Supporting Information

Sonogashira Coupling of Functionalized Trifloyl Oxazoles and Thiazoles with Terminal Alkynes: Synthesis of Disubstituted Heterocycles.

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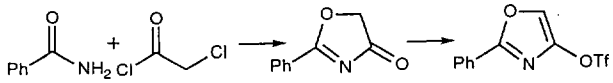
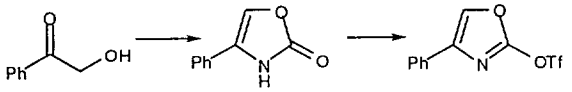
Experimental section: ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 400 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million using the solvent internal standard (chloroform, 7.24 and 77.00 ppm, respectively). Infrared resonance spectra were recorded on a Nexus™ 670 FTIR spectrometer. High resolution mass spectra were obtained on a Finigan™ MAT-90 spectrometer. CH_3CN, THF, benzene, toluene, and CH_2Cl_2 were obtained from a dry solvent system (alumina) and used without further drying. 1,4-Dioxane was distilled from sodium benzophenone ketal prior to use. Et_3N and 2,6-lutidine were distilled over KOH. Phosgene was purchased as a 1.93 M solution in toluene from Fluka™ and used as supplied. $(CH_3CN)_4CuPF_6$[1] and CuI[2] were prepared and purified, respectively, by known methods. $Pd(PPh_3)_4$ was synthesized[3] by a known method. Anhydrous $ZnCl_2$ and LiCl (Aldrich, Inc.) were fused and flame dried, respectively, by exposure to flame under reduced pressure prior to use. All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under argon pressure. Analytical thin layer chromatography was performed on Sorbent Technologies 0.20 mm silica gel 60 Å plates. Flash chromatography[4] was performed on Sorbent Technologies 32-63 μm 60 Å silica gel.



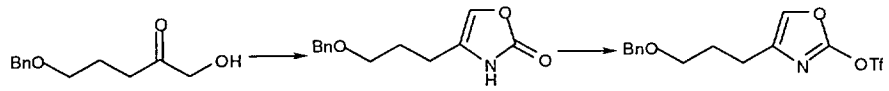
Trifluoro-methanesulfonic acid 2-phenyl-oxazol-4-yl ester 1a. In an argon-filled round bottom flask were combined benzamide (1.52 g, 12.56 mmol) and chloroacetylchloride (1.0 mL, 12.56 mmol).[5] The neat mixture was heated to 110 °C for 1 h, then concentrated *in vacuo* and recrystallized from CH_2Cl_2. The chloroimide product was added slowly to a 0 °C mixture of 502 mg NaH (12.56 mmol, 60% in oil) in 210 mL 1,4-dioxane (0.06 M).[6] After stirring 30 min, the mix was warmed to rt, then heated to reflux for 4.5 h. The mix was then cooled, filtered through Celite, and concentrated *in vacuo*. The crude oxazolone was dissolved in 50 mL CH_2Cl_2 (0.25 M) and cooled to –78 °C. To the solution was added 3.49 mL Et_3N (25.12 mmol, 2 eq), then 3.17 mL Tf_2O (18.84 mmol, 1.5 eq). After

(1) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90-92.
(2) *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp. 39-41.
(3) Hegedus, L. S. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons Ltd.: New York, 1994; Chapter 5, pp. 448.
(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
(5) Polya, J. B.; Spotsword, T. M. *Recl. Trav. Chim. Pays-Bas*, **1948**, *67*, 927-941.
(6) Rodehorst, R. M.; Koch, T. H. *J. Am. Chem. Soc.* **1975**, *97*, 7298-7304.

warming to rt over 30 min, the reaction was quenched with H_2O, extracted 3× into CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% EtOAc/hexanes) yielded 1.55 g (42% yield over 3 steps) of the desired trifloyloxazole as an orange solid (mp < 25 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.48 (m, 3H), 7.72 (s, 1H), 7.99-8.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.7 (q, J = 319), 126.3, 126.5, 128.8, 131.4, 146.1, 159.7; IR (neat) νmax 3185, 3146, 3069, 2927, 2856, 1587, 1435, 1219, 1138, 1006, 858; HRMS(CI, CH_4) *m/z* calc'd for $C_{10}H_7F_3NSO_4$ $[M+H]^+$ 294.0048, found: 294.0036.

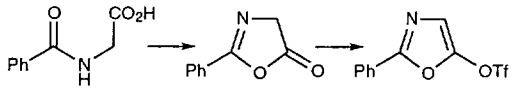


Trifluoro-methanesulfonic acid 4-methyl-oxazol-2-yl ester (1b). A 100 mL round bottom flask is charged with a stir bar and 2-hydroxyacetophenone (1.75 g, 12.86 mmol). To the reaction mixture is added benzene (18 mL) and *N,N*-dimethylaniline (3.85 mL). The reaction is cooled to 0 °C and phosgene is added (7.66 mL, 1.93 M in toluene, 14.68 mmol). The reaction is stirred for an additional 30 min at 0 °C before conc NH_4OH (~15 mL) is added carefully with a pipet. The reaction is allowed to stir an additional 30 min at 0 °C and then quenched by the addition of conc H_2SO_4 until a pH of ~3 is obtained. The reaction is then diluted with water (100 mL) and EtOAc (100 mL). The organic layer is separated and the aqueous layer is re-extracted with EtOAc (2×100 mL). The combined organic layers are then washed with brine (100 mL), dried with $MgSO_4$, filtered, and conc *in vacuo*. The crude solid is purified on SiO_2 (30% EtOAc/Hexanes) to give 1.50 g (73% yield) of oxazolone as an orange solid. The pure oxazolone (1.50 g, 9.31 mmol) is then added to a 100 mL round bottom flask charged with a stir bar and dissolved in CH_2Cl_2 (31 mL). The reaction mixture is cooled to –78 °C and 2,6-lutidine (2.00 g, 16.62 mmol) is added. Tf_2O is added (3.93 g, 13.96 mmol) to the cooled, stirred reaction. The cold bath and is removed and the reaction is warmed to rt with stirring for 30 min. The reaction is quenched by the addition of water (100 mL) and the organic layer is separated. The aqueous layer is re-extracted with additional CH_2Cl_2 (2×100 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and conc *in vacuo*. The crude oil was purified on SiO_2 (10% EtOAc/hexanes) to give 2.15 g (79%) of pure trifloyloxazole **2b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.68-7.66 (m, 2H), 7.43-7.37 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.9, 141.5, 132.5, 128.9, 125.2, 124.9, 118.4 (q, J=320 Hz); IR (neat) νmax 3164, 3064, 1777, 1598, 1447, 1343, 1236, 1133, 850, 733; HRMS(EI) *m/z* calc'd for $C_{10}H_6F_3NO_4S$ $[M]^+$ 292.9970, found: 292.9970.

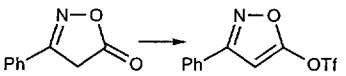


Trifluoro-methanesulfonic acid 4-(3-benzyloxy-propyl)-oxazol-2-yl ester (1c). Prepared as per **1b**. This compound proved to be chemically unstable and had to be used immediately after preparation and purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24

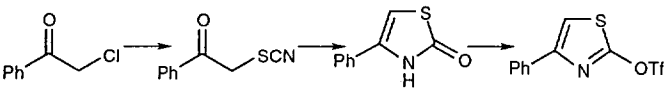
(m, 5H), 7.19 (s, 1H), 4.48, (s, 2H), 3.49 (t, 2H, J=6.0 Hz), 2.60 (t, 2H, J=7.6 Hz), 1.91 (tt, 2H, J=6.0, 7.6 Hz).



Trifluoro-methanesulfonic acid 2-methyl-oxazol-5-yl ester (1d). To an argon filled flask containing 1.0 g hippuric acid (5.587 mmol) was added 3.0 mL Ac_2O (31.68 mmol, 5.67 eq), and the mix was heated to 80 °C for 1 h.[7] The reaction mix was cooled, quenched with 10% aq $NaHCO_3$, and extracted 3× into EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oxazolone was dissolved in 22 mL CH_2Cl_2 (0.25 M) and cooled to –78 °C. To the reaction was added 1.55 mL Et_3N (11.17 mmol, 2 eq), followed by 1.41 mL Tf_2O (8.37 mmol, 1.5 eq). After 15 min, the reaction was allowed to come to rt, then stirred 45 min until finished. The mixture was quenched with H_2O, extracted 3× into CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) yielded 393 mg desired trifloyloxazole (24% over two steps) as a yellow oil, which was utilized in subsequent reactions immediately due to instability: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 7.46-7.52 (m, 3H), 7.96-7.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 116.2, 118.6 (q, J=319), 126.7, 128.9, 130.9, 156.3, 159.4; IR (neat) νmax 3102, 3067, 3018, 2962, 2928, 1521, 1436, 1220, 1135, 1006, 826; HRMS(CI, CH_4) *m/z* calc'd for $C_{10}H_6F_3NSO_4$ $[M]^+$ 292.9970, found: 293.0001.



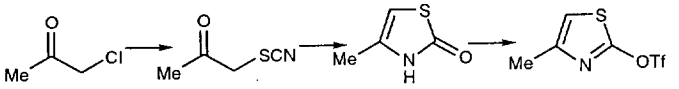
Trifluoro-methanesulfonic acid 3-methyl-isoxazol-5-yl ester (1e). To a 500 mg sample of commercially available (Aldrich™) isoxazolone (3.10 mmol) was added 12.4 mL (0.25 M) CH_2Cl_2. To the mixture was added 0.86 mL Et_3N (6.21 mmol, 2 eq) and the resulting solution was cooled to –78 °C. To the reaction was added 0.78 mL Tf_2O (4.65 mmol, 1.5 eq), and the solution was stirred for 10 min. The reaction was warmed to rt, stirred an add'l 10 min, then quenched with H_2O. The layers were separated, and the aqueous layer was extracted 3× into CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% EtOAc/hexanes) provided 856 mg (94%) of the desired trifloylisoxazole as white, needle-like crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 7.47-7.49 (m, 3H), 7.74-7.77 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.6 (q, J = 320), 126.5, 127.9, 129.1, 131.0, 161.5, 164.7; IR (neat) νmax 3180, 3140, 3031, 2950, 2860, 1587, 1432, 1220, 1138, 1006, 858; HRMS(EI) *m/z* calc'd for $C_{10}H_6F_3NO_4S$ $[M]^+$ 292.9970, found: 292.9956.



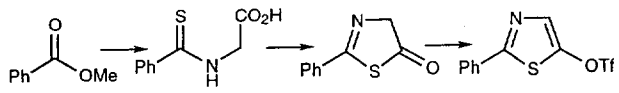
Trifluoro-methanesulfonic acid 4-methyl-thiazol-2-yl ester (1f). In a round bottom flask were combined 1.2 g 2-chloroacetophenone (7.72 mmol), 2.62 g KSCN (27.0

(7) Vandenberg, G. E.; Harrison, J. B.; Carter, H. E.; Magerlein, B. J. In *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, 946-948.

mmol, 3.5 eq), 70 mg KI (0.463 mmol, 0.06 eq), and 7.8 mL DMF (1.0 M). The reaction was heated to 80 °C for 2 h, then concentrated *in vacuo*. The crude mix was dissolved in 3.4 mL H_2O (2.25 M) and cooled to 0 °C. To the slurry was slowly added 34 mL H_2SO_4 (0.23 M).[8] After stirring for 15 min, the mixture was poured onto ice and stirred 5 min. The mixture was extracted 3× into EtOAc. The combined organic layers were washed 4× with H_2O, 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield desired thiazolone directly. The crude mix was then dissolved in 29 mL CH_2Cl_2 (0.25 M) and cooled to –78 °C. To the reaction was added 2.14 mL Et_3N (15.44 mmol, 2 eq), then 1.95 mL Tf_2O (11.58 mmol, 1.5 eq). The reaction was stirred at –78 °C 10 min, to rt 30 min, then quenched with H_2O. The aqueous layers were extracted 3× into CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% EtOAc/hexanes) provided 1.84 g (77%) of the desired trifloylthiazole as an orange-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.35-7.43 (m, 3H), 7.95-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.8, 118.2, 126.1, 128.9, 133.0, 150.9, 160.1; IR (neat) νmax 3120, 3031, 2985, 2931, 2359, 1536, 1430, 1220, 1135, 823; HRMS(CI, CH_4) *m/z* calc'd for $C_{10}H_6F_3NS_2O_3$ $[M]^+$ 308.9741, found: 308.9752.



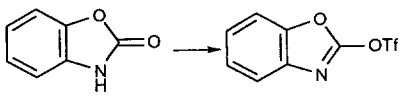
Trifluoro-methanesulfonic acid 4-methyl-thiazol-2-yl ester (1g). Prepared as per **1f**, using chloroacetone. Purification by flash chromatography (silica, 0→2% EtOAc/hexanes) provided 73% of the desired trifloylthiazole as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, d, J=1.0), 6.76 (1H, d, J=1.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 117.4, 118.2 (q, J=320), 142.6, 144.3; IR (neat) νmax 3120, 2985, 2931, 2360, 1538, 1436, 1222, 1131, 825; HRMS(CI, CH_4) *m/z* calc'd for $C_5H_4F_3NS_2O_3$ $[M]^+$ 246.9585, found: 246.9636.



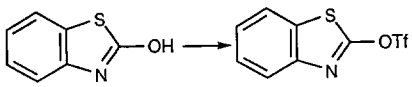
Trifluoro-methanesulfonic acid 2-methyl-thiazol-5-yl ester (1h). To a sample of $PhCO_2Me$ (1 mL, 8.04 mmol) in 30 mL PhMe (0.27 M) was added 3.25 g Lawesson's reagent (8.035 mmol, 2 eq) and the resulting mixture was heated to reflux 20 h.[9] The reaction was cooled to rt, diluted with 60/40 C_6H_6/pet ether and stirred, then filtered, concentrated *in vacuo*, and run through a short silica plug (hexanes) and the eluent was concentrated. To the resulting 325 mg thiolate (2.14 mmol) were added 176 mg glycine (2.35 mmol, 1.1 eq), 1.2 mL 3N aq NaOH (1.65 eq), and 1.10 mL Et_2O (1.9 M), and the mixture was stirred vigorously for 22 h. The mix was acidified with conc HCl, cooled to 0 °C, crystallized, and filtered. To the resulting thioamide in 10.7 mL 1,4-dioxane (0.2 M) was added 0.28 mL PBr_3 (2.19 mmol, 1.36 eq) at rt.[10] After 7 min, the reaction mix was filtered through Celite and rinsed with Et_2O. The Et_2O layer was washed 3× with 10% aq $NaHCO_3$, 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The

(8) Prakash, O.; Saini, N. *Synth. Comm.* **1993**, *23*, 1455-1462.
(9) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768-770.
(10) Glatz, B.; Helmchen, G.; Muxfeldt, H.; Porcher, H.; Prewo, R.; Senn, J.; Stezowski, J. J.; Stojda, R. J.; White, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 2171-2181.

thiazolone was dissolved in 21 mL CH_2Cl_2 (0.1 M), cooled to –78 °C, then 0.59 mL Et_3N (4.28 mmol, 2 eq) and 0.54 mL Tf_2O (3.21 mmol, 1.5 eq) were added. The reaction was stirred 10 min, then to rt 30 min, quenched with H_2O, extracted 3× into CH_2Cl_2, washed 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% EtOAc/hexanes) provided 100 mg (7% over 4 steps) of the desired trifloylthiazole as a yellow oil , which was utilized in subsequent reactions immediately due to instability: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.46 (m, 3H), 7.67 (s, 1H), 7.84-7.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.6, 117.4 (q, J=320), 126.7, 129.1, 130.3, 140.2, 157.6; IR (neat) νmax 3124, 3042, 2985, 2957, 2360, 1535, 1429, 1220, 1135, 820; HRMS(CI, CH_4) *m/z* calc'd for $C_{10}H_6F_3NS_2O_3$ $[M]^+$ 308.9741, found: 308.9752.

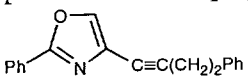


Trifluoro-methanesulfonic acid benzoxazol-2-yl ester(1i). To a 500 mg sample of commercially available (Aldrich, Inc.) 2-benzoxazolinone (4.20 mmol) was added 16.8 mL (0.25 M) CH_2Cl_2. To the mixture was added 1.17 mL Et_3N (8.40 mmol, 2 eq) and the resulting solution was cooled to –78 °C. To the reaction was added 1.06 mL Tf_2O (6.30 mmol, 1.5 eq), and the solution was stirred for 10 min. The reaction was warmed to rt, stirred an add'l 20 min, then quenched with H_2O. The layers were separated, and the aqueous layer was extracted 3× into CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) provided 986 mg (88%) of the desired trifloylbenzoxazole as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.37 (m, 3 H), 7.56-7.58 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 113.4, 119.2 (q, J = 322), 128.5, 126.1, 126.8, 141.0, 146.6; IR (neat) νmax 3180, 3145, 3060, 2925, 2856, 1585, 1435, 1219, 1139, 1000, 858; HRMS(EI) *m/z* calc'd for $C_8H_4F_3NO_4S$: 266.9813 $[M]^+$, found: 266.9856.



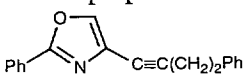
Trifluoro-methanesulfonic acid benzothiazol-2-yl ester (1j). To a 500 mg sample of commercially available (Aldrich, Inc.) 2-hydroxybenzothiazole (3.31 mmol) was added 13.2 mL (0.25 M) CH_2Cl_2. To the mixture was added 0.92 mL Et_3N (6.62 mmol, 2 eq) and the resulting solution was cooled to –78 °C. To the reaction was added 0.83 mL Tf_2O (4.96 mmol, 1.5 eq), and the solution was stirred for 10 min. The reaction was warmed to rt, stirred an add'l 40 min, then quenched with H_2O. The layers were separated, and the aqueous layer was extracted 3× into CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) provided 793 mg (85%) of the desired trifloylbenzothiazole as a gray oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, J=1.6, 7.6), 7.54 (1H, dd, J=7.9, 1.6), 7.80 (1H, d, J=7.6), 7.97 (1H, d, J=7.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.2, 113.4, 118.4 (q, J=320), 125.5, 126.0, 126.5, 136.2, 141.3; IR (neat) νmax 3121, 3061, 2985, 2930, 2357, 1534, 1425, 1226, 1135, 820; HRMS(EI) *m/z* calc'd for $C_8H_4F_3NO_3S_2$ $[M]^+$: 282.9585, found: 282.9578.

General procedure for Sonogashira coupling using Et_3N (Method A). The following procedure for the preparation of **2a** is representative.



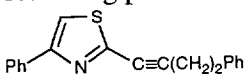
2-Phenyl-4-(4-phenyl-but-1-ynyl)-oxazole (2a). To a round bottom flask containing 50 mg **1a** (0.1706 mmol) in 1.7 mL DMF (0.1 M) under argon was added 20 mg $Pd(PPh_3)_4$ (.00853 mmol, 5 mol %). After stirring for 15 min at rt, the following reagents were added sequentially: 24 µL **3a** (0.1876 mmol, 1.1 eq), 6.5 mg CuI (.01706 mmol, 10 mol %), and 0.12 mL Et_3N (0.8530 mmol, 5 eq). The reaction was heated to 65 °C for 4 h until no triflate remained. The reaction was cooled to rt, quenched with H_2O, and EtOAc was added. The layers were separated, and the aqueous layer was extracted 3× into EtOAc. The combined organic layers were washed 4× with H_2O, 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2% EtOAc/hexanes) affords 40 mg (86%) of the desired product as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.70 (2H, t, J=7.8), 2.91 (2H, t, J=7.8), 7.26 (5H, m), 7.43 (3H, m), 7.71 (1H, s), 8.03 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 34.3, 68.6, 95.2, 126.0, 126.6, 126.8, 128.5, 128.9, 131.4, 132.5, 139.4, 157.2; IR (neat) vmax 3185, 3140, 3062, 2920, 1865, 1741, 1587, 1430, 1215, 1130; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NO$ $[M]^+$ 273.1154, found: 273.1146.

Larger scale Sonogashira coupling using Et_3N (Method A). The following procedure for the preparation of **2a** is representative.



2-Phenyl-4-(4-phenyl-but-1-ynyl)-oxazole (2a). To a round bottom flask containing 294 mg **1a** (1.00 mmol) in 10.0 mL DMF (0.1 M) under argon was added 58 mg $Pd(PPh_3)_4$ (0.050 mmol, 5 mol %). After stirring for 15 min at rt, the following reagents were added sequentially: 155 µL **3a** (1.10 mmol, 1.1 eq), 19 mg CuI (0.100 mmol, 10 mol %), and 0.69 mL Et_3N (5.00 mmol, 5 eq). The reaction was heated to 65 °C for 18 h until no triflate remained. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 500 mL EtOAc, washed 4× with H_2O. The aqueous layer was back-extracted 2× into EtOAc. The combined organic layers were washed 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 0→3% EtOAc/hexanes) affords 230 mg (84%) of the desired product as a brown oil, possessing spectral data identical to that in the above example.

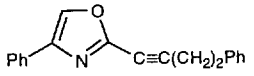
General procedure for Sonogashira coupling using 2,6-lutidine (Method B). The following procedure for the preparation of **2f** is representative.



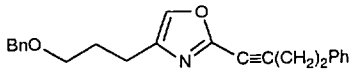
4-Methyl-2-(4-phenyl-but-1-ynyl)-thiazole (2f). To a round bottom flask containing 50 mg **1f** (0.1634 mmol) in 1.6 mL DMF (0.1 M) under argon was added 19 mg $Pd(PPh_3)_4$ (.01634 mmol, 5 mol %). The following reagents were added sequentially: 25 µL **3a** (0.1797 mmol, 1.1 eq), 6 mg CuI (.03268 mmol, 10 mol %), and 95 µL 2,6-lutidine (0.8170 mmol, 5 eq). The reaction was stirred at rt 18 h until no triflate remained. The reaction was quenched with H_2O, and EtOAc was added. The layers were separated, and the aqueous layer was extracted 3× into EtOAc. The combined organic layers were washed 4× with H_2O, 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) provides a 43 mg (91%) of the desired

product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (2H, t, J=7.6), 2.98 (2H, t, J=7.6), 7.21-7.42 (9H, m), 7.90 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 35.4, 77.6, 94.5, 120.0, 123.1, 124.3, 124.7, 139.9, 153.4, 155.8; IR (neat) νmax 3060, 2985, 2940, 2360, 1860, 1760, 1585, 1429, 1215, 1130, 820; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NS$ $[M]^+$ 289.0925, found: 289.1000.

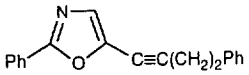
General procedure for Sonogashira coupling using 1,4-dioxane (Method C). The following procedure for the preparation of **2b** is representative.



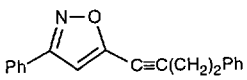
4-Methyl-2-(4-phenyl-but-1-ynyl)-oxazole (2b). To a round bottom flask containing 171 mg **1b** (0.58 mmol) in 1,4-dioxane (0.1 M) under argon were added sequentially: 34 mg $Pd(PPh_3)_4$ (0.029 mmol, 5 mol %), 84 mg **3a** (0.638 mmol, 1.1 eq), 5.8 mg CuI (0.058 mmol, 10 mol %), and 0.340 mL 2,6-lutidine (2.90 mmol, 5 eq). The reaction was stirred at rt 16 h until no triflate remained. The reaction mixture was diluted with EtOAc, flushed through a pad of SiO_2, and concentrated *in vacuo*. Purification by flash chromatography (silica, 5% EtOAc/hexanes) afforded 120 mg (76%) of the desired product as a light brown solid (mp 79-80 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.72 (d, 2H, J=7.2 Hz), 7.39 (t, 2H, J=7.2 Hz), 7.32-7.22 (m, 6H), 2.96 (t, 2H, J=7.6 Hz), 2.74 (t, 2H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 141.3, 139.7, 133.8, 130.2, 128.6, 128.4, 128.2, 126.5, 125.4, 93.2, 69.4, 33.9, 21.3; IR (neat) νmax 3017, 2240, 1542, 1451, 1216, 757, 697; HRMS(CI, NH_3) *m/z* calc'd for $C_{19}H_{16}NO$ $[M+H]^+$ 274.1232, found: 274.1212.



4-(3-Benzyloxy-propyl)-2-(4-phenyl-but-1-ynyl)-oxazole (2c). Preparation by Method C using triflate **1c** and alkyne **3a** with a reaction time of 6 h. Purification by flash chromatography (20% EtOAc/hexanes) provides an 83% yield of the desired product as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 7H), 7.23-7.20 (m, 4H), 4.48 (s, 2H), 3.48 (t, 2H, J=6.6 Hz), 2.92 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz), 2.59 (t, 2H, J=7.2 Hz), 1.93 (tt, 2H, J=6.6, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 141.2, 139.8, 138.4, 134.6, 128.4, 128.2, 127.6, 127.5, 127.4, 126.4, 92.4, 72.8, 69.7, 69.0, 34.1, 28.1, 22.8, 21.3; IR (neat) νmax 3062, 3029, 2928, 2858, 2246, 1587, 1536, 1453, 1101, 1028; HRMS(CI, NH_3) *m/z* calc'd for $C_{23}H_{24}NO_2$ $[M+H]^+$ 346.1807, found: 346.1848.

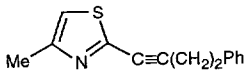


2-Methyl-5-(4-phenyl-but-1-ynyl)-oxazole (2d). Preparation by Method A using triflate **1d** and alkyne **3a** with a reaction time of 12 h. Purification by flash chromatography (silica, 2% EtOAc/hexanes) provides a 73% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (2H, t, J=7.6), 2.82 (2H, t, J=7.6), 7.18-7.36 (5H, m), 7.42-7.56 (4H, m), 7.63-7.68 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 34.6, 67.9, 98.2, 127.4, 128.3, 129.5, 130.4, 136.9, 156.6, 160.4; IR (neat) νmax 3186, 3060, 2925, 1860, 1740, 1585, 1430, 1215, 1131, 820; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NO$ $[M]^+$ 273.1154, found: 273.1149.

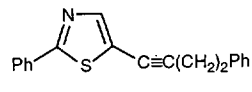


3-Methyl-5-(4-phenyl-but-1-ynyl)-isoxazole (2e). Preparation by Method A using triflate **1e** and alkyne **3a** with a reaction time of 20

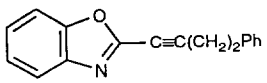
h. Purification by flash chromatography (silica, 1% EtOAc/hexanes) provides an 89% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75-2.79 (t, J = 7.4, 2H), 2.93-2.97 (t, J = 7.4, 2H), 6.60 (s, 1H), 7.22-7.26 (m, 3H), 7.30-7.34 (m, 2H), 7.43-7.44 (m, 3H), 7.75-7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 34.3, 68.5, 100.1, 105.1, 126.8, 128.4, 128.6, 128.9, 130.1, 139.9, 154.3, 162.5; IR (neat) νmax 3185, 3065, 2921, 1860, 1742, 1583, 1437, 1215, 1130, 825; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NO$ $[M]^+$ 273.1154, found: 273.1152.



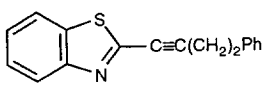
4-Methyl-2-(4-phenyl-but-1-ynyl)-thiazole (2g). Preparation by Method A using triflate **1g** and alkyne **3a**, with a reaction time of 8 h. Purification by flash chromatography (silica, 2→4 % EtOAc/hexanes) provides a 78% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (d, J_0.8, 3H), 2.72 (t, J = 7.4, 2H), 2.93 (t, J = 7.4, 2H), 6.80 (d, J = 0.8, 1H), 7.21-7.32 (m, 5H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.0, 21.7, 34.5, 75.1, 94.7, 114.5, 126.5, 128.4, 128.5, 140.2, 148.4, 153.3; IR (neat) νmax 3065, 2988, 2940, 2360, 1865, 1761, 1585, 1430, 1215, 1131, 820; HRMS(EI) *m/z* calc'd for $C_{14}H_{13}NS$ $[M]^+$ 227.0769, found: 227.0800.



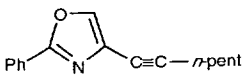
2-Methyl-5-(4-phenyl-but-1-ynyl)-thiazole (2h). Preparation by Method A using triflate **1h** and alkyne **3a**, with a reaction time of 20 h. Purification by flash chromatography (silica, 0→4 % EtOAc/hexanes) provides a 64% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (2H, t, J=7.4), 2.75 (2H, t, J=7.4), 7.44-7.52 (4H, m), 7.83-7.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 35.2, 66.8, 94.6, 116.4, 126.7, 128.5, 129.4, 130.1, 132.7, 156.7; IR (neat) νmax 3060, 2985, 2940, 2360, 1860, 1761, 1585, 1429, 1215, 1130, 820; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NS$ $[M]^+$ 289.0925, found: 289.0956.



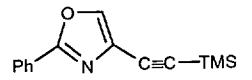
2-(4-Phenyl-but-1-ynyl)-benzoxazole (2i). Preparation by Method C using triflate **1i** and alkyne **3a**, with a reaction time of 16 h. Purification by flash chromatography (silica, 2% EtOAc/hexanes) affords a 73% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, J = 7.4, 2H), 2.82 (t, J = 7.4, 2 H), 7.18-7.28 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 35.3, 69.1, 102.3, 111.2, 113.5, 125.6, 125.9, 126.7, 139.6, 141.0; IR (neat) νmax 3180, 3060, 2926, 1861, 1738, 1587, 1428, 1213, 1130, 821; HRMS(EI) *m/z* calc'd for $C_{17}H_{13}NO$ $[M]^+$ 247.0997, found: 247.0964.



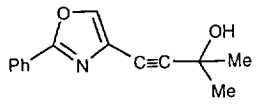
2-(4-Phenyl-but-1-ynyl)-benzothiazole (2j). Preparation by Method C using triflate **1j** and alkyne **3a**, with a reaction time of 16 h. Purification by flash chromatography (silica, 2→5 % EtOAc/hexanes) provides a 85% yield of the desired product as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (t, J = 11.5, 2 H), 2.98 (t, J = 11.5, 2 H), 7.23-7.33 (m, 5 H), 7.38-7.42 (m, 1 H), 7.46-7.50 (m, 1 H), 7.81 (d, J = 7.9, 1H), 8.01 (d, J = 7.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 34.6, 69.7, 101.6, 111.4, 113.0, 125.8, 126.0, 126.3, 137.4, 139.1; IR (neat) νmax 3165, 3035, 2950, 1863, 1735, 1575, 1420, 1217, 1132; HRMS(EI) *m/z* calc'd for $C_{17}H_{13}NS$ $[M]^+$ 263.0769, found: 263.0775.



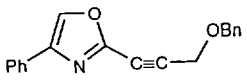
4-Hept-1-ynyl-2-phenyl-oxazole (2k). Preparation by Method A using triflate **1a** and alkyne **3b**, with a reaction time of 24 h. Purification by flash chromatography (silica, 0→2 % EtOAc/hexanes) provides a 71% yield of the desired product as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J=7.0), 1.32 (2H, tq, J=6.0, 7.0), 1.40 (2H, tt, J=6.0, 8.8), 1.60 (2H, tt, J=7.0, 8.8), 2.40 (2H, t, J=7.0), 7.44 (3H, m), 7.73 (1H, s), 7.98-8.04 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0. 19.4. 22.2. 28.1. 31.1. 70.3. 94.5. 126.5. 128.4. 128.8. 130.7. 133.8. 140.2; IR (neat) νmax 3060, 2990, 2955, 2360, 1865, 1763, 1575, 1420, 1215, 1130, 822; HRMS(EI) *m/z* calc'd for $C_{16}H_{17}NO$ $[M]^+$ 239.1310, found: 239.1307.



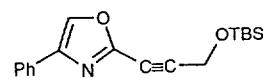
2-Phenyl-4-(trimethyl-silanylethynyl)-oxazole (2l). Preparation by Method A using triflate **1a** and alkyne **3c**, with a reaction time of 20 h. Purification by flash chromatography (silica, 0→4 % EtOAc/hexanes) provides a 69% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (9H, s), 7.34-7.45 (3H, m), 7.82 (1H, s), 8.02-8.05 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2, 67.5, 95.1, 124.7, 126.6, 129.1, 130.2, 131.6, 160.2; IR (neat) νmax 3185, 3060, 2170, 1865, 1740, 1587, 1430, 1215, 1130; HRMS(EI) *m/z* calc'd for $C_{14}H_{15}NOSi$ $[M]^+$ 241.0923, found: 241.0941.



2-Methyl-4-(2-phenyl-oxazol-4-yl)-but-3-yn-2-ol (2m). Preparation by Method A using triflate **1a** and alkyne **3d** with a reaction time of 24 h. Purification by flash chromatography (silica, 0→10% EtOAc/hexanes) provides a 42% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (6H, s), 7.46-7.49 (3H, m), 7.72 (1H, s), 7.99-8.01 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2, 70.6, 71.2, 92.3, 125.9, 126.7, 126.9, 131.3, 135.4, 139.7; IR (neat) νmax 3650, 3185, 3060, 2950, 1865, 1585, 1432, 1215, 1130, 820; HRMS(EI) *m/z* calc'd for $C_{14}H_{13}NO_2$ $[M]^+$ 227.0946, found: 227.0960.

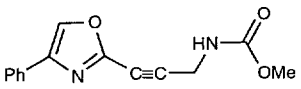


2-(3-Benzyloxy-prop-1-ynyl)-4-phenyl-oxazole (2n). Preparation by Method B using triflate **1b** and alkyne **3e**, with a reaction time of 12 h. Purification by flash chromatography (silica, 5% EtOAc/hexanes) provides a 54% yield of the desired product as a white solid (mp 75-77 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.75-7.43 (m, 2H), 7.42-7.30 (m, 8H) 4.67 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 141.8, 134.4, 128.8, 128.5, 128.3, 128.1, 128.0, 125.6, 88.4, 74.3, 71.0, 57.2, 29.7; IR (neat) νmax 3102, 2927, 2857, 1735, 1449, 1354, 1243, 1069, 747; HRMS(EI) *m/z* calc'd for $C_{19}H_{15}NO_2$ $[M]^+$ 289.1103, found: 289.1107.

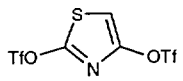


2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-prop-1-ynyl]-4-phenyl-oxazole (2o). Preparation by Method B using triflate 1b and alkyne 3f, with a reaction time of 10 h. Purification by flash chromatography (silica, 2% EtOAc/hexanes) provides a 75% yield of the desired product as a colorless oil: 1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.73-7.71 (m, 2H), 7.41-

7.37 (m, 2H), 7.33-7.28 (m, 1H), 4.54 (s, 2H), 0.91 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 141.7, 134.3, 130.2, 128.8, 128.4, 125.6, 90.9, 72.7, 51.8, 25.7, 18.2, -5.2; IR (neat) νmax 2955, 2931, 2858, 2361, 2251, 1540, 1471, 1258, 1099, 908, 734; HRMS(CI, NH_3) *m/z* calc'd for $C_{18}H_{24}NO_2Si$ $[M+H]^+$ 314.1576, found: 314.1602.

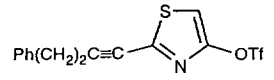


[3-(4-Phenyl-oxazol-2-yl)-prop-2-ynyl]-carbamic acid methyl ester (2p). Preparation by Method C using triflate **1b** and alkyne **3g**, with a reaction time of 5 h. Purification by flash chromatography (silica, 30% EtOAc/hexanes) provides a 73% yield of the desired product as a yellow solid (mp 100-102 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.72-7.69 (m, 2H), 7.41-7.30 (m, 3H), 5.00 (bs, 1H), 4.27-4.24 (m, 2H), 3.70 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.1, 141.7, 134.4, 130.0, 128.8, 128.5, 125.6, 88.5, 71.3, 52.6, 31.3; IR (neat) νmax 3020, 2401, 1730, 1514, 1216, 909, 755; HRMS(EI) *m/z* calc'd for $C_{14}H_{12}N_2O_3$ $[M]^+$ 256.0848, found: 256.0858.



Trifluoro-methanesulfonic acid 4-trifluoromethanesulfonyloxy-thiazol-2-yl ester (4). To a 250 mg sample of commercially available (Aldrich, Inc.) 2,4-thiazolidinedione (90% tech. grade, 1.92 mmol) was added 7.7 mL (0.25 M) CH_2Cl_2. To the mixture was added 1.07 mL Et_3N (7.68 mmol, 4 eq) and the resulting solution was cooled to –78 °C. To the reaction was added 0.97 mL Tf_2O (5.76 mmol, 3 eq), and the solution was stirred for 10 min. The reaction was warmed to rt, stirred an add'l 20 min, then quenched with H_2O. The layers were separated, and the aqueous layer was extracted 3× into CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 2→4% EtOAc/hexanes) provided 584 mg (80%) of the desired ditrifloylthiazole as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.5, 118.7 (q, J = 320), 145.3, 159.0; IR (neat) νmax 3136, 1529, 1439, 1320, 1220, 1130, 996; HRMS(CI, CH_4) *m/z* calc'd for $C_5H_1F_6N_1O_6S_3$ $[M]^+$ 380.8870, found: 380.8867.

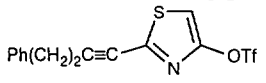
General procedure for selective Sonogashira coupling of 2,4-ditrifloylthiazole (4). The following procedure for the preparation of **5a** is representative.



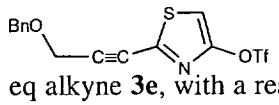
Trifluoro-methanesulfonic acid 2-(4-phenyl-but-1-ynyl)-thiazol-4-yl ester (5a). To a round bottom flask containing 40 mg **4** (0.105 mmol) in 1.1 mL DMF (0.1 M) under argon were added sequentially: 6 mg $Pd(PPh_3)_4$ (0.0525 mmol, 5 mol %), 15 μL **3a** (0.105 mmol, 1 eq), 2 mg CuI (0.0105 mmol, 10 mol %), and 15 μL 2,6-lutidine (0.5249 mmol, 5 eq). The reaction was stirred at rt 1 h until no triflate remained. The reaction was quenched with H_2O, and EtOAc was added. The layers were separated, and the aqueous layer was extracted 3× into EtOAc. The combined organic layers were washed 4× with H_2O, 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) affords 36 mg (95%) of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, J = 7.6, 2H), 2.94 (t, J = 7.6, 2H), 6.99 (s, 1H), 7.22-7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 34.1, 74.2, 98.2,

107.4, 118.7 (q, J = 319), 126.7, 128.4, 128.6, 139.7, 147.9, 150.0; IR (neat) νmax 3060, 2985, 1865, 1586, 1430, 1215, 1130, 820; HRMS(EI) *m/z* calc'd for $C_{14}H_{10}F_3NS_2O_3$ $[M]^+$ 361.0054, found: 361.0041. Regiochemistry of cross-coupling confirmed by comparison of ^{13}C NMR data with that of **4**, and through NOE analysis of **6a**.

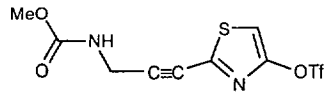
Larger scale procedure for selective Sonogashira coupling of 2,4-ditrifloylthiazole (4). The following procedure for the preparation of **5a** is representative.



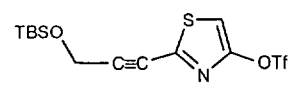
Trifluoro-methanesulfonic acid 2-(4-phenyl-but-1-ynyl)-thiazol-4-yl ester (5a). To a round bottom flask containing 381 mg **4** (1.00 mmol) in 10.0 mL DMF (0.1 M) under argon were added sequentially: 58 mg $Pd(PPh_3)_4$ (0.050 mmol, 5 mol %), 141 μL **3a** (1.00 mmol, 1 eq), 19 mg CuI (0.100 mmol, 10 mol %), and 0.58 mL 2,6-lutidine (5.00 mmol, 5 eq). The reaction was stirred at rt 18 h until no triflate remained. The reaction was concentrated *in vacuo*, dissolved in 500 mL EtOAc. The mixture was washed 4× with H_2O. The aqueous layer was back-extracted 2× into EtOAc. The combined organic layers were washed 1× with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica, 1% EtOAc/hexanes) affords 346 mg (96%) of the desired product as a yellow oil possessing spectral data identical to that in above example.



Trifluoro-methanesulfonic acid 2-(3-benzyloxy-prop-1-ynyl)-thiazol-4-yl ester (5b). Prepared as per **5a**, utilizing 1.1 eq alkyne **3e**, with a reaction time of 18 h. Purification by flash chromatography (silica, 5→7% EtOAc/hexanes) provides a 71% yield of the desired product as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.64 (s, 2H), 7.09 (s, 1H), 7.31-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.4, 72.3, 78.3, 92.9, 108.6, 118.6 (q, J=319), 128.1, 128.4, 128.6, 136.8, 146.4, 150.2 (IR (neat) νmax 3186, 3152, 3065, 3031, 2985, 2920, 1865, 1741, 1585, 1427, 1215, 1130; HRMS(EI) *m/z* calc'd for $C_{14}H_{10}F_3NS_2O_4$ $[M]^+$ 377.0003, found: 377.0006. Regiochemistry of cross-coupling confirmed by comparison of ^{13}C NMR data with that of **4**, and through NOE analysis of **6b**.

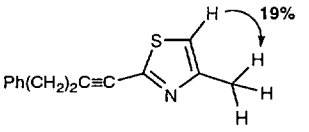


Trifluoro-methanesulfonic acid 2-(3-methoxycarbonylamino-prop-1-ynyl)-thiazol-4-yl ester (5c). Prepared as per **5a**, utilizing 1.2 eq alkyne **3g**, with a reaction time of 10 h. Purification by flash chromatography (silica, 20→40% EtOAc/hexanes) provides a 75% yield of the desired product as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 4.23 (d, J = 5.6, 2H), 5.13 (bs, 1 H), 7.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 52.7, 75.3, 93.0, 108.6, 118.5 (q, J=319), 146.7, 150.1, 156.6; IR (neat) νmax 3505, 3185, 2985, 1865, 1650, 1586, 1432, 1215, 1130; HRMS(EI) *m/z* calc'd for $C_9H_7F_3N_2S_2O_5$ $[M]^+$ 343.9748, found: 343.9787. Regiochemistry of cross-coupling confirmed by comparison of ^{13}C NMR data with that of **4**, and through NOE analysis of **6c**.

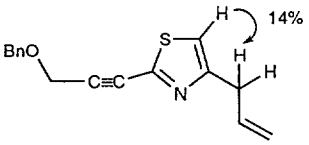


Trifluoro-methanesulfonic acid 2-[3-(*tert*-butyl-dimethyl-silanyloxy)-prop-1-ynyl]-thiazol-4-yl ester (5d). Prepared as per **5a**, utilizing 1.3 eq alkyne **3f**, with a reaction time of 18 h.

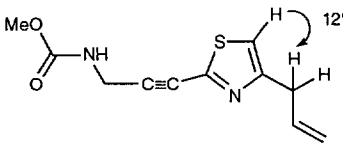
Purification by flash chromatography (silica, 1% EtOAc/hexanes) provides a 73% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.91 (s, 9H), 4.54 (s, 2H), 7.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.15, 19.33, 26.80, 53.01, 96.52, 109.33, 119.67 (q, J = 319), 131.93, 148.04, 151.24; IR (neat) νmax 3065, 2972, 1865, 1635, 1586, 1425, 1210, 1132, 816; HRMS(CI, NH_3) *m/z* calc'd for $C_{13}H_{19}F_3SiNS_2O_4$ $[M+H]^+$ 402.0477, found: 402.0458. Regiochemistry of cross-coupling confirmed by comparison of ^{13}C NMR data with that of **4**, and through correlation with data from **5a-5c**.



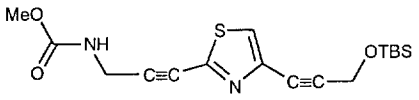
4-Methyl-2-(4-phenyl-but-1-ynyl)-thiazole (6a/2g). A sample of 86 mg LiCl (2.02 mmol, 5 eq) was flame dried in a sealed tube. To the sample were added 146 mg triflate (0.404 mmol), 4.0 mL 1,4-dioxane (0.1 M), 84 μL Me_4Sn (0.607 mmol, 1.5 eq), and 23 mg $Pd(PPh_3)_4$ (0.0202 mmol, 5 mol %). The mixture was heated to 100 °C for 18 h. The mixture was concentrated *in vacuo*, purified by flash chromatography (silica, 1→5% EtOAc/hexanes) to afford 75 mg (82%) of the desired product as a yellow oil: spectral data matches **2g**. An NOE signal between thiazole *C-5* ^{1}H and Me ^{1}H (19%) confirms regiochemistry of cross–couplings.



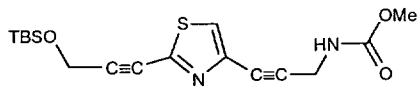
4-Allyl-2-(3-benzyloxy-prop-1-ynyl)-thiazole (6b). Prepared as per **6a**, utilizing triflate **5b** and 1.5 eq allyltributyltin. Purification by flash chromatography (silica, 6% EtOAc/hexanes) affords a 78% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, J = 6.9, 2H), 4.41 (s, 2H), 4.65 (s, 2H), 5.13 (dd, J = 1.2, 5.6, 1H), 5.17 (dd, J = 1.2, 12.4, 1H), 6.01 (ddd, J = 5.6, 6.9, 12.4, 1 H), 6.94 (s, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 35.9, 57.6, 72.0, 79.5, 90.0, 115.9, 117.3, 128.0, 128.1, 128.5, 134.7, 137.1, 156.3; IR (neat) νmax 3185, 3150, 3060, 3032, 2986, 2920, 1860, 1742, 1583, 1425, 1210, 1130, 727; HRMS(EI) *m/z* calc'd for $C_{16}H_{15}NSO$ $[M]^+$ 269.0874, found: 269.0856. An NOE signal between thiazole *C-5* ^{1}H and allyl chain α-CH_2 ^{1}H (14%) confirms regiochemistry of cross–couplings.



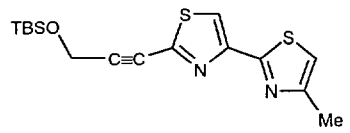
[3-(4-Allyl-thiazol-2-yl)-prop-2-ynyl]-carbamic acid methyl ester (6c). Prepared as per **6a**, utilizing triflate **5c** and 1.5 eq allyltributyltin. Purification by flash chromatography (silica, 20→25% EtOAc/hexanes) affords a 78% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, J = 6.9, 2H), 4.41 (s, 2H), 4.65 (s, 2H), 5.13 (dd, J = 1.2, 5.6, 1H), 5.17 (dd, J = 1.2, 12.4, 1H), 6.01 (ddd, J = 5.6, 6.9, 12.4, 1 H), 6.94 (s, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 35.9, 42.4, 79.5, 89.8, 115.4, 117.3, 117.7, 139.2, 145.3, 158.2; IR (neat) νmax 3575, 3180, 2929, 1863, 1651, 1585, 1431, 1215, 1129; HRMS(EI) *m/z* calc'd for $C_{11}H_{12}N_2SO_2$ $[M]^+$ 236.0619, found: 236.0630. An NOE signal between thiazole *C-5* ^{1}H and allyl chain α-CH_2 ^{1}H (12%) confirms regiochemistry of cross–couplings.



(3-{4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-prop-1-ynyl]-thiazol-2-yl}-prop-2-ynyl)-carbamic acid methyl ester (6d). To a round bottom flask containing 47 mg triflate **5c** (0.1366 mmol) in 1.4 mL 1,4-dioxane (0.1 M) at rt were added sequentially: 8 mg $Pd(PPh_3)_4$ (0.06831 mmol, 5 mol %), 30 mg alkyne **3f** (0.1776 mmol, 1.3 eq.), 3 mg CuI (0.01366 mmol, 10 mol %), and 95 μL Et_3N (0.6831 mmol, 5 eq.). The reaction mix was heated to 65 °C for 16 h. The crude mix was concentrated *in vacuo* and purified by flash chromatography (silica, 10→60% EtOAc/hexanes) to afford 36 mg (72%) of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (6H, s), 0.95 (9H, s), 3.63 (3H, s), 4.20 (2H, s), 4.60 (2H, s), 5.20 (1H, bs), 7.03 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.1, 19.8, 25.9, 30.1, 42.8, 58.2, 79.1, 90.4, 90.8, 109.1, 109.4, 140.0, 143.1, 159.2; IR (neat) νmax 3595, 3185, 2986, 1863, 1655, 1635, 1560, 1210, 1130, 810; HRMS(EI) *m/z* calc'd for $C_{17}H_{24}N_2SO_3Si$ $[M]^+$ 364.1277, found: 364.1260.

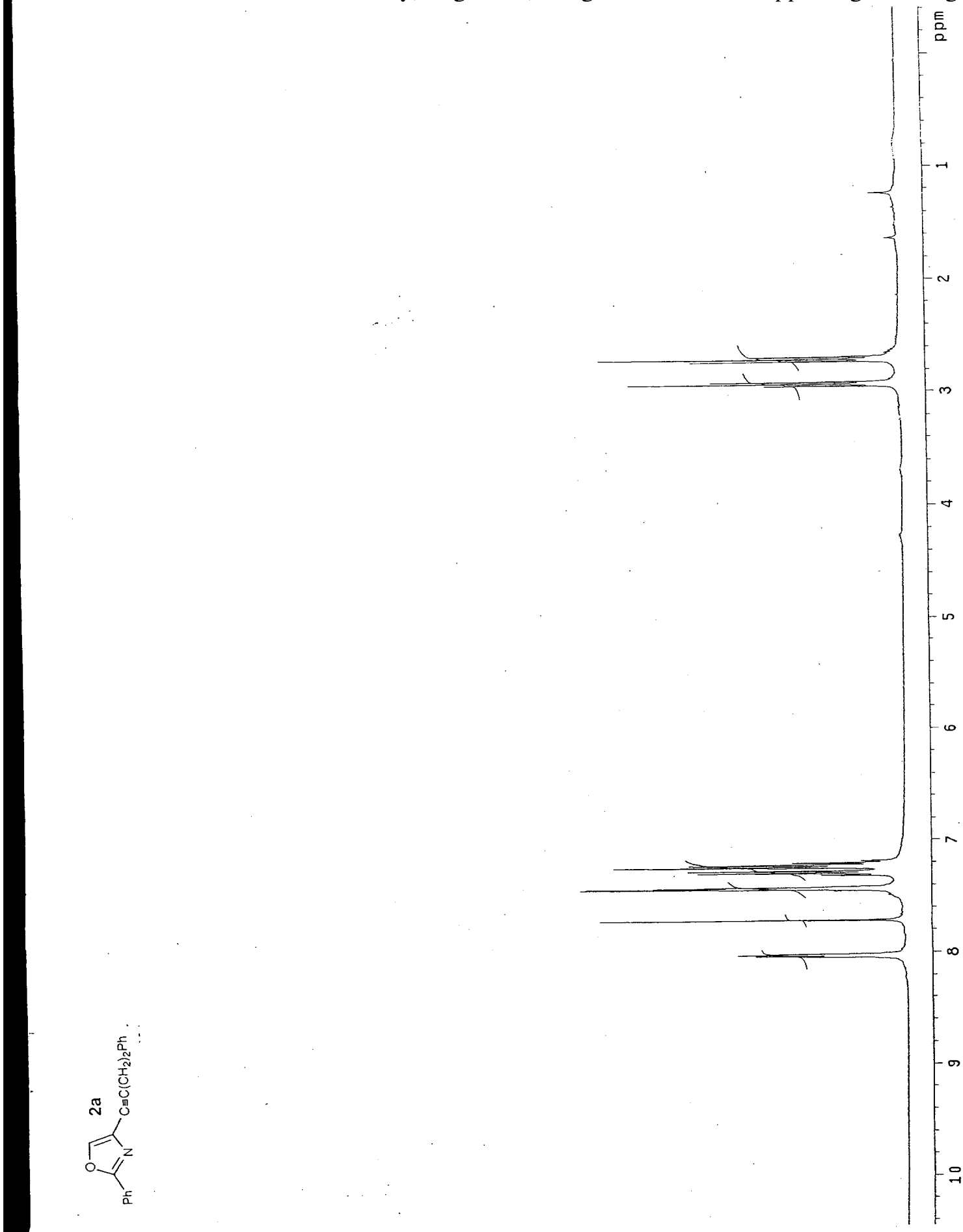


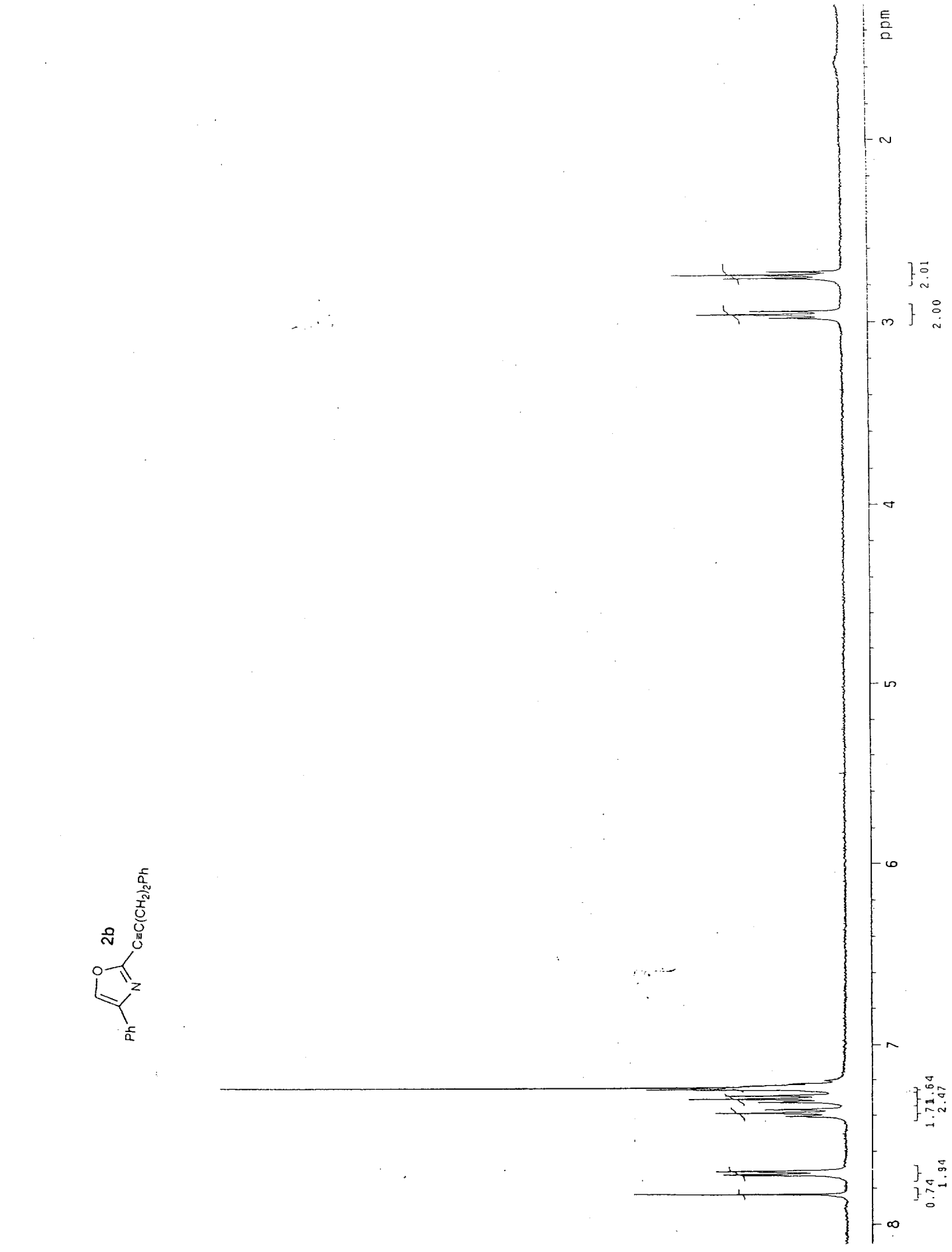
(3-{2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-prop-1-ynyl]-thiazol-4-yl}-prop-2-ynyl)-carbamic acid methyl ester (6e). Prepared as per **6d**, utilizing triflate **5d** and alkyne **3f**, with a reaction time of 18 h. Purification by flash chromatography (silica, 20→100% EtOAc/hexanes) affords a 75% yield of the desired product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (6H, s), 1.01 (9H, s), 3.56 (3H, s), 4.20 (2H, s), 4.63 (2H, s), 5.65 (1H, bs), 7.07 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.6, 20.6, 26.7, 30.3, 42.6, 55.6, 76.4, 88.4, 92.3, 109.4, 131.0, 135.6, 151.4, 160.2; IR (neat) νmax 3595, 3186, 2987, 1860, 1657, 1635, 1560, 1210, 1130, 810; HRMS(EI) *m/z* calc'd for $C_{17}H_{24}N_2SO_3Si$ $[M]^+$ 364.1277, found: 364.1291.

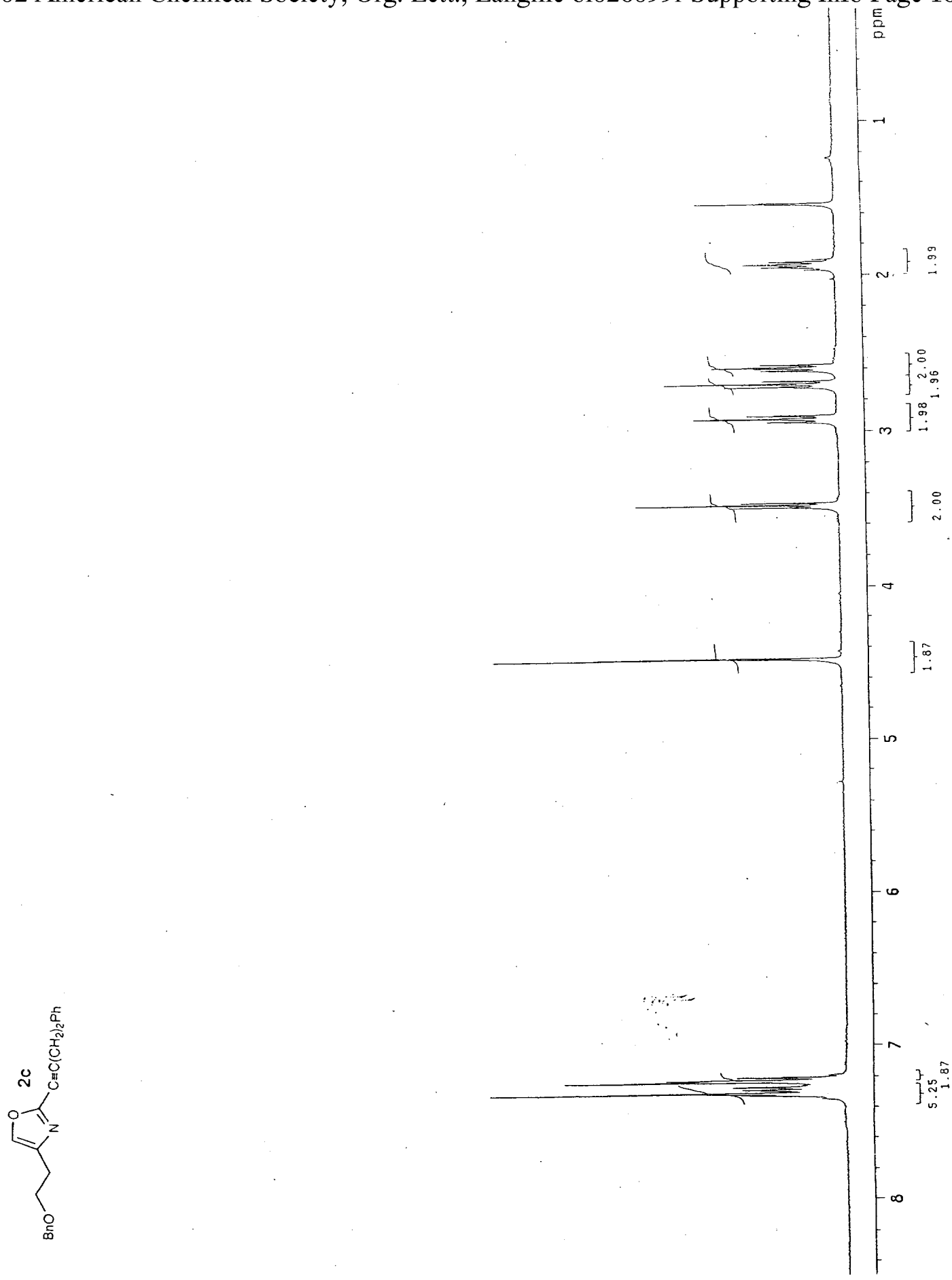


2'-[3-(*tert*-Butyl-dimethyl-silanyloxy)-prop-1-ynyl]-4-methyl-[2,4']bithiazolyl (6f). Prepared as per **6a**, utilizing triflate **5d** and 1.5 eq stannane[11]. Purification by flash chromatography (silica, 1→4% EtOAc/hexanes) provides a 64% yield of the desired product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (6H, s), 0.92 (9H, s), 2.51 (3H, d, J=0.8), 4.61 (2H, s), 7.01 (1H, d, J=0.8), 7.10 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.2, 18.5, 19.6, 27.1, 57.3, 97.3, 105.7, 118.7, 120.3, 139.4, 146.3, 152.3, 154.0; IR (neat) νmax 3062, 2950, 1854, 1657, 1545, 1200, 1175; HRMS(EI) *m/z* calc'd for $C_{16}H_{22}N_2S_2OSi$ $[M]^+$ 350.0943, found: 350.0962.

(11) Prepared by treatment of triflate **1g** with $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, 1,4-dioxane, 100 °C, 18 h. Due to instability, stannane is not completely purified before use.



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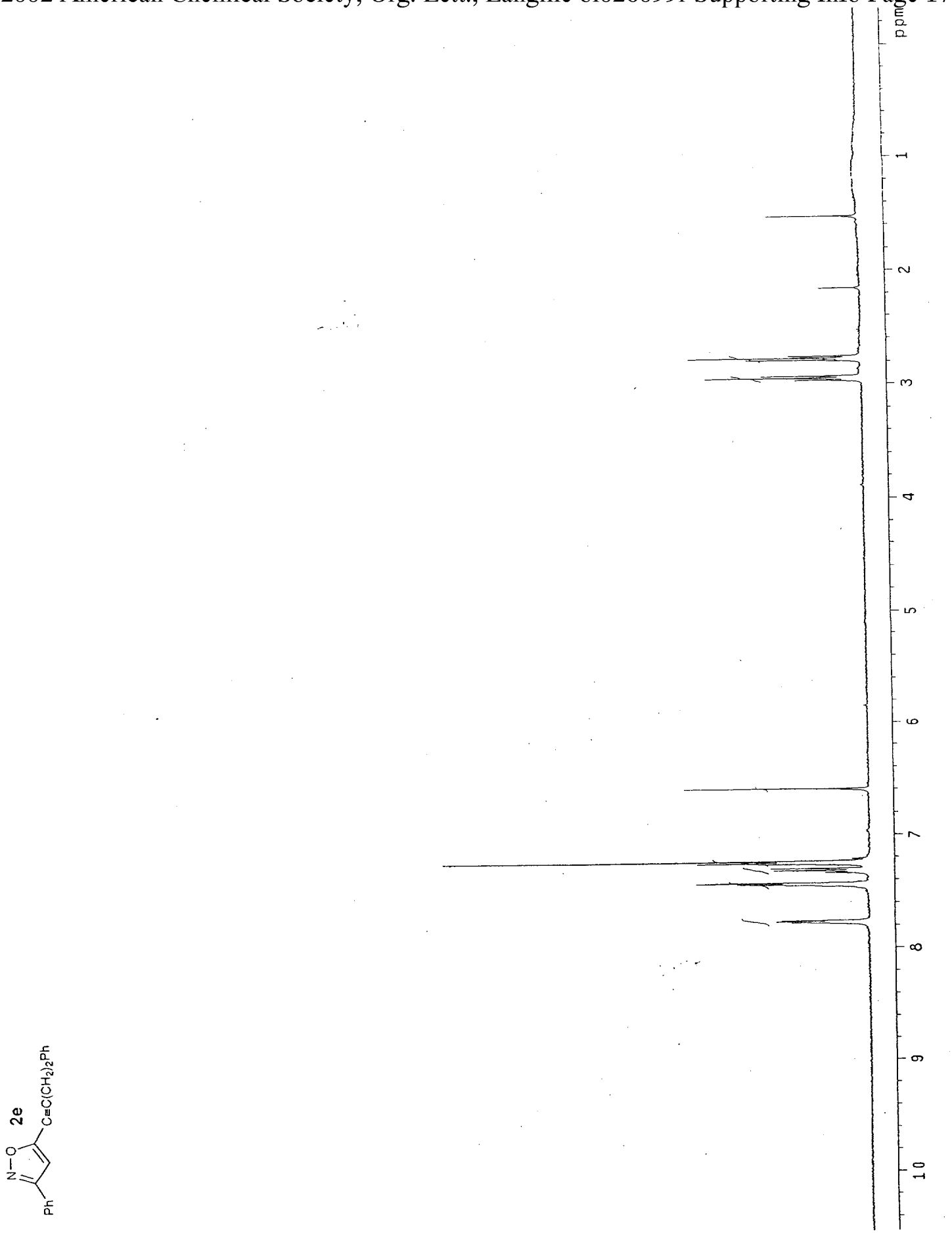

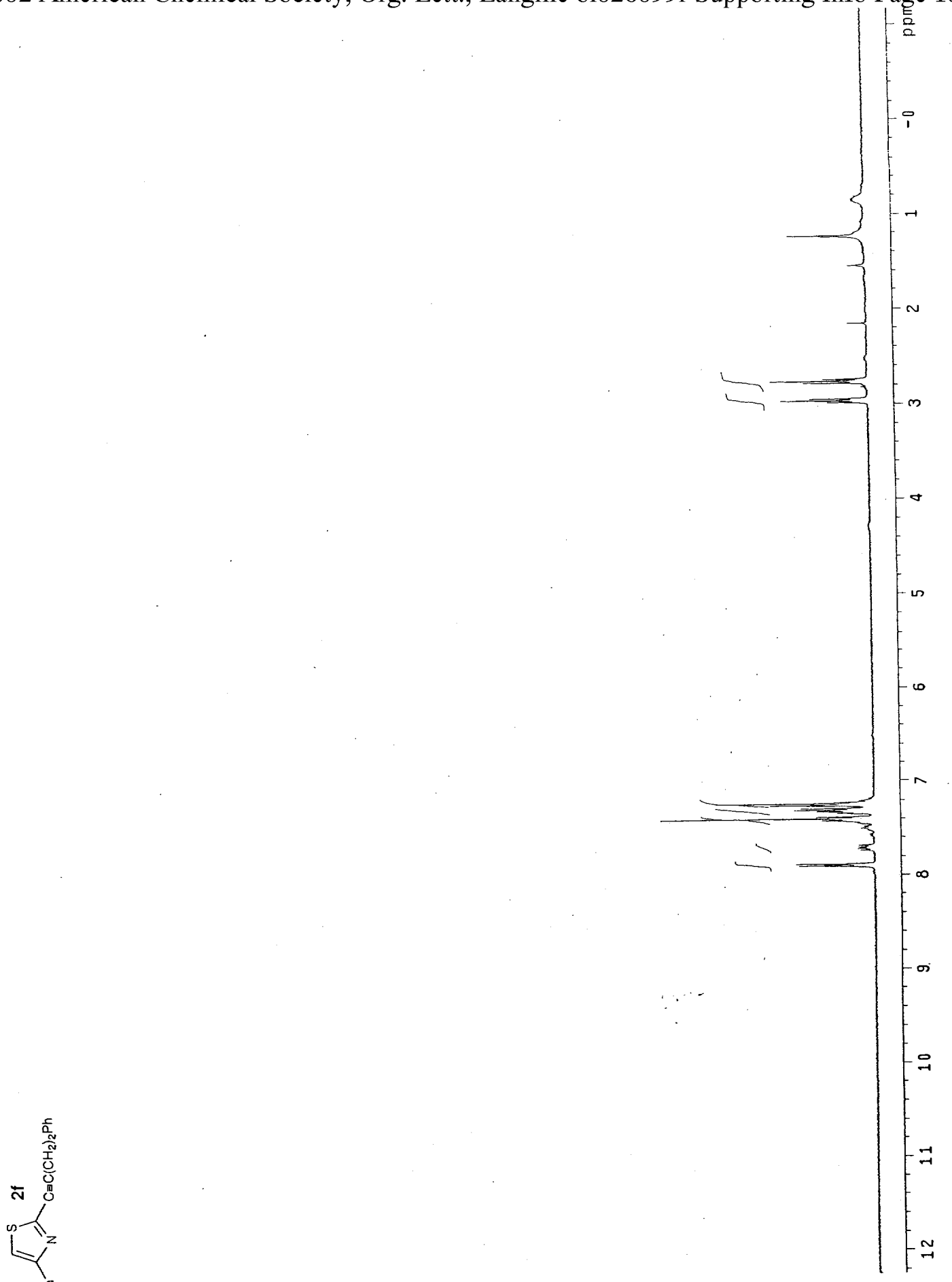
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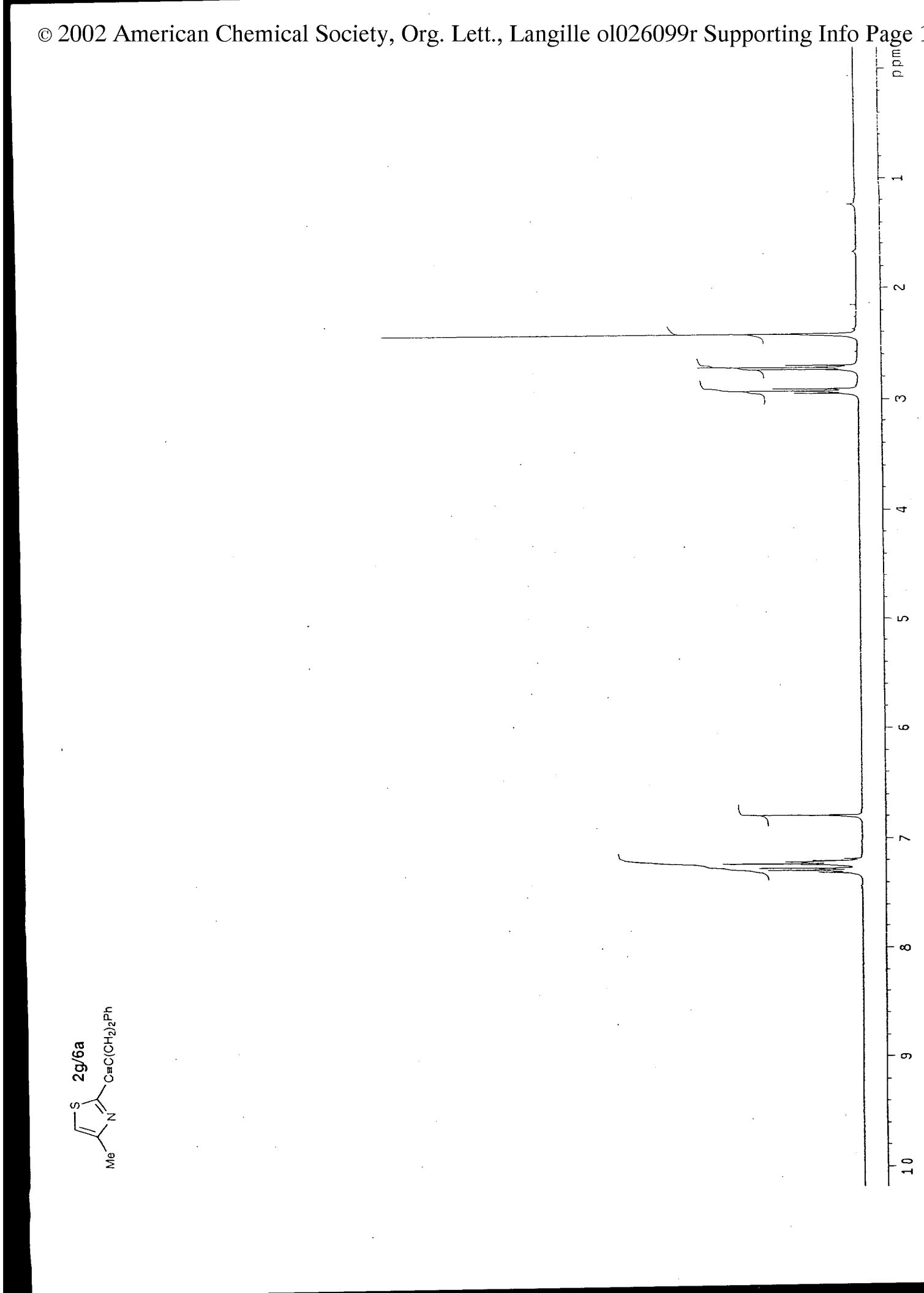
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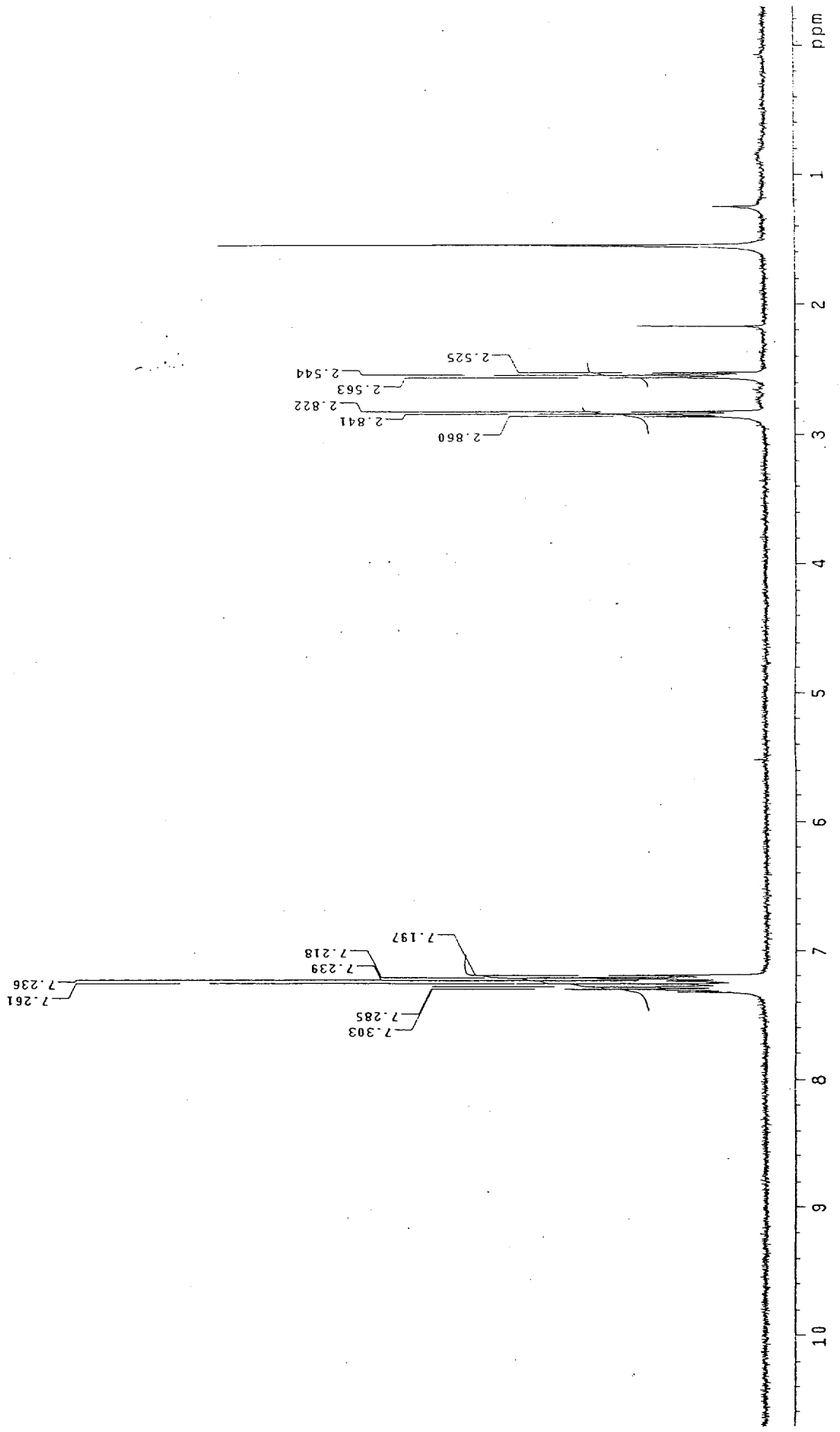
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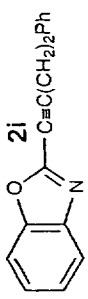
2i
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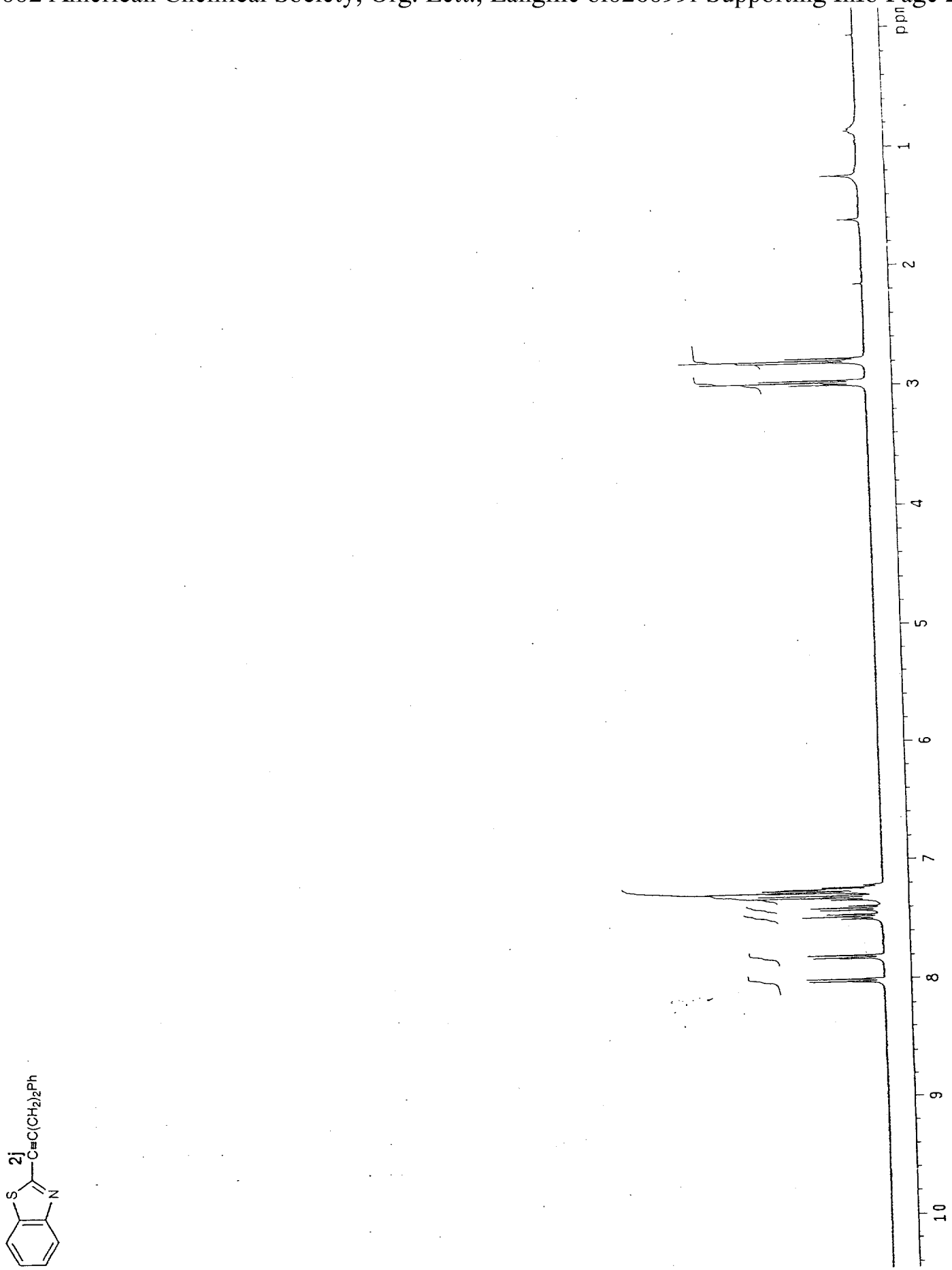
O
N


ppm
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4
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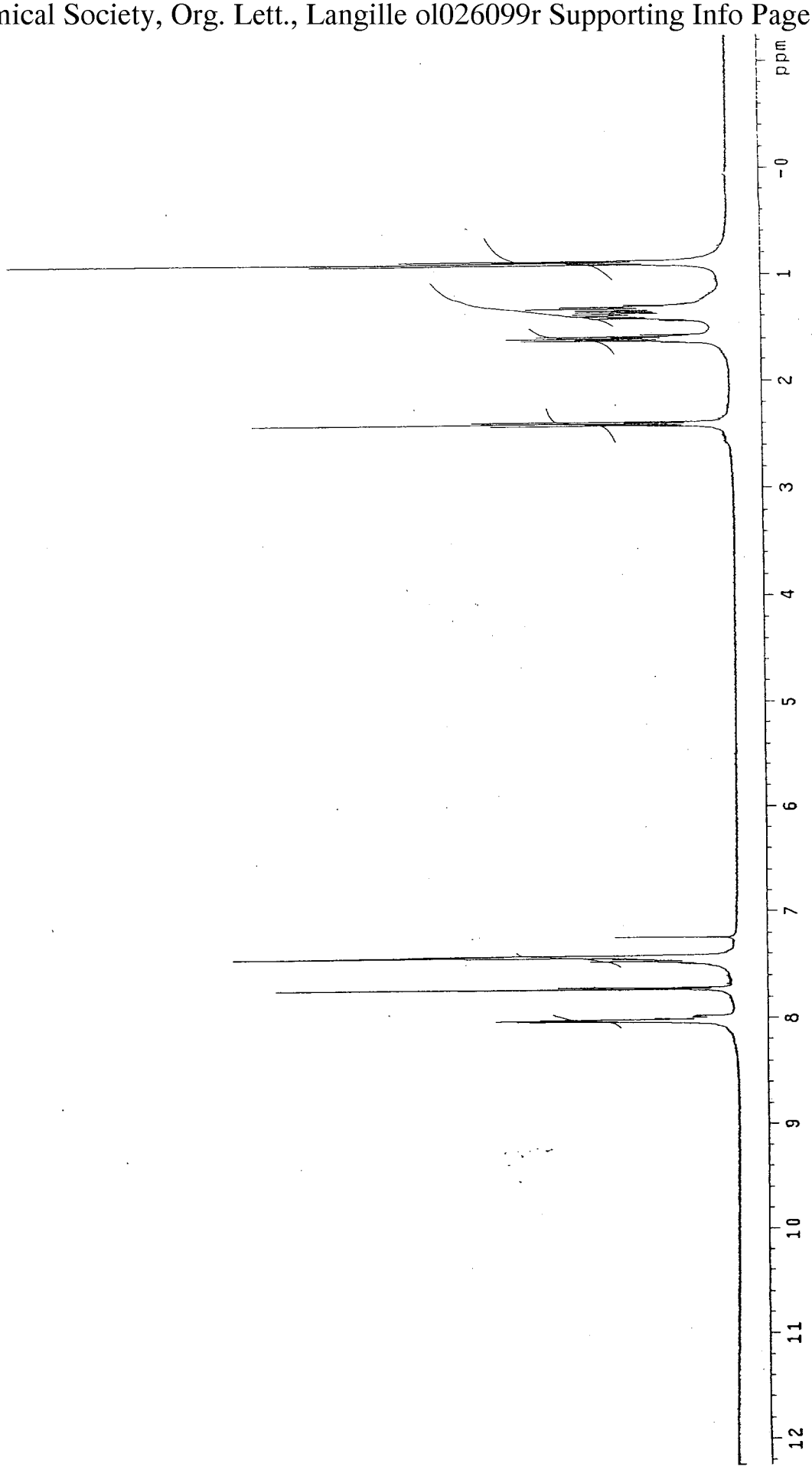
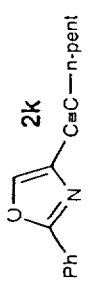
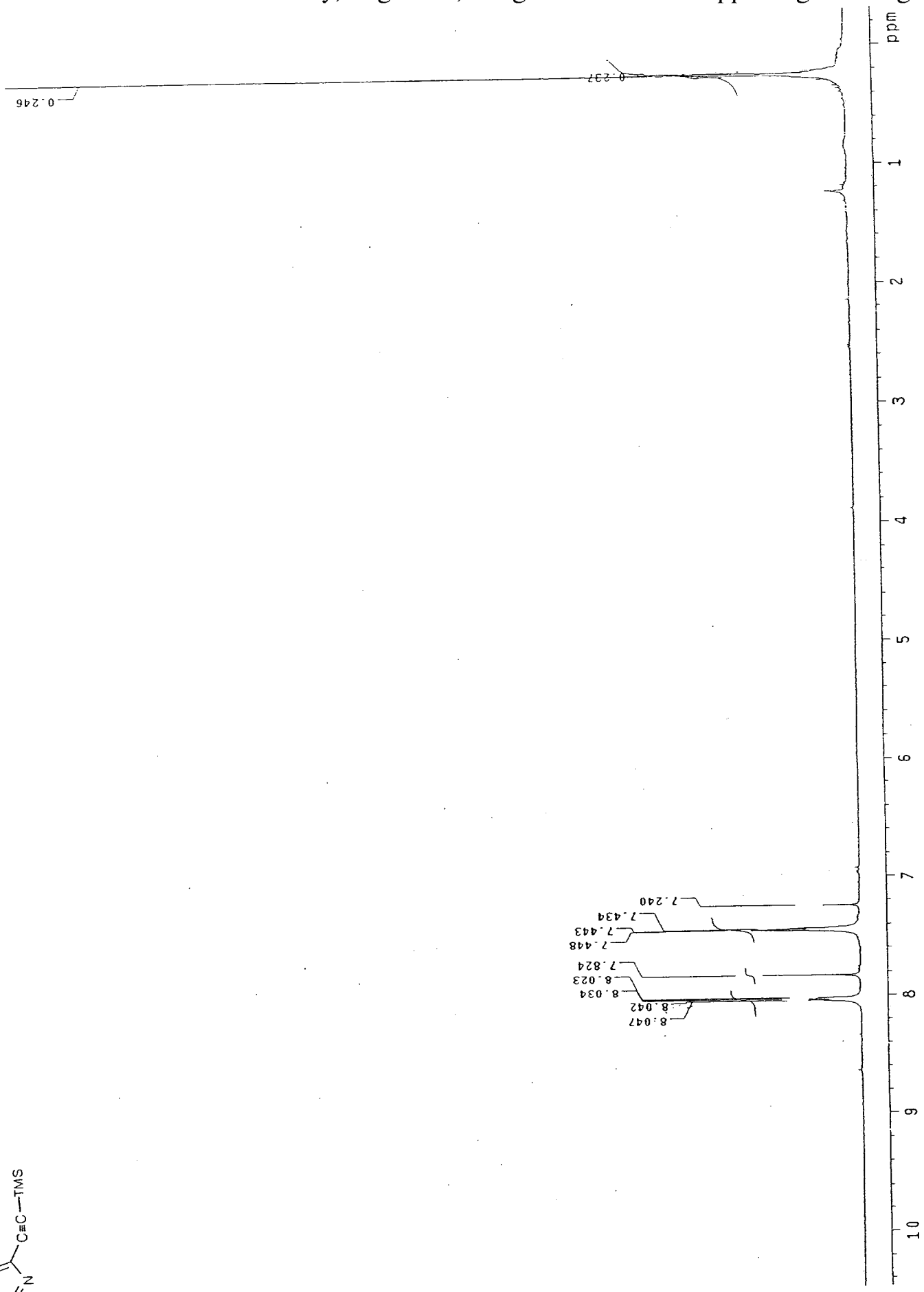
6
7
8
9
10
2j
C≡C(CH2)2Ph
S
N


ppm
-0
1
2
3
4
5
6
7
8
9
10
11
12


2k
C≡C—n-pent
O
N
Ph


0.246
0.237
ppm
1
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3
4
5
6
7
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9
10
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7.434
7.443
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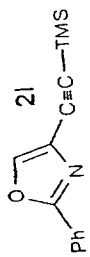
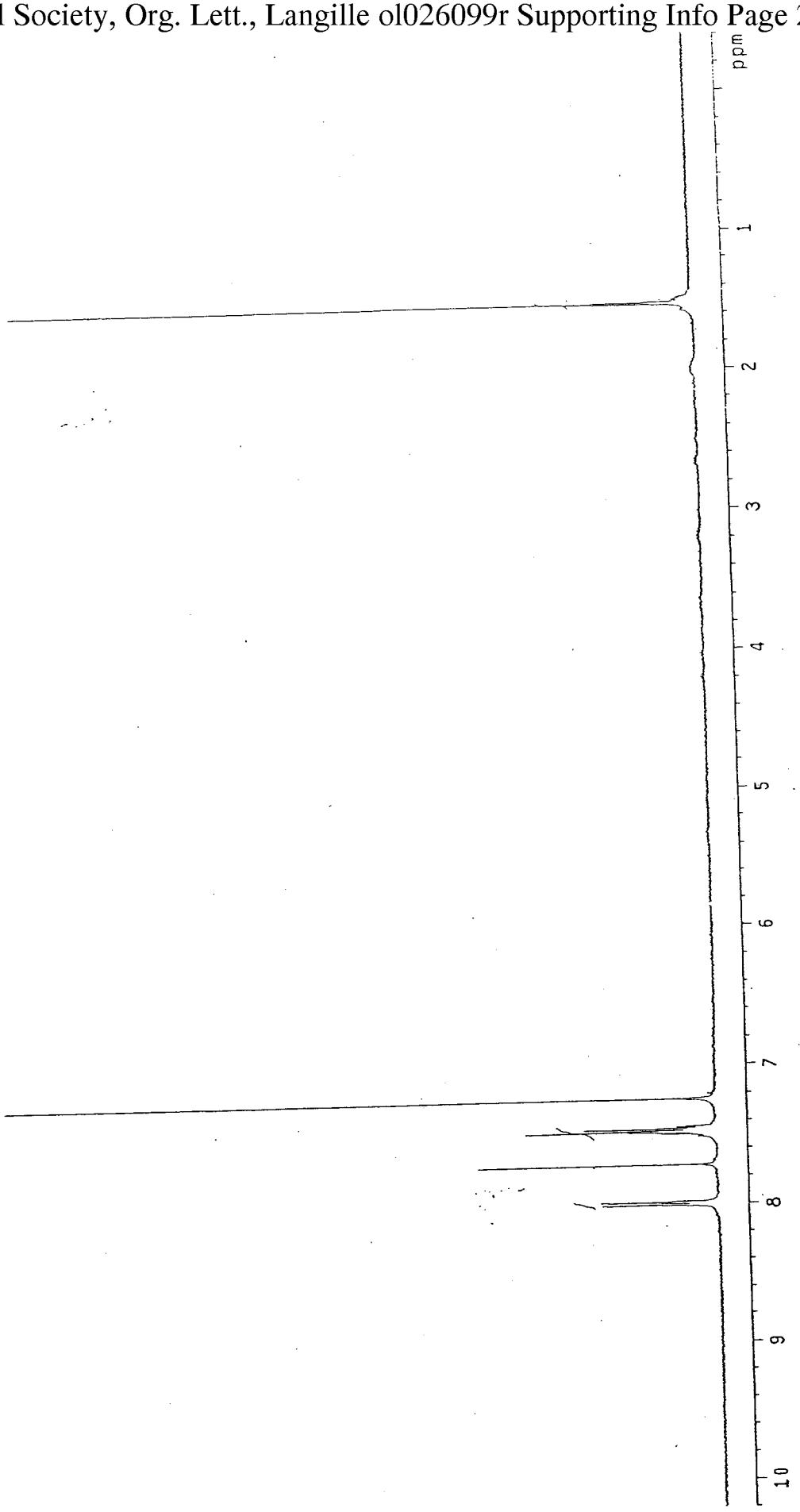
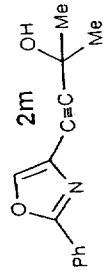
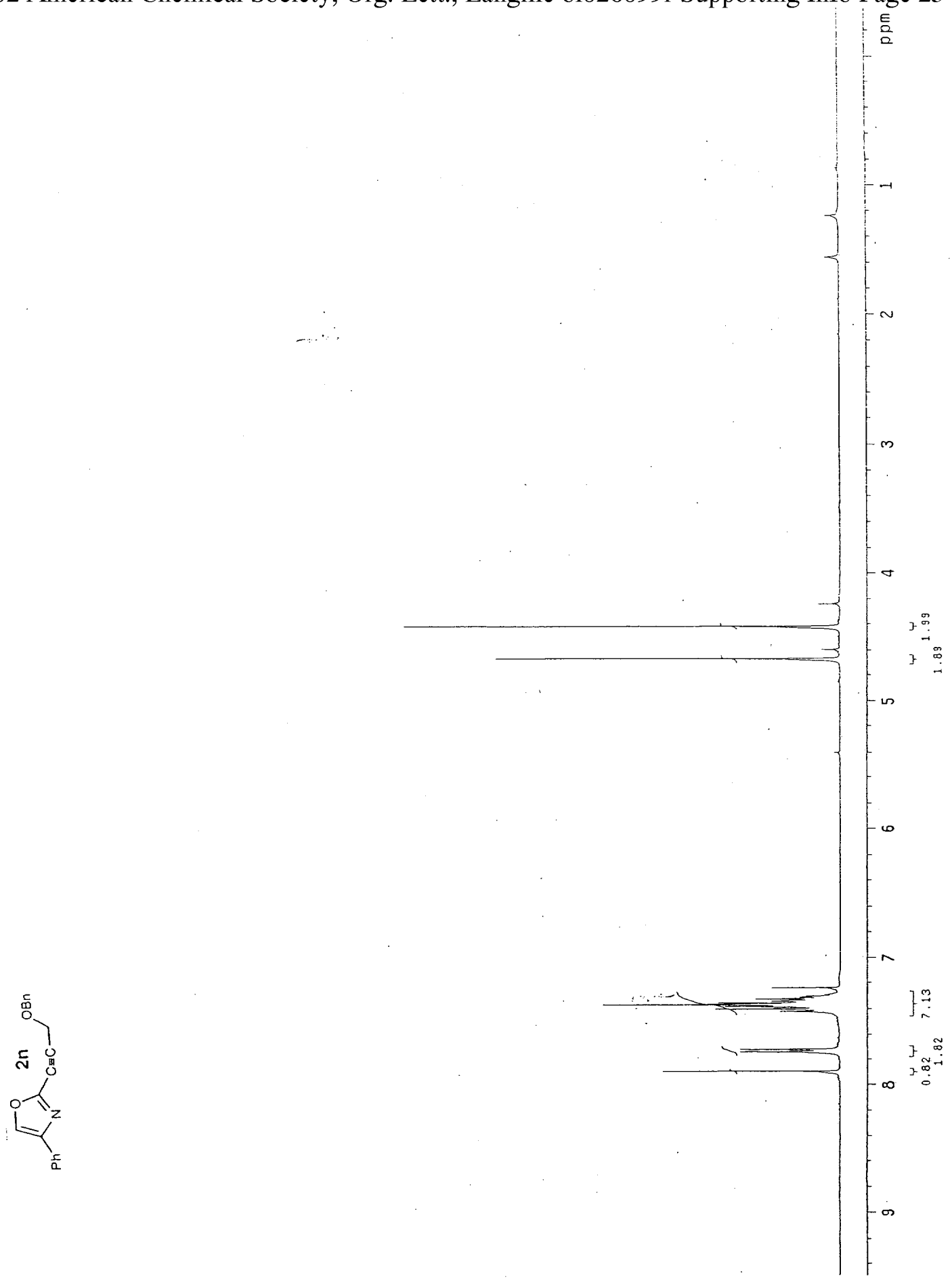
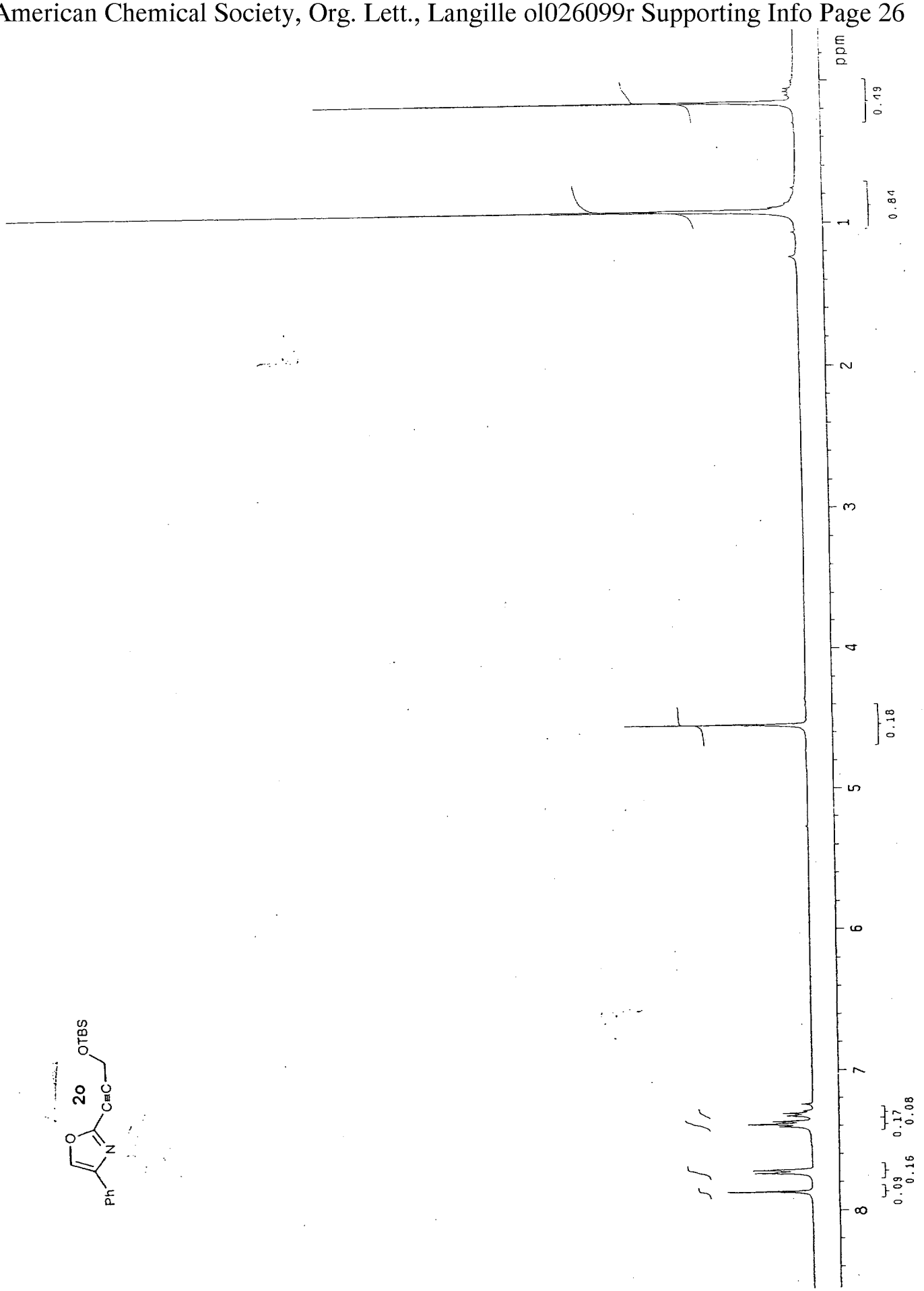
7.824
8.023
8.034
8.042
8.047


21
C≡C—TMS
O
N
Ph








ppm
0.19
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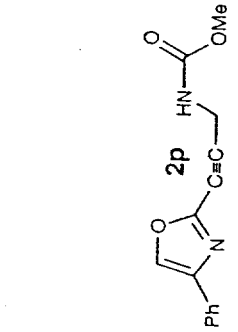
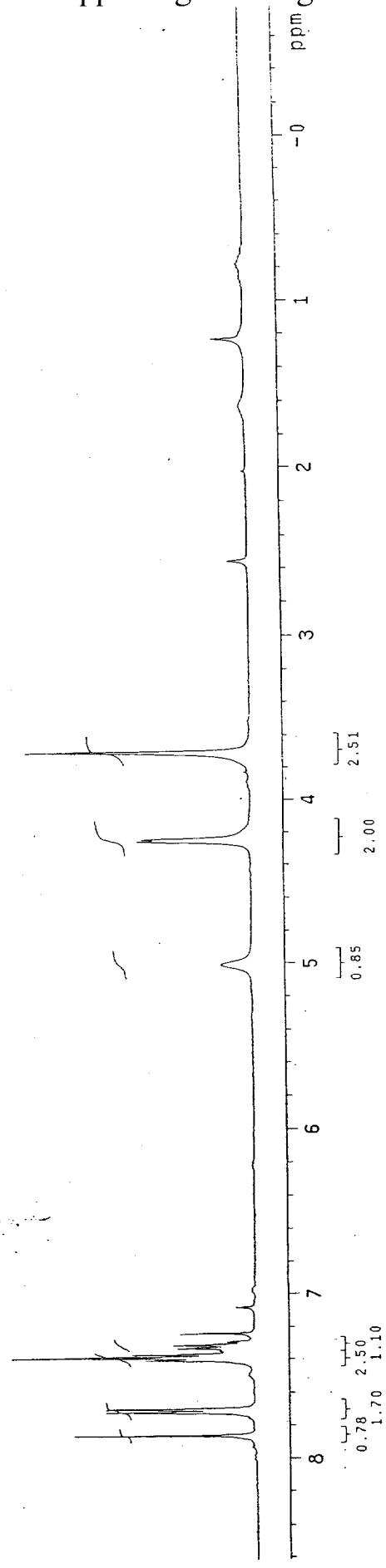
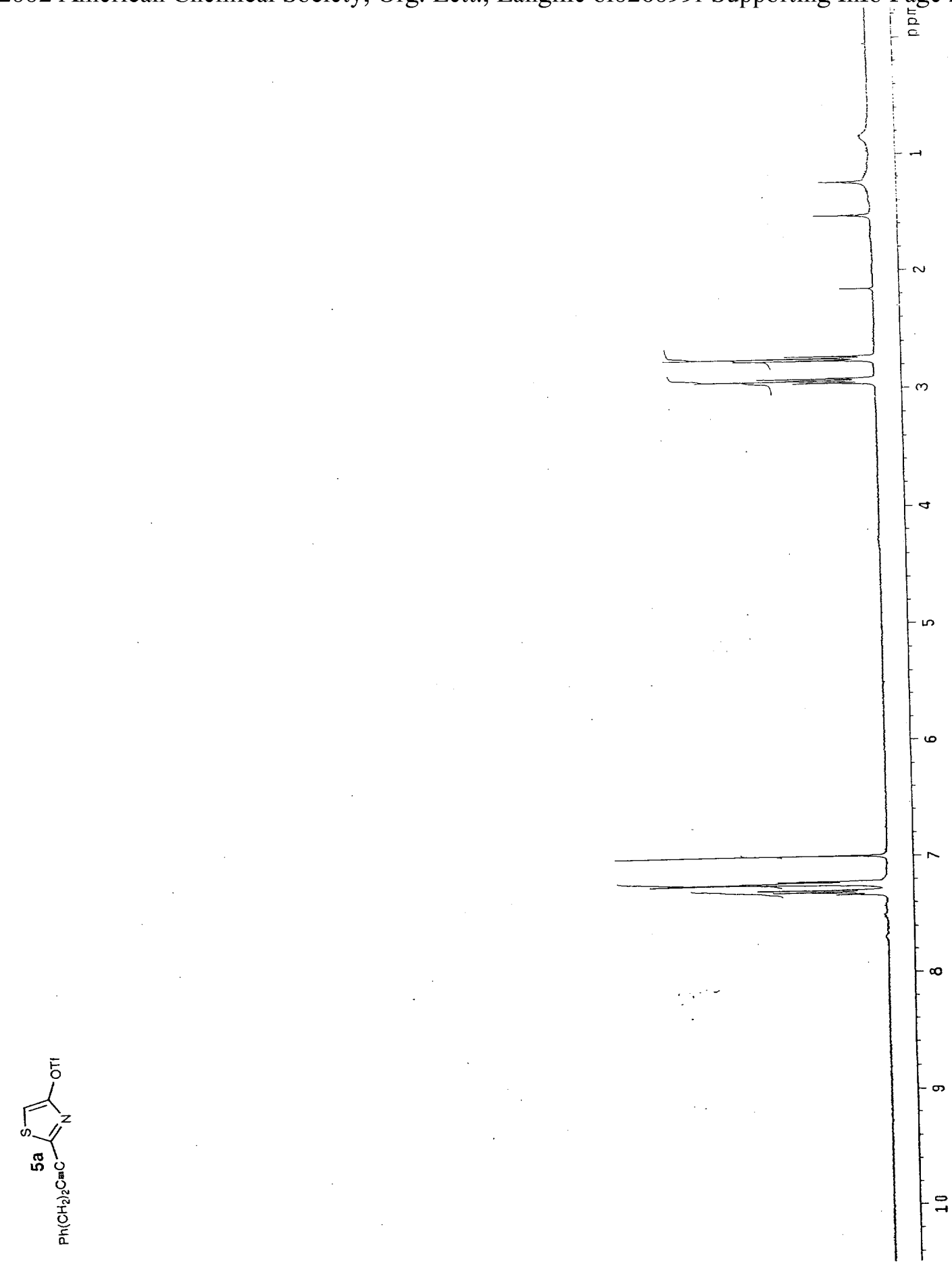
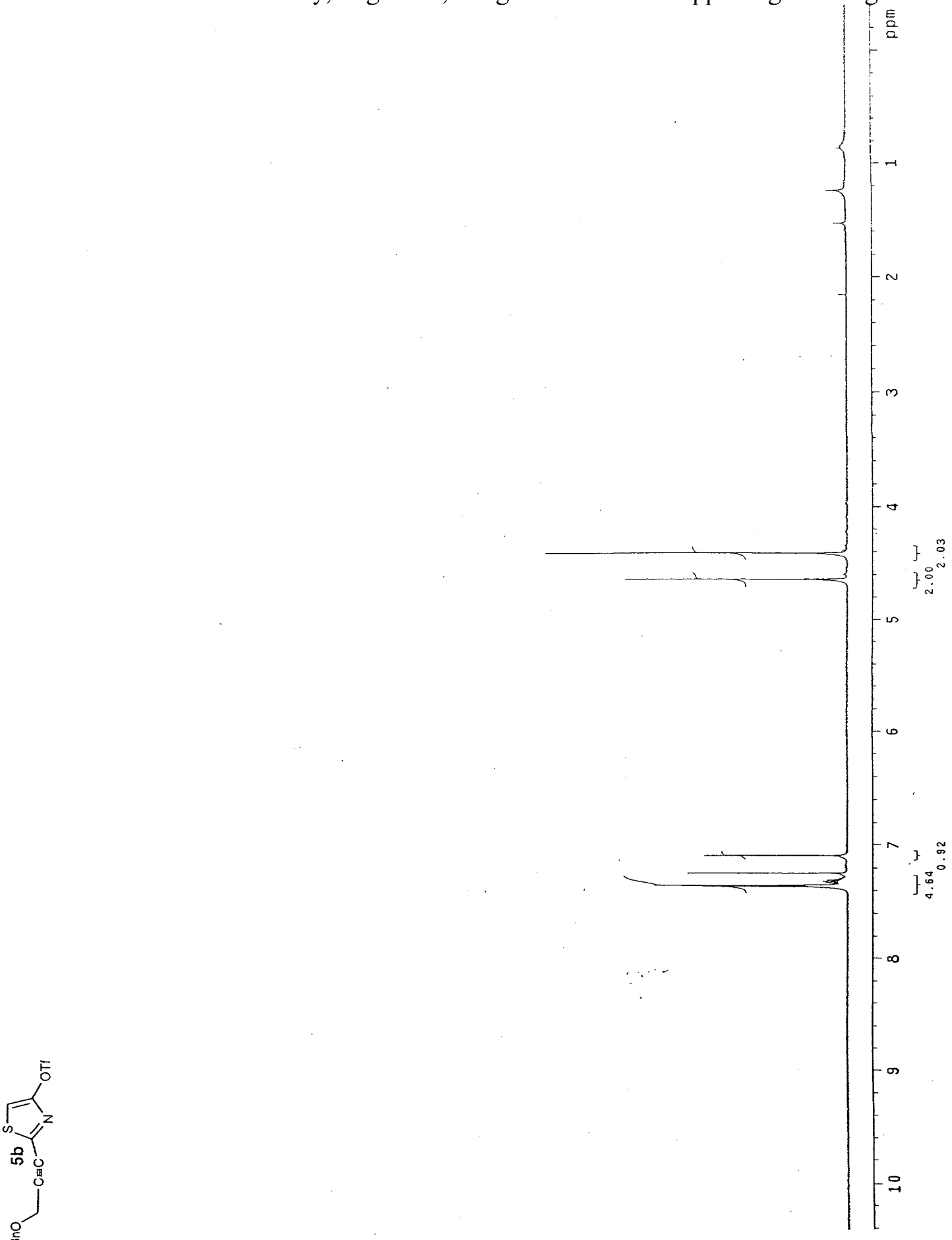
0.18
0.17
0.08
0.09
0.16
OTBS
20
C≡C
O
N
Ph






ppm
1
2
3
4
5
6
7
8
9
10
OTf
S
N
5a
Ph(CH2)2C≡C


ppm
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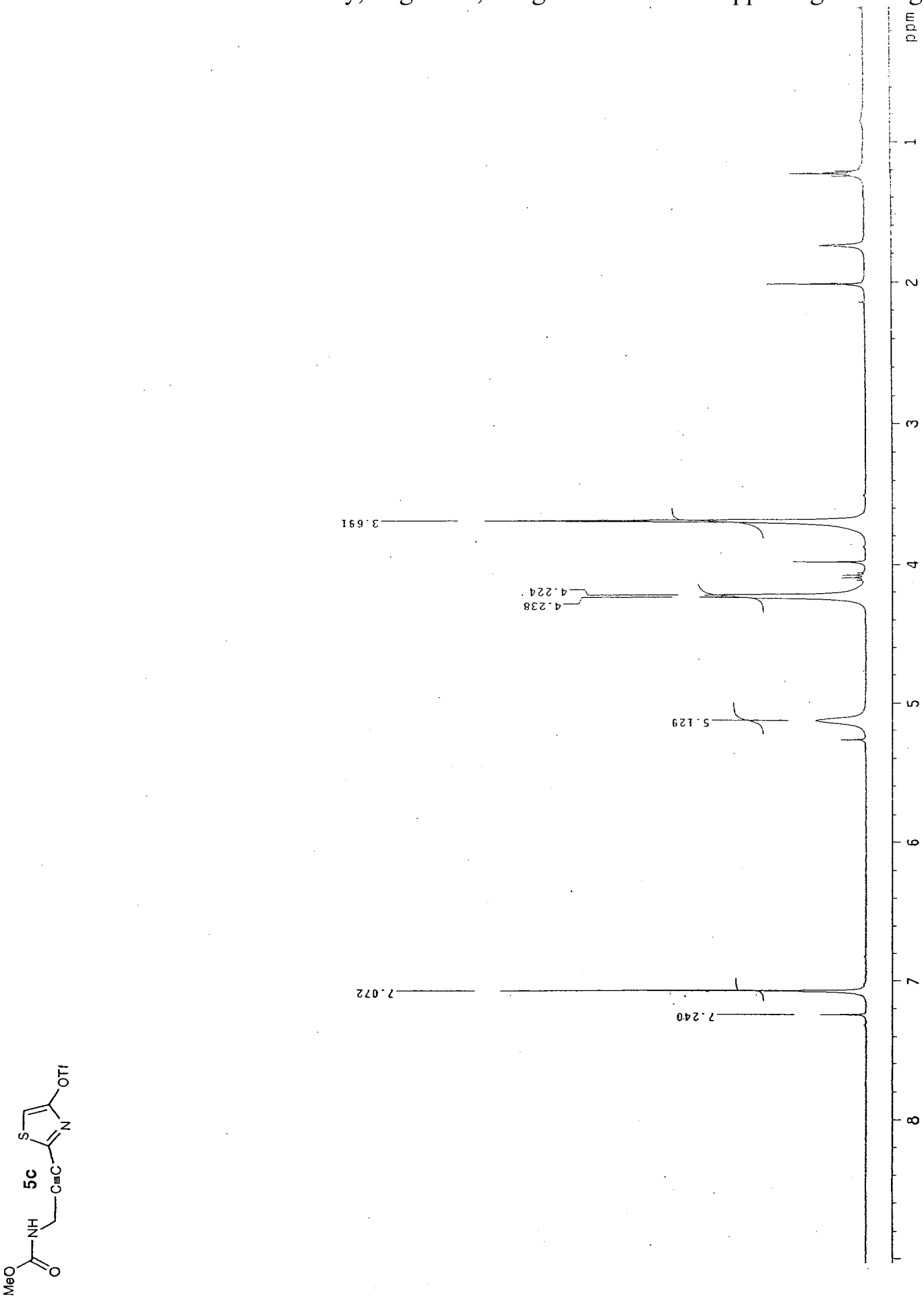
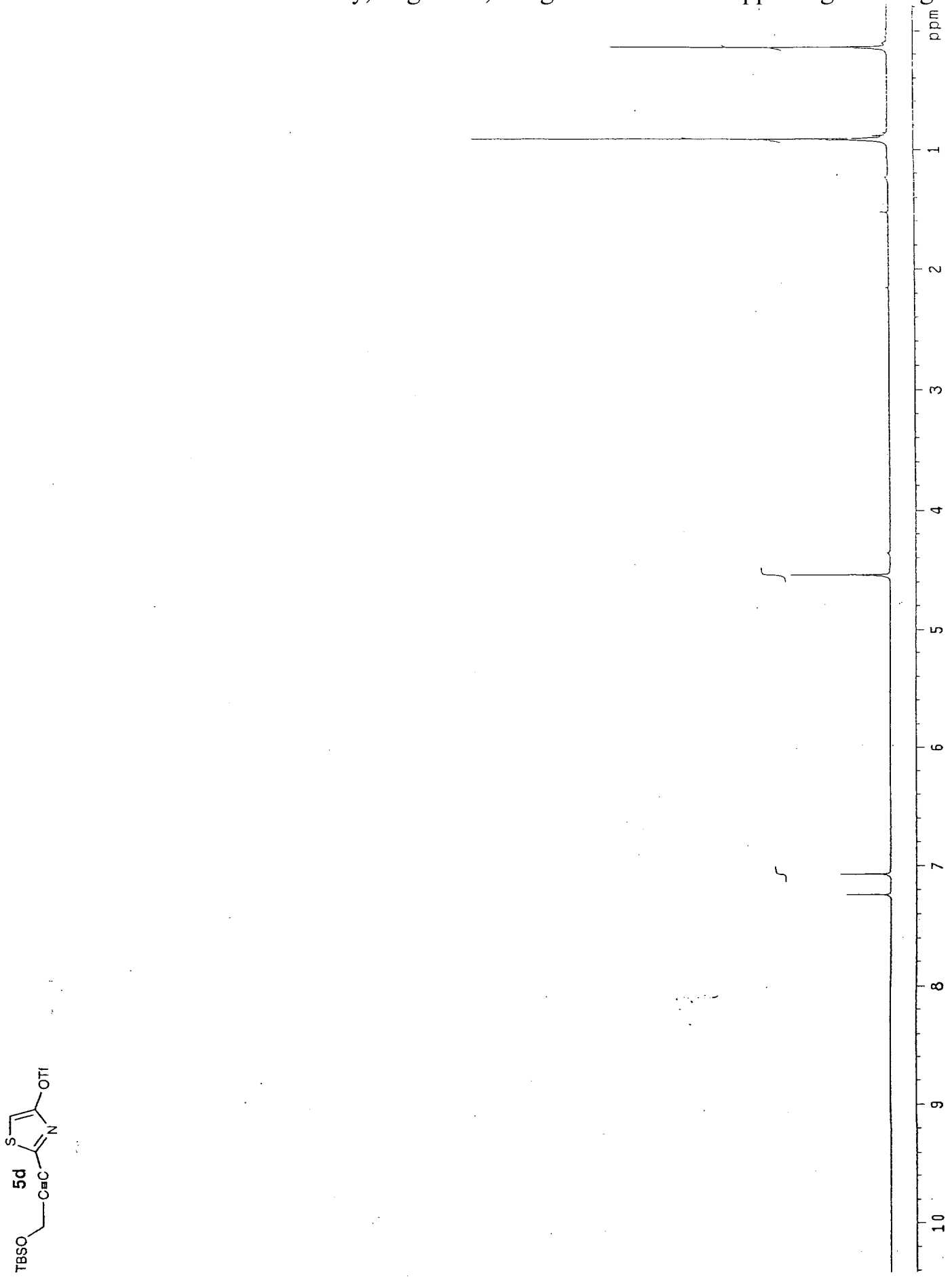
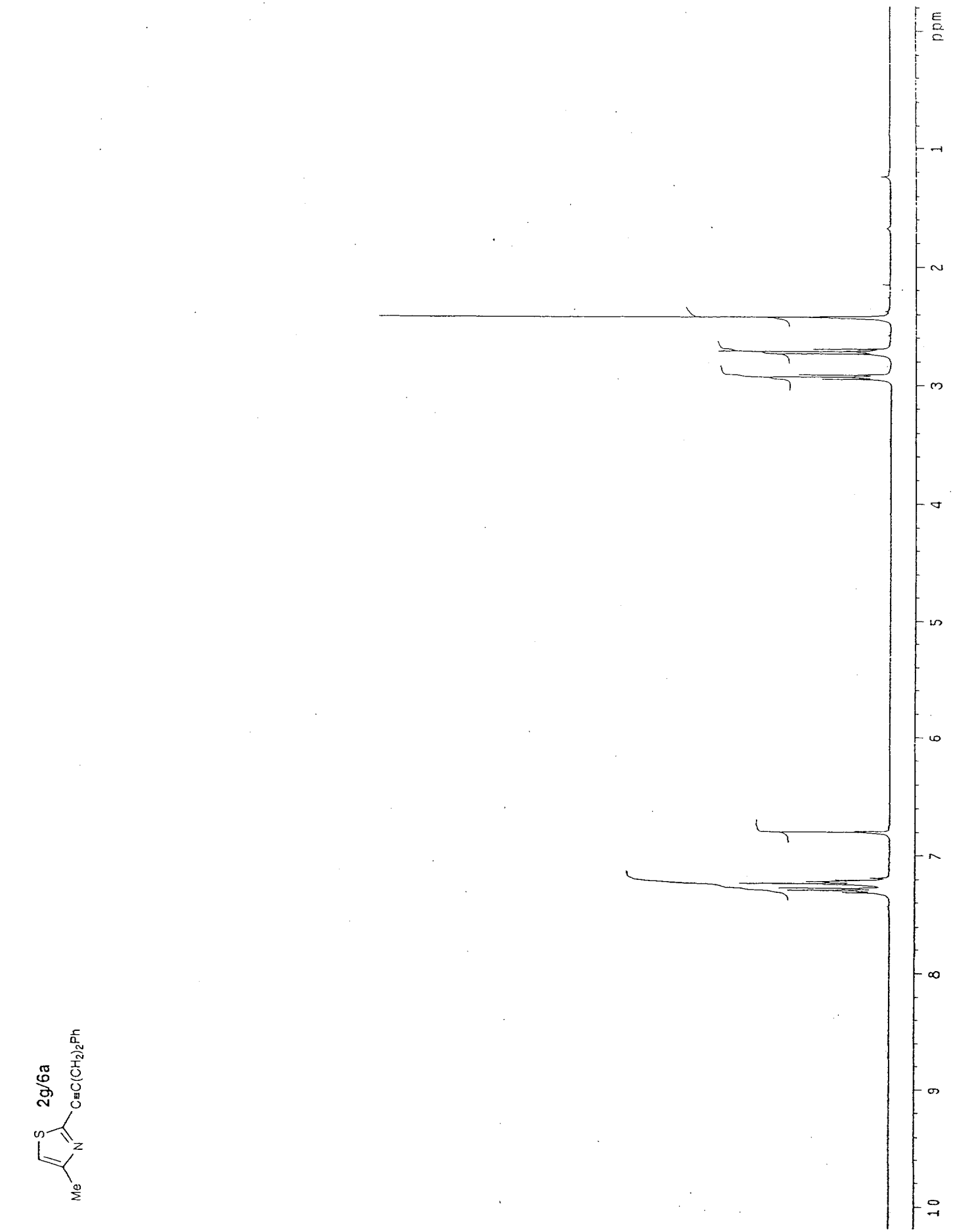
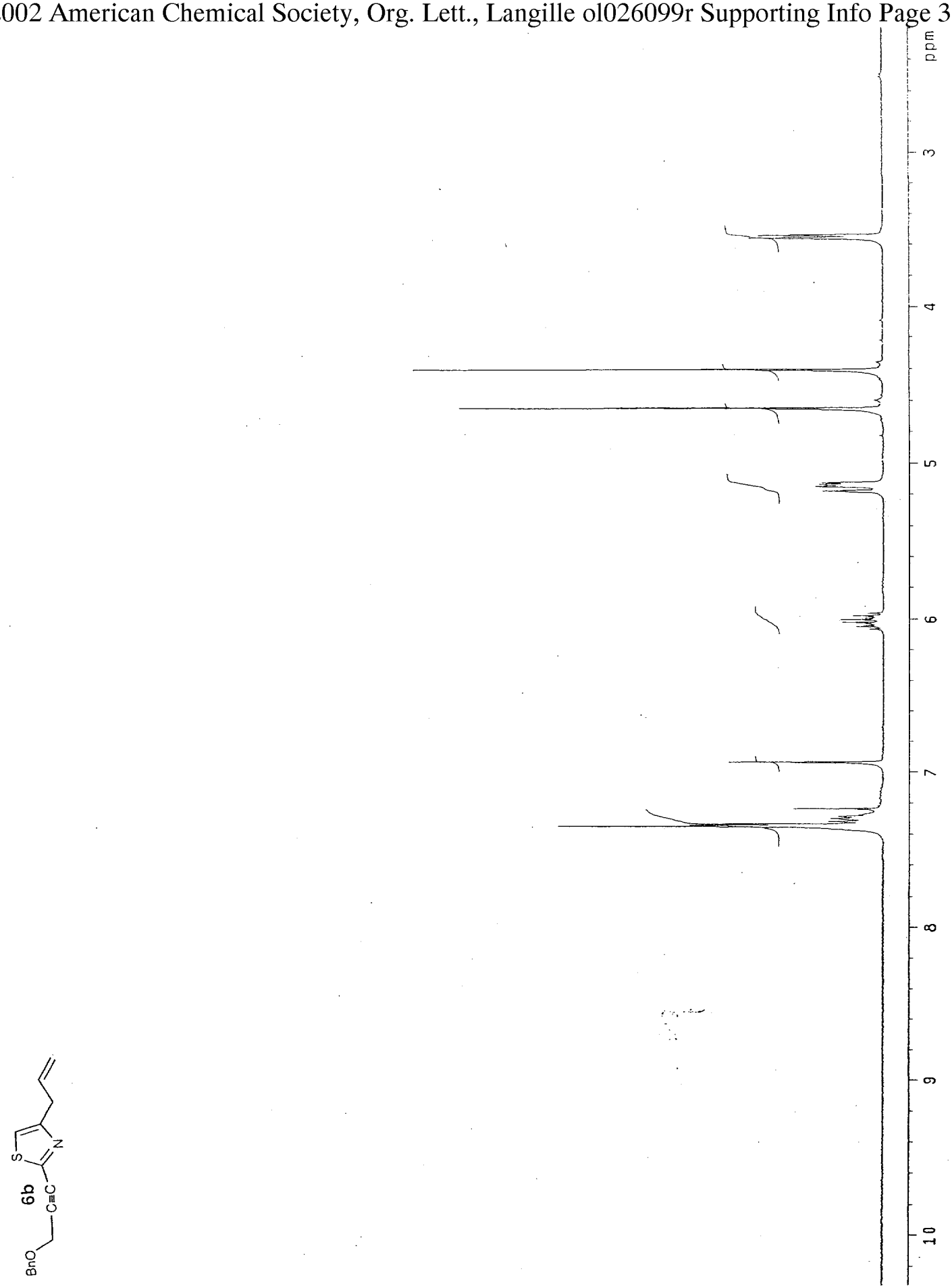
2
3
4
5
6
7
8
9
10
2.00
2.03
4.64
0.92
OTf
S
N
5b
C≡C
BnO

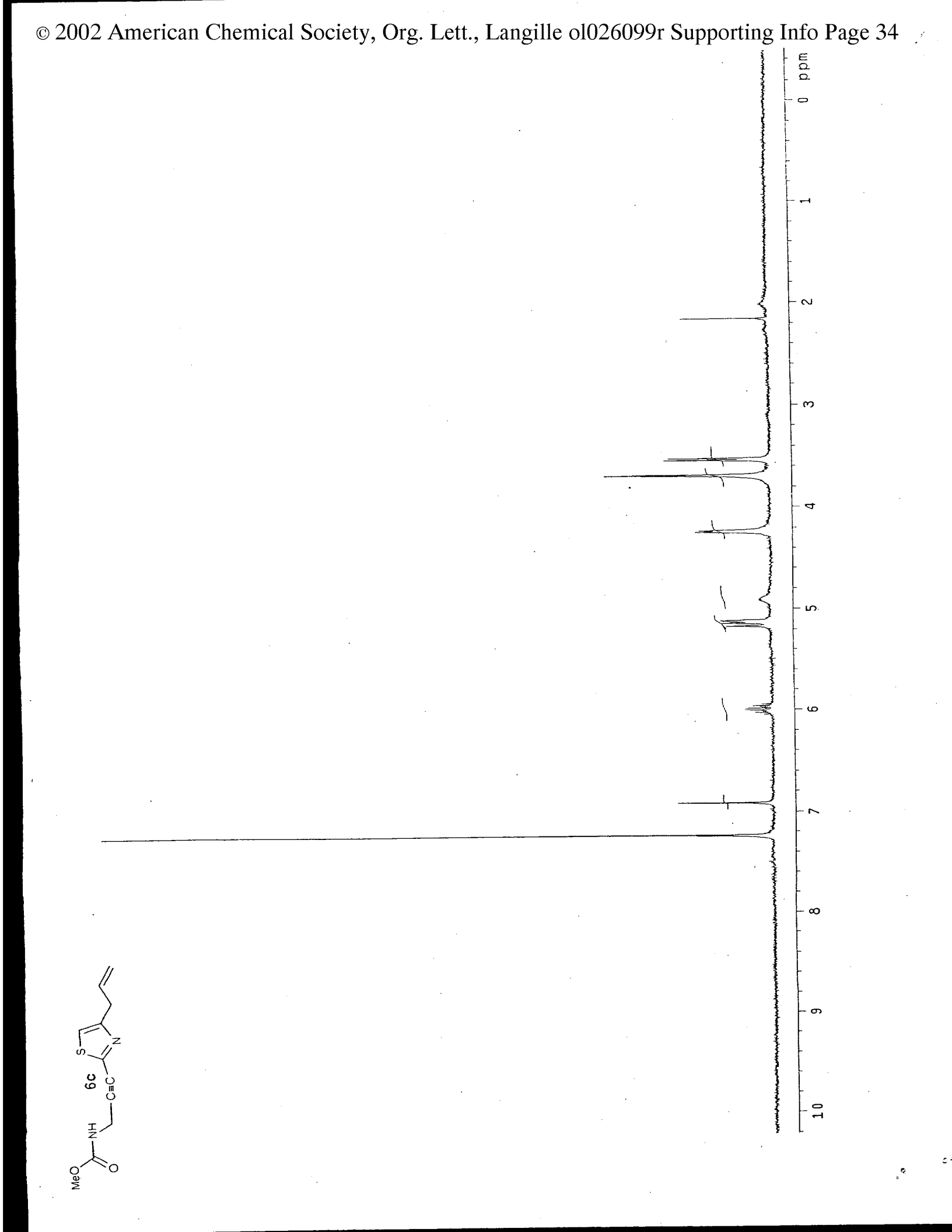





ppm
1
2
3
4
5
6
7
8
9
10

2g/6a
S
N
Me
C≡C(CH2)2Ph


ppm
3
4
5
6
7
8
9
10
6b
BnO
C≡C
S
N


ppm
0
1
2
3
4
5
6
7
8
9
10
6c
MeO
NH
O
C≡C
S
N