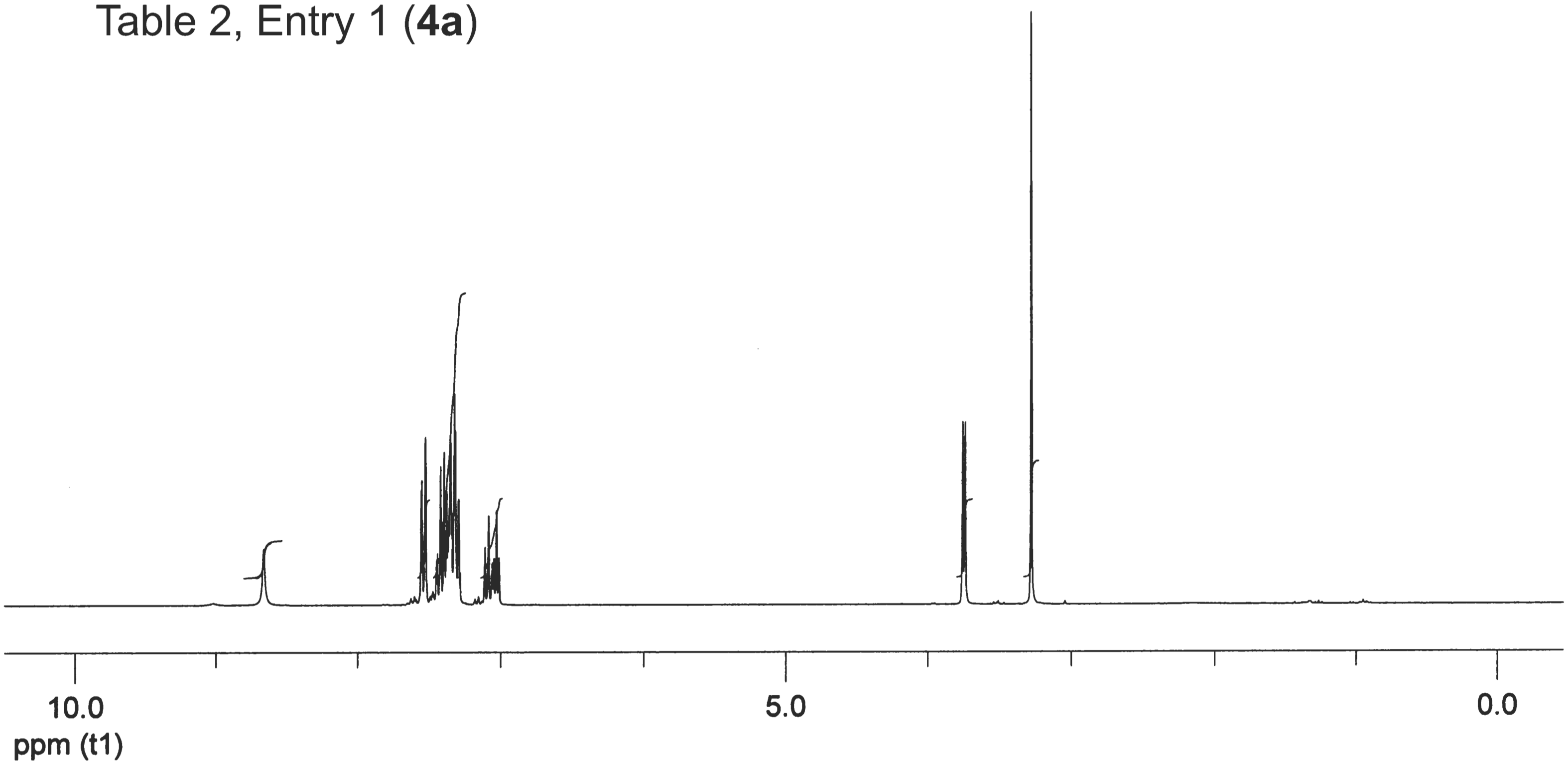
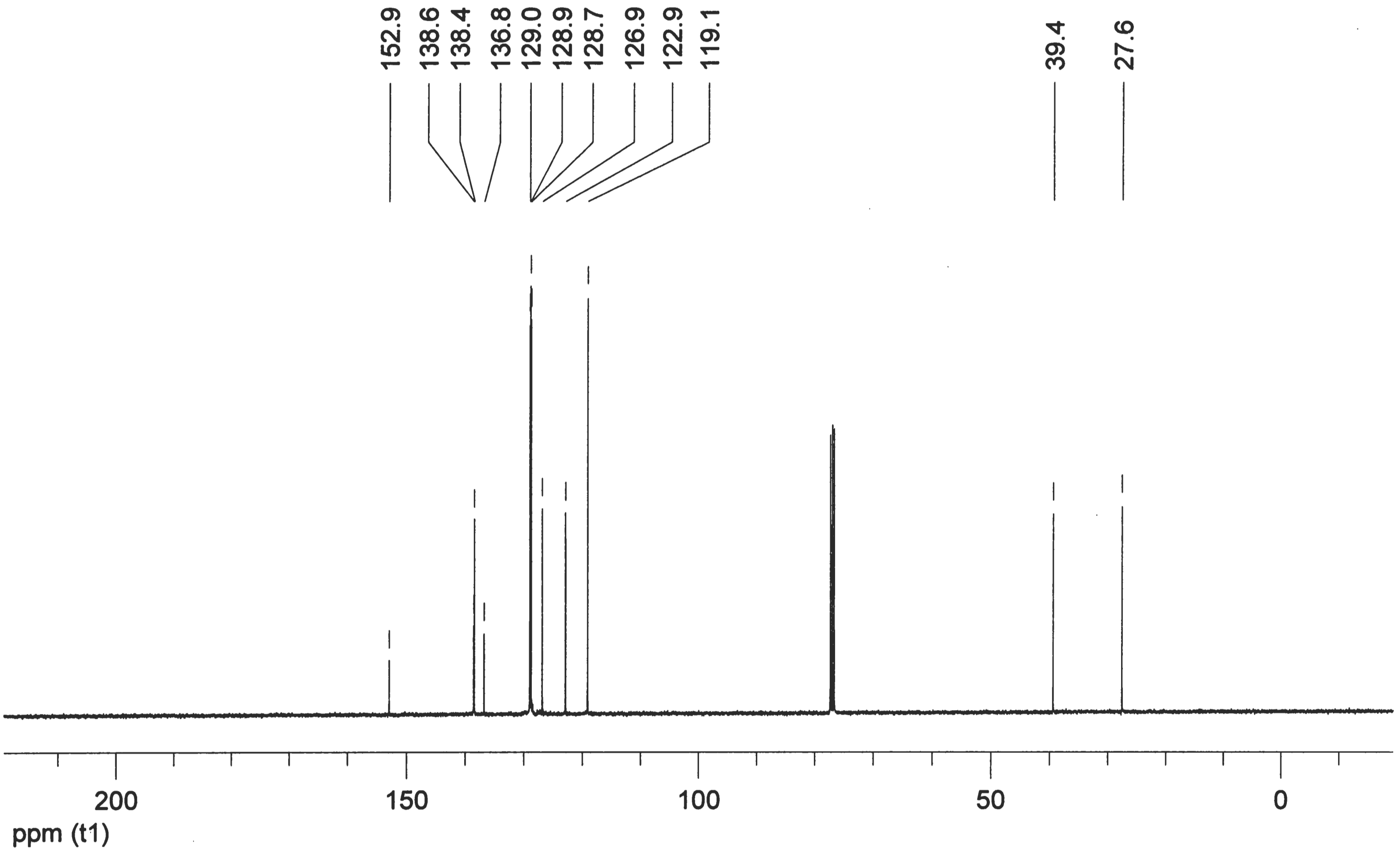


Table 2, Entry 1 (**4a**)





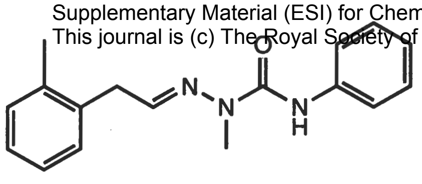
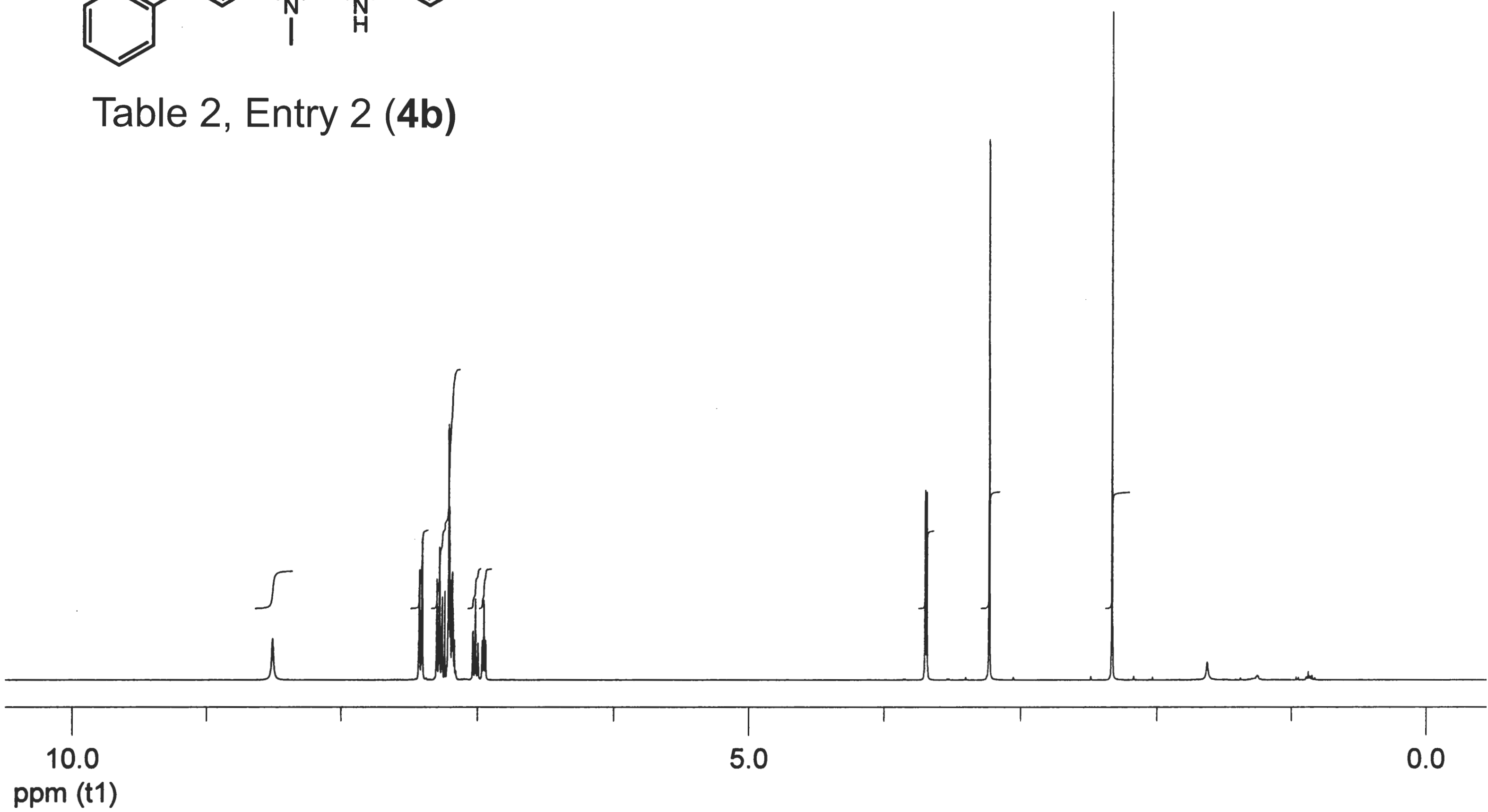
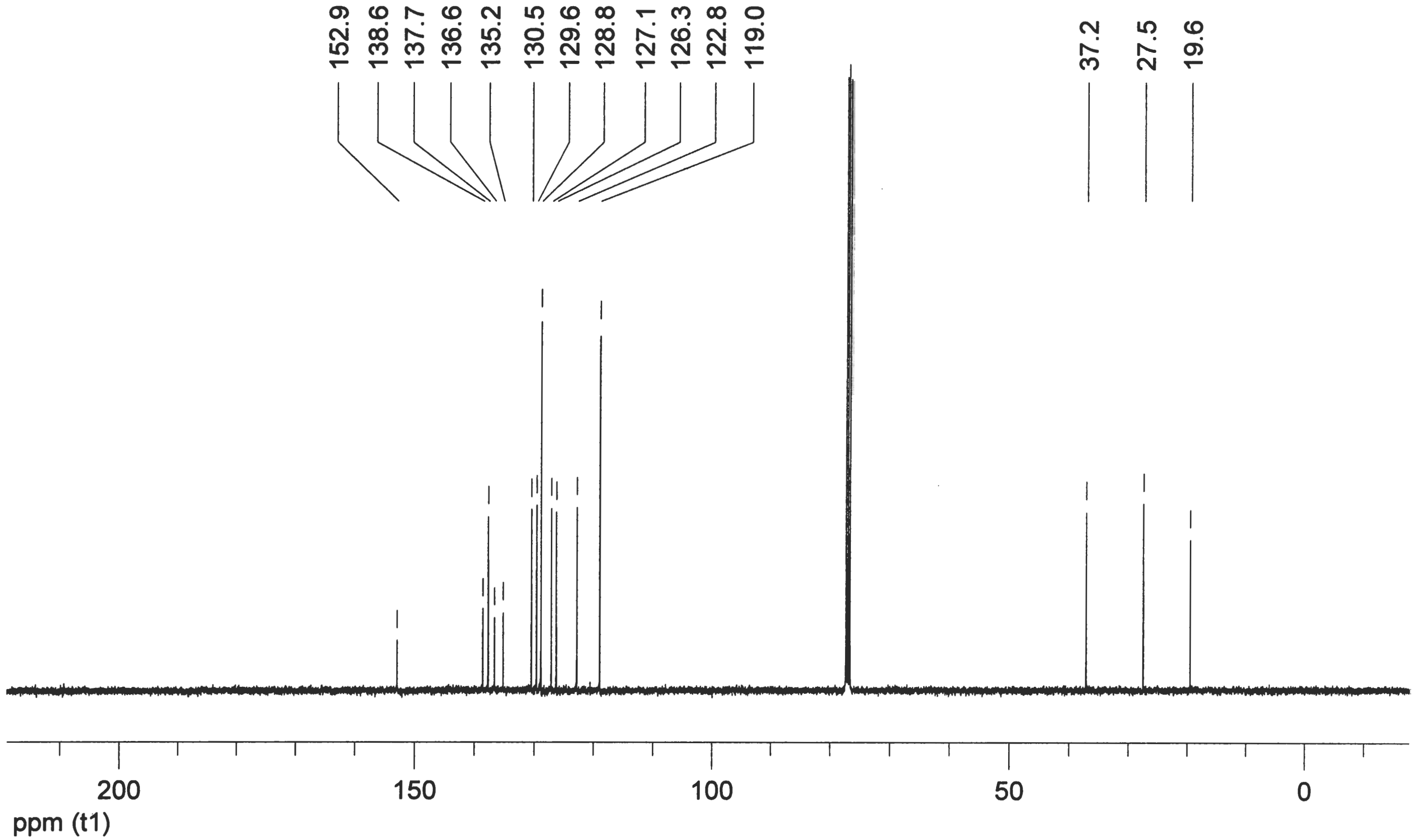


Table 2, Entry 2 (**4b**)





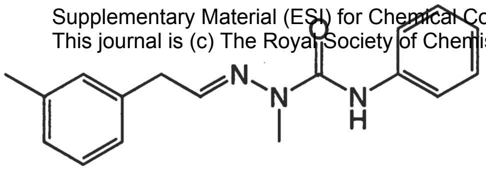
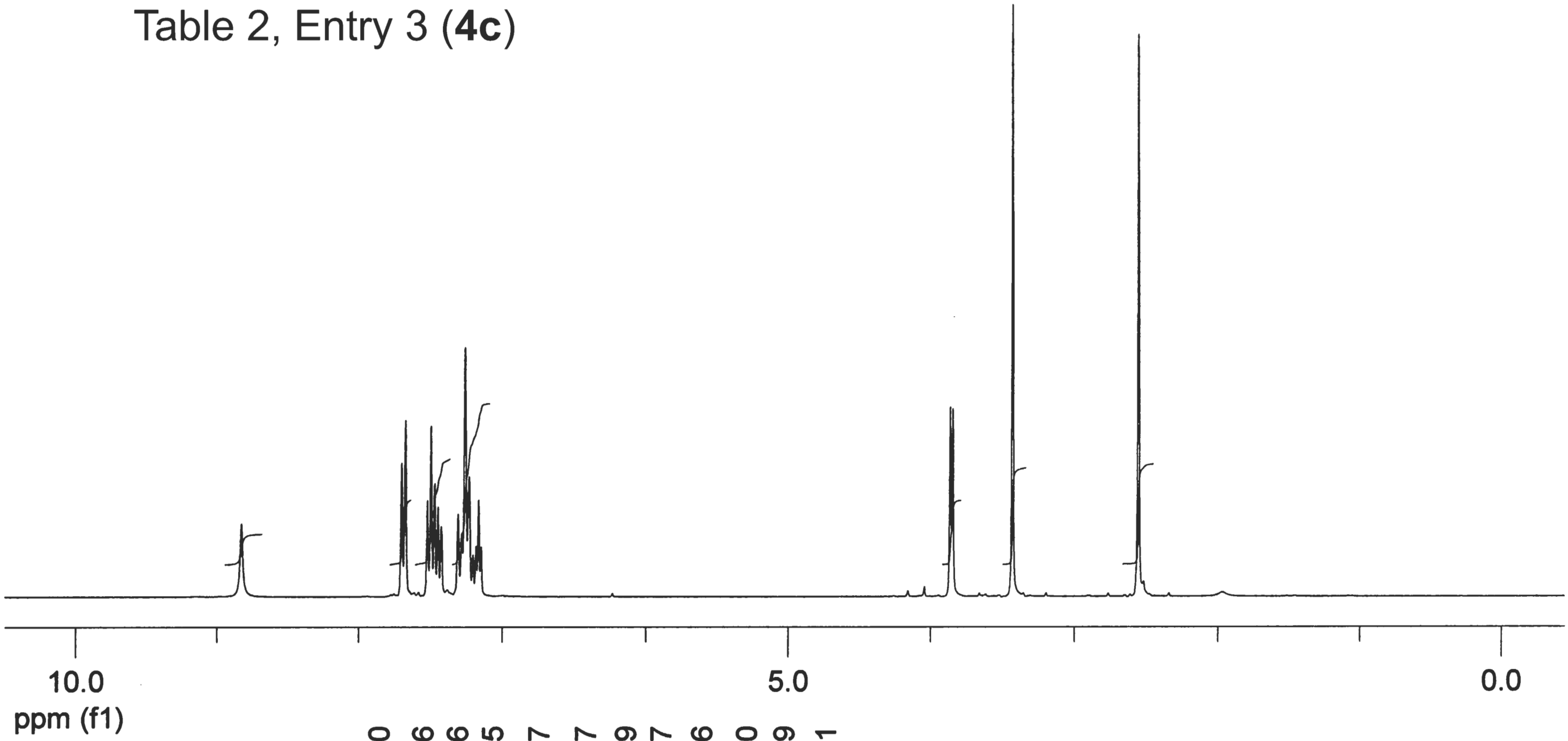
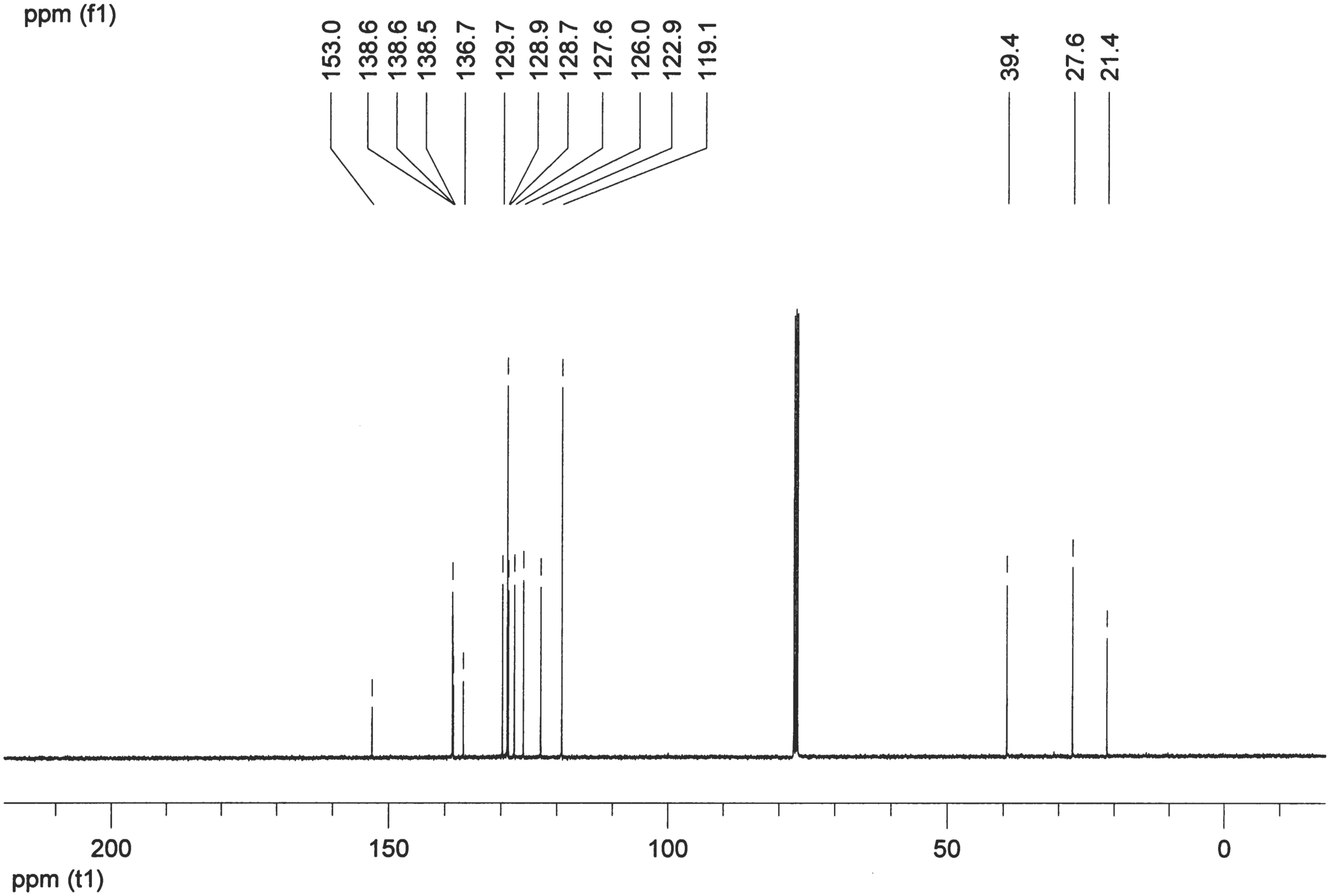


Table 2, Entry 3 (**4c**)





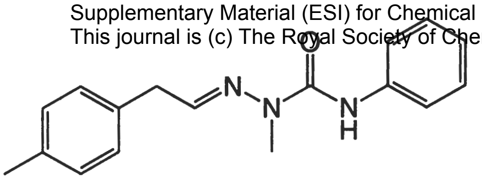
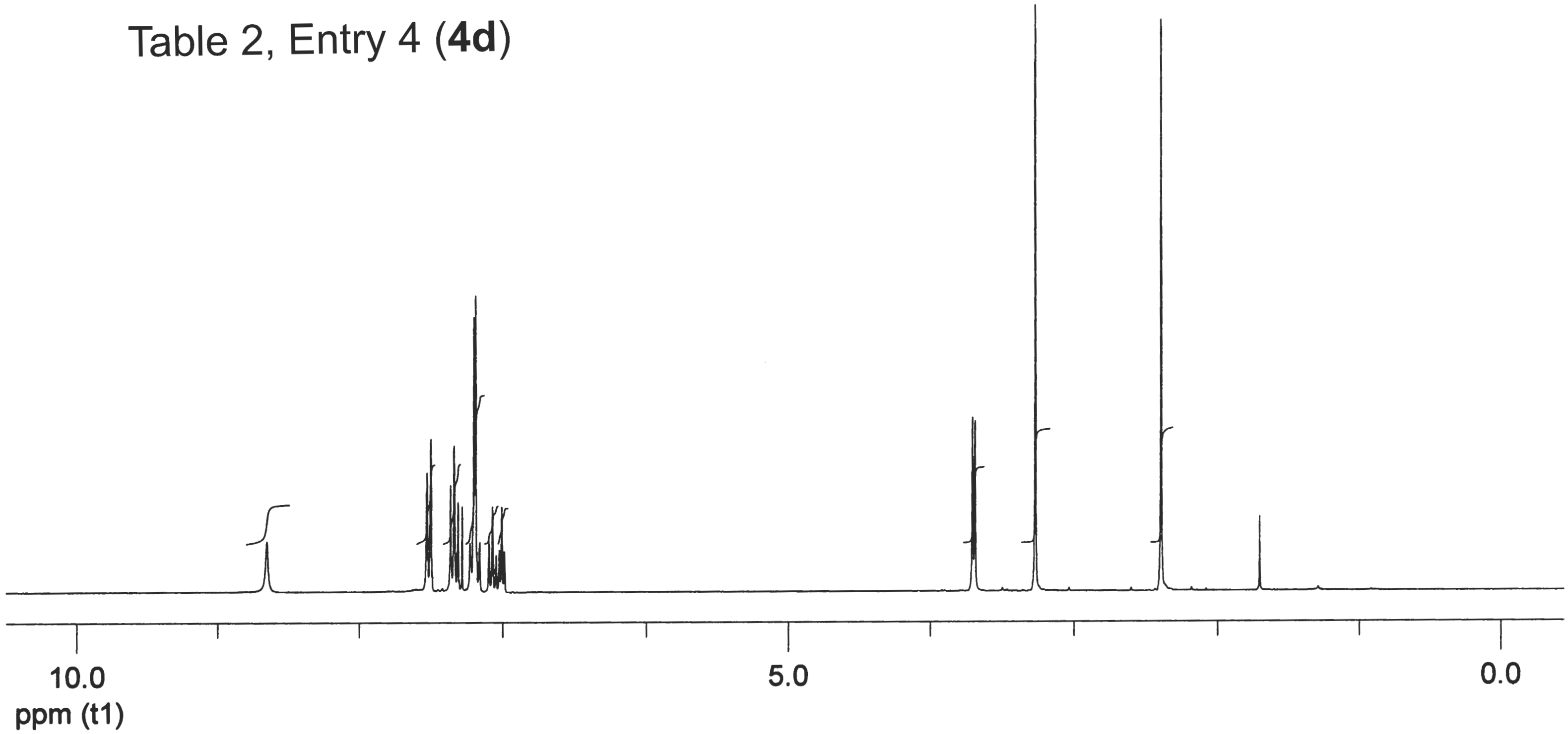
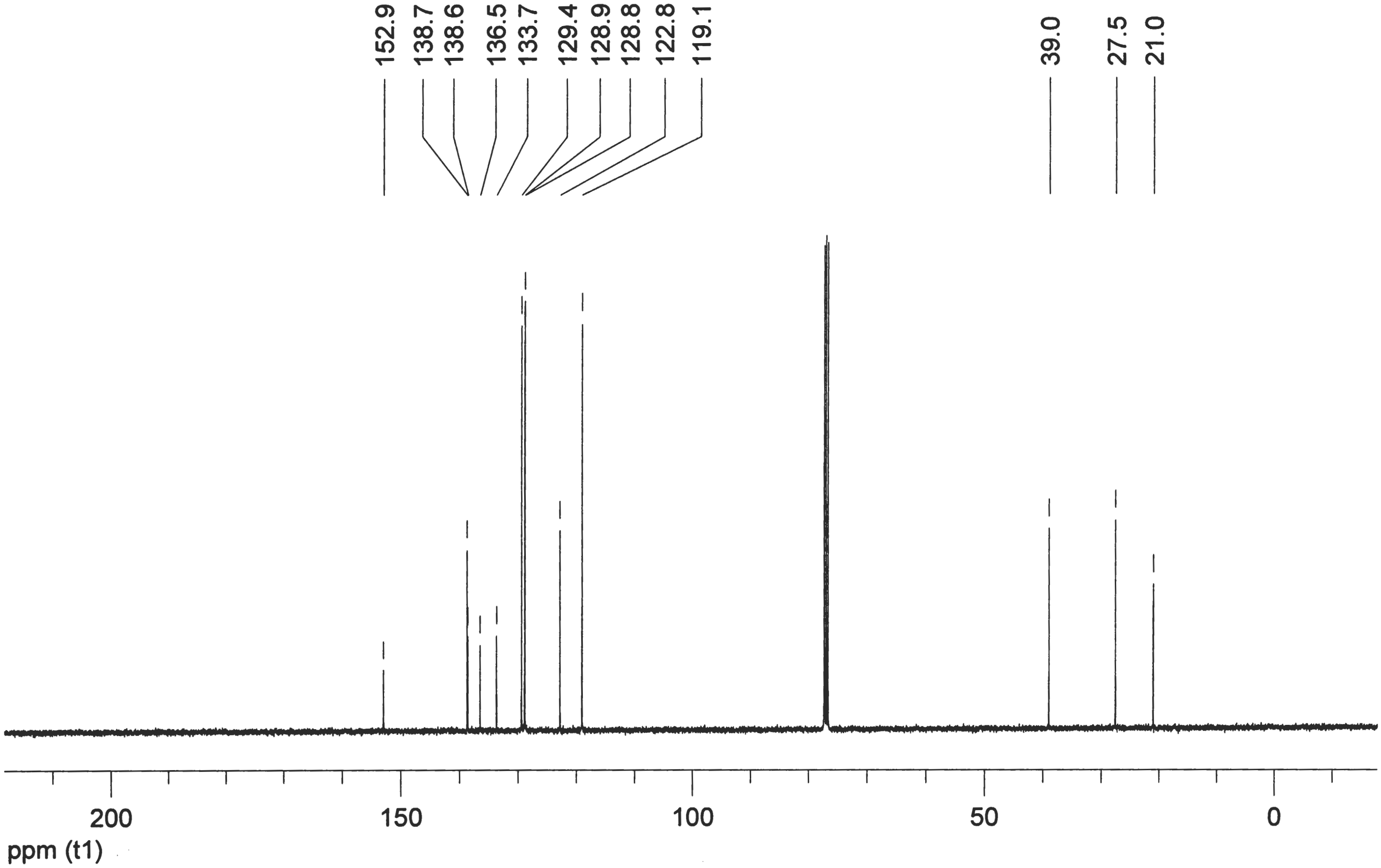


Table 2, Entry 4 (**4d**)





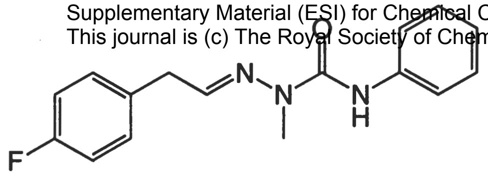
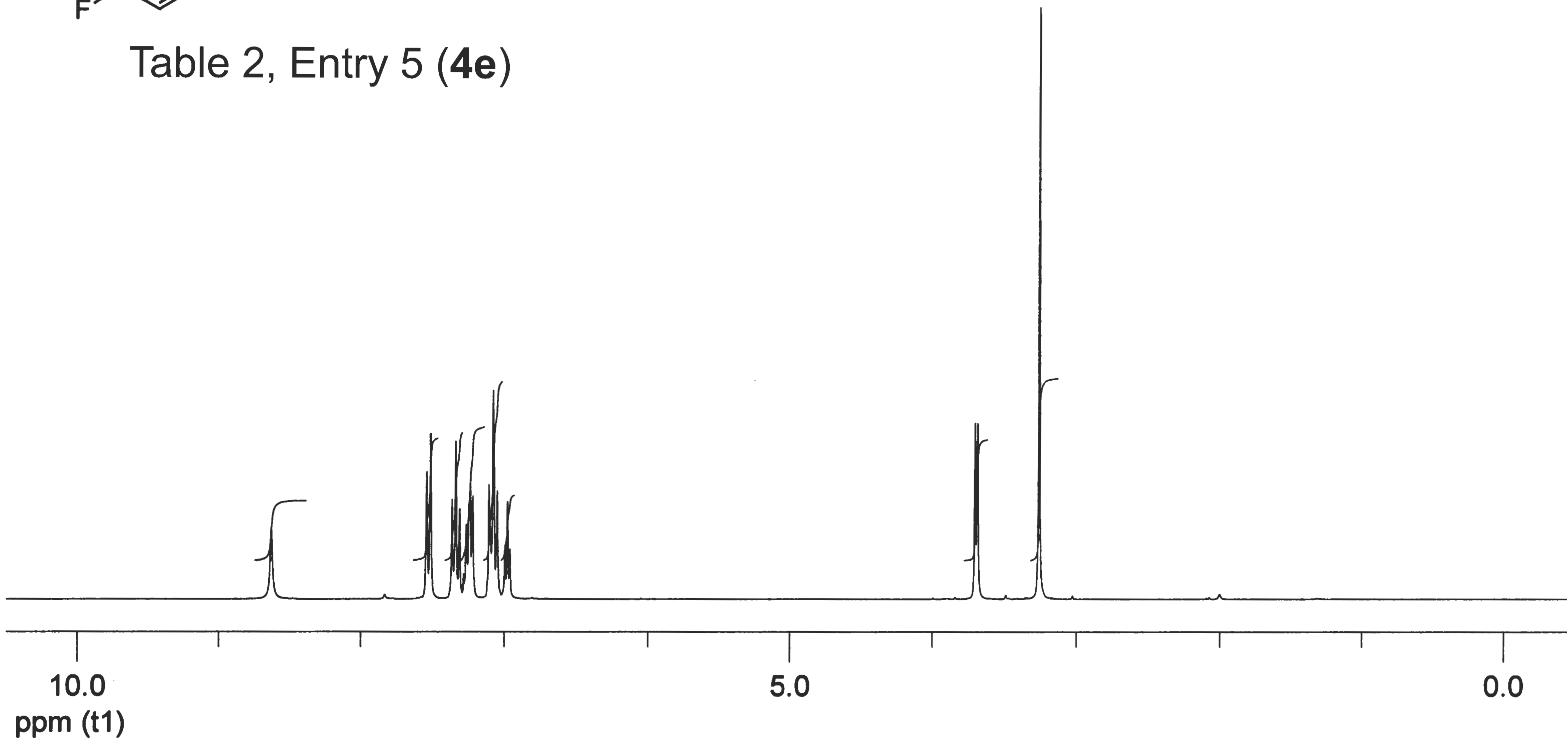
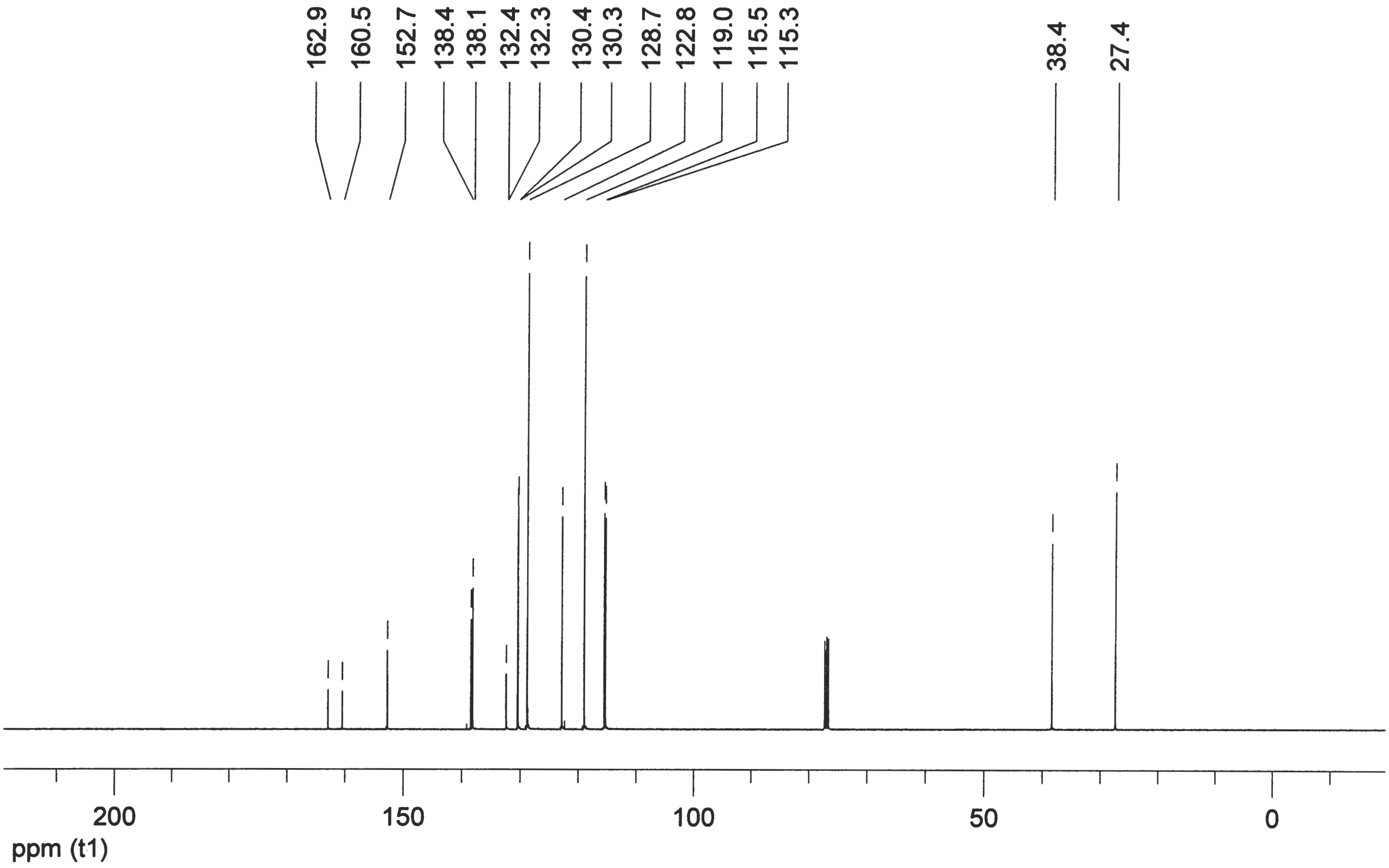


Table 2, Entry 5 (**4e**)





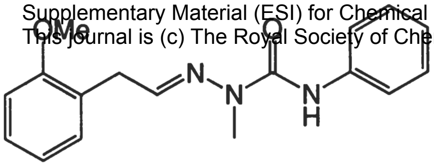
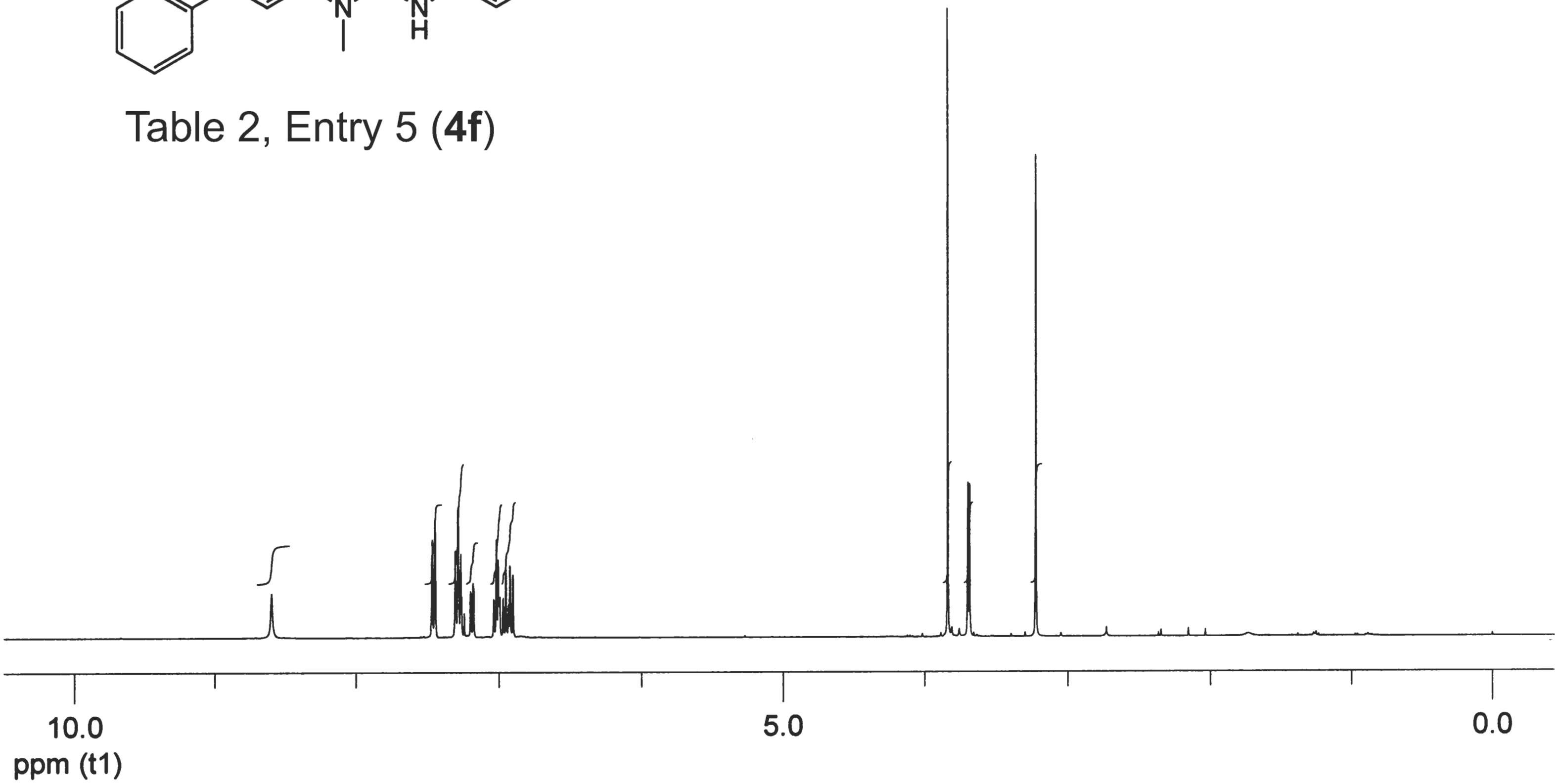
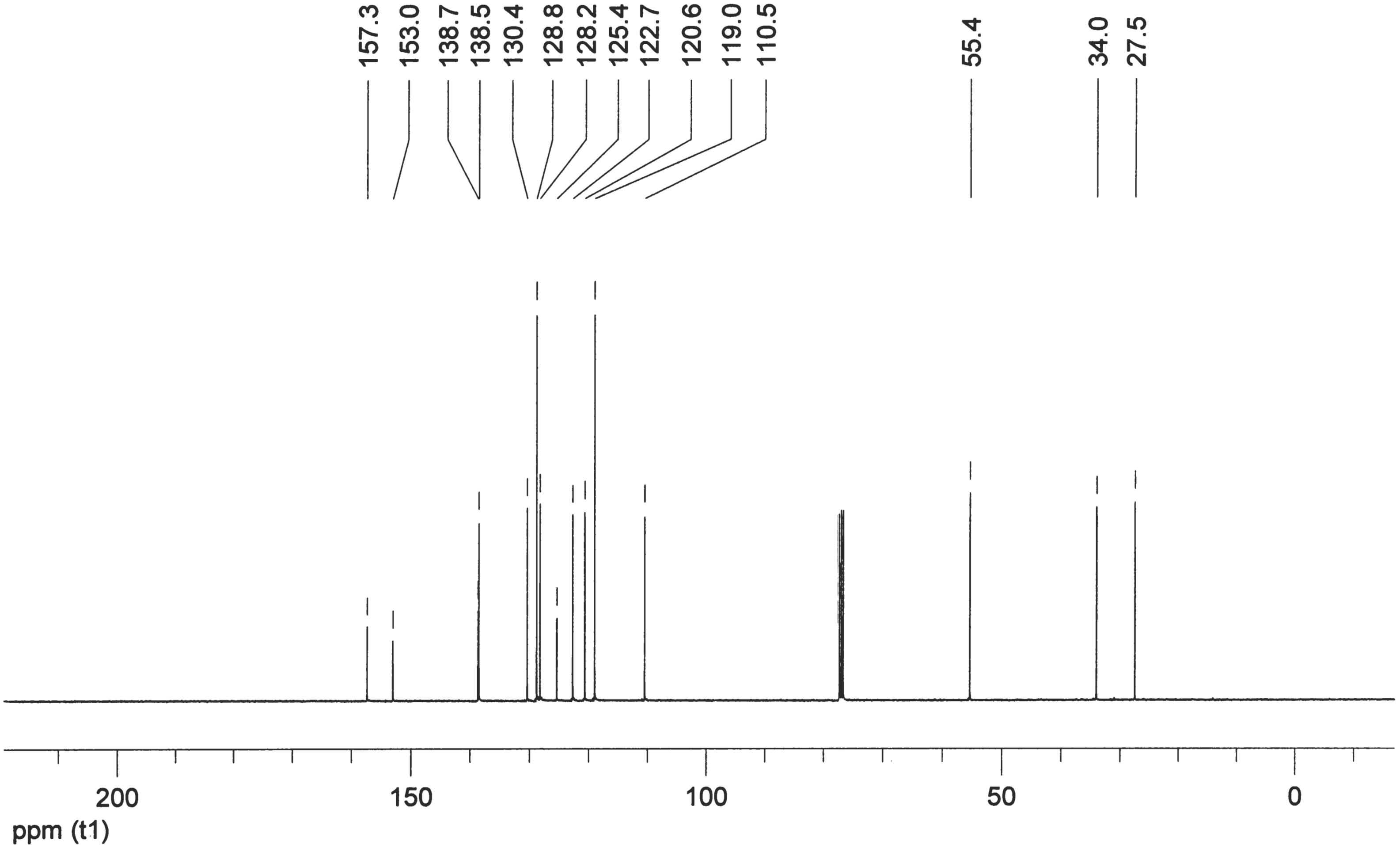


Table 2, Entry 5 (**4f**)





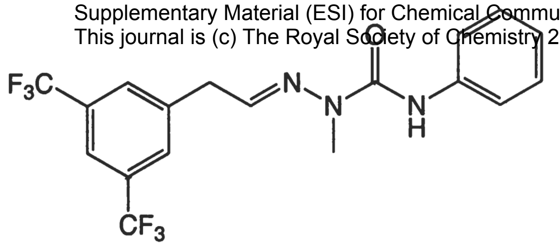
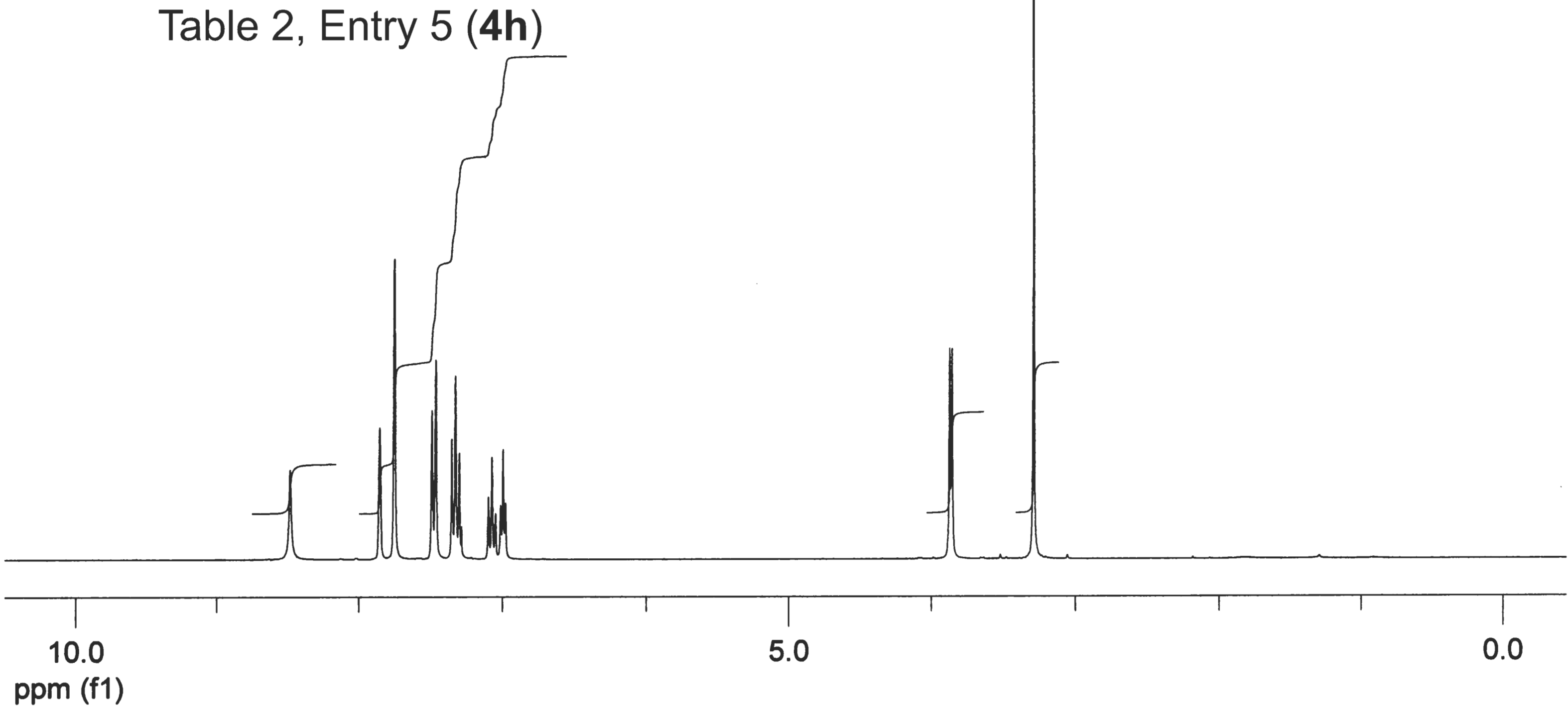
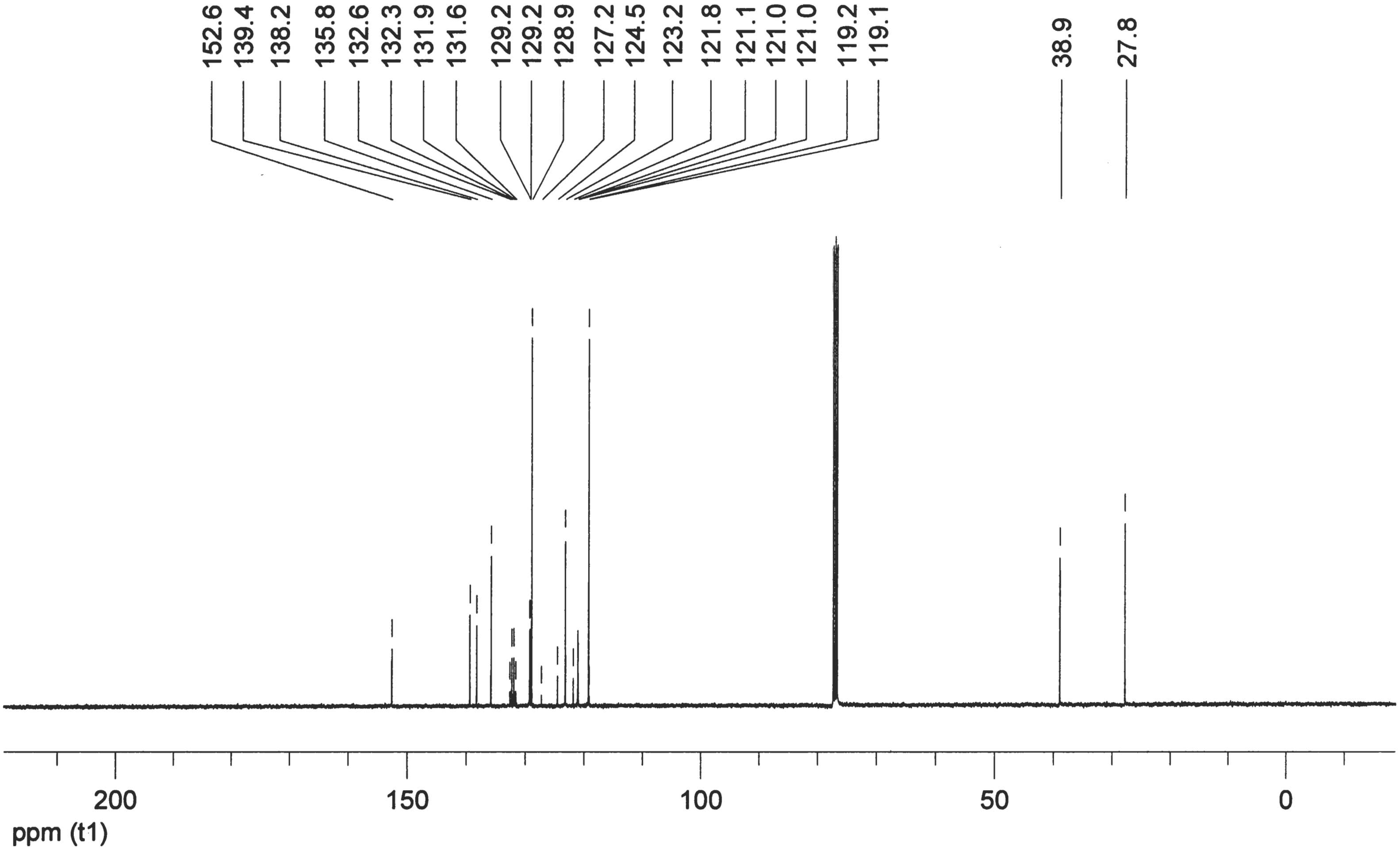


Table 2, Entry 5 (**4h**)





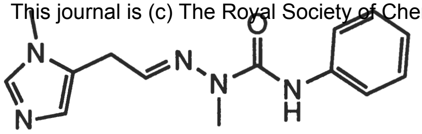
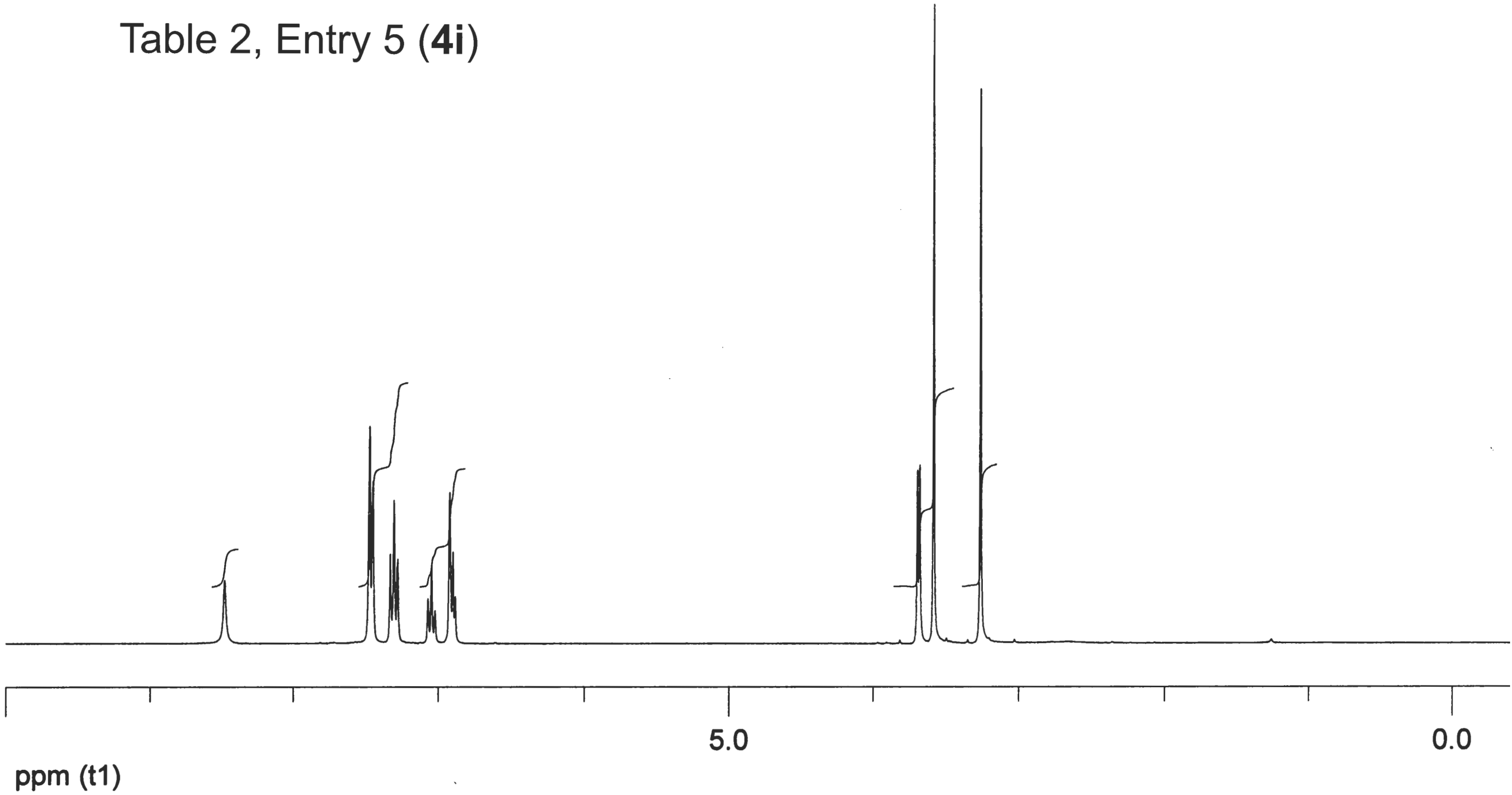
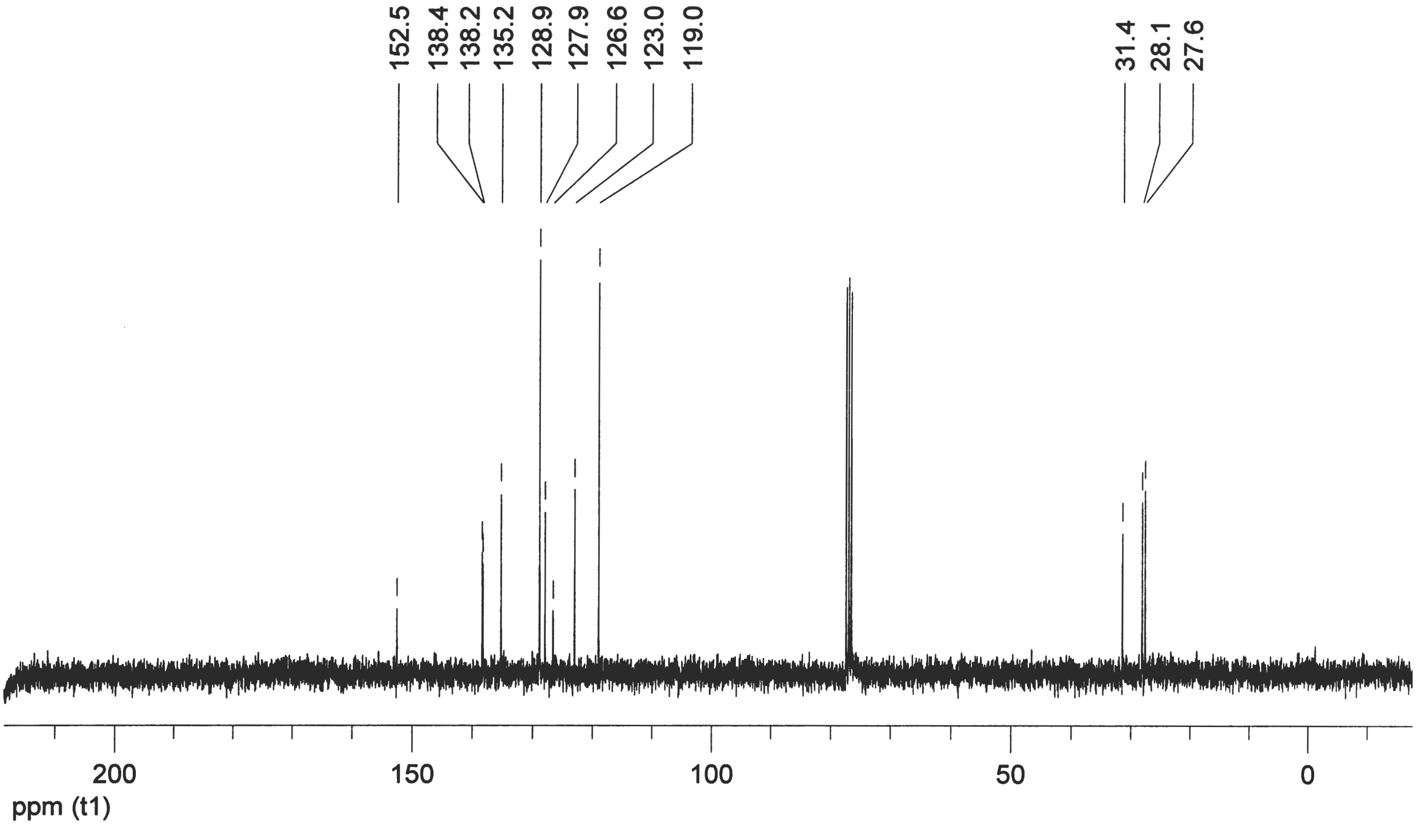


Table 2, Entry 5 (**4i**)





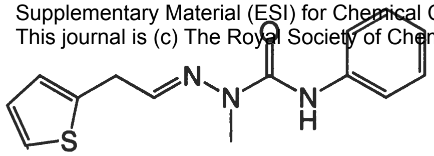


Table 2, Entry 5 (**4j**)