Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Selective Thioacylation of Amines in Water: A Convenient Preparation of Secondary Thioamides and Thiazolines

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Contents

1. General details

Reagents were obtained from commercial supplier, and used without further purification. Thioamide for Entry No. 9,15, 16, 17 and 18 were prepared by thionation of corresponding amide by reported method.[1] Melting point were measured by scientific-MP-DS melting point apparatus. Thin-layer chromatography (TLC) was conducted with E-Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized *via* UV and Iodine. Column chromatographic purification of products was performed on silica gel (60-120 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE II 400 MHz and 600 MHz.. Chemical shifts were expressed in parts per millions (**δ)** downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra was obtained in Agilent 5975C GC-MS with DB5-MS (30.0 m x 0.25 mm) and Elemental analysis was performed on Elementar vario MICRO cube CHNS analyser.

1- U. Pathak, L. K. Pandey and R. Tank, *J. Org. Chem.*, 2008, 73, 2890.

2. Experimental procedure

(1) General experimental procedure for thioacylation of primary amines (entry 1-5,7-13) - Amine (2 mmol) mixed with 300 µl of water taken in a test tube fitted with a condenser. Contents were neutralised carefully with 5N HCl. Thioamide (2 mmol) was added and this was followed by addition of 0.5 mmol of reactant amine. Reaction mixture was heated at a temperature indicated in table 1 (main manuscript) with constant stirring till the reaction is complete. Monotoring of the reaction was done by GC-MS and TLC. On completion of the reaction contents were cooled and acidified with 5 N HCl. An oily layer or ppt. gets separated which was removed either by phase separtion or extraction with DCM or filtration and washed with 5% sodium bicarbonate solution. Organic layer was dried over sodium sulphate and solvent removal under vacuum yielded the desired compound. Further purification can be achieved either by column chromatography or recrystalliastion. In case of entry 13, after completion of the reaction conents were neutralised with 5% sodium carbonate solution, extracted with DCM and the compound was purified by column chromatography.

(2) Experimental procedure for the preparation of N-Propyl-thionicotinamide (entry 6)- Propylamine 2.5 mmol (212 µl) was mixed with 350 µl of water and thionicotinamide 2 mol (276 mg) was added. Reaction was heated at 70-80 °C till completion. On completion of the reaction contents were cooled. Light yellow ppt. of the product appears which were removed by filtration. Further purification was achieved by recrystallisation from DCM- hexane.

(3) Procedure for the preparation of 2-substituted thiazolines from primary thioamides and aminoethanol (entry 14-17) 2-Aminoethanol (3 mmol) mixed with 500 µl of water was taken in a test tube fitted with a condenser. Contents were neutralised carefully with aq. HBr. This was followed by addition of thioamide (2 mmol), and 2-aminoethanol 0.5 mmol. Reaction mixture was heated at a temperature indicated in table 1 (main manuscript) with constant stirring and monitored by TLC. On near complete disappearence of thioamide aq. HBr (48%), 200 µl was added, and reaction was continued as indicated in table 1(main manuscript). On completion of the reaction, contents were cooled and treated with 5% sodium bicarbonate solution. Either an oily layer or ppt. appears. Isolation was done either by solvent extarction or filtration. Solid products were further purified by recrystallisation from DCM-hexane, and for oils purification was achieved by column chromatography.

3. Spectroscopic characterization data

N-Propyl-thiobenzamide (2): Oil[1a]; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.72-7.71 (m,2H), 7.47 (S, 1H) ,7.45-7.35 (m,3H), 3.80-3.75 (m,2H), 1.81-1.76 (m,2H), 1.04 (t,3H, *J*=7.2 Hz); EIMS: m/z 77 (34%), 104 (87%), 105 (9%), 121 (100%), 122 (14%), 150 (22%), 178 (59%), 179 [M^+](88%); Anal. Calcd for $C_{10}H_{13}NS$. C, 66.99; H, 7.31; N, 7.81; S, 17.89. Found C, 66.90; H, 7.19; N, 7.92; S, 17.99.

1-Pyrrolidin-1-yl-ethanethione (3): Solid mp 64-66 °C[1b]; ^{1}H NMR (400MHz, $CDCl_3$): δ 3.85 (t,2H, *J*=7.2 Hz), 3.60 (t, 2H, *J*=6.8 Hz) 2.59 (s, 3H), 2.11-2.07 (m,2H), 2.03-2.00 (m,2H); EIMS: m/z 59 (24%), 68 (80%), 70 (34%), 96 (18%), 129 [M^+](100%). C, 55.77; H, 8.58; N, 10.84; S, 24.81; Anal. Calcd for $C_6H_{11}NS$. C, 55.77; H, 8.58; N, 10.84; S, 24.81. Found. C, 55.72; H, 8.59; N, 10.88; S, 24.81

N-Phenethyl-thioacetamide (4): Solid mp 48-50 °C[1c;] ^{1}H NMR (400MHz, $CDCl_3$): δ 7.34-7.21 (m, 5H), 3.94-3.89 (m, 2H), 2.97(t, 2H, *J*=7.2 Hz), 2.49 (s,3H); EIMS: m/z 59 (15%), 78 (9%), 91 (11%), 103 (12%), 104 (100%), 105 (15%), 179 [M^+] (37%); Anal. Calcd for $C_{10}H_{13}NS$. C, 66.99; H, 7.31; N, 7.81; S, 17.89. Found C, 66.23; H, 7.35; N, 7.70; S, 18.72.

N-Benzyl-thioacetamide (5): Solid mp 65-66 °C[1d;] ^{1}H NMR (400MHz, $CDCl_3$): δ 7.40-7.31 (m, 5H), 4.81 (d,2H, *J*= 4 Hz)), 2.58 (s, 3H); EIMS: m/z 59 (12%), 65 (15%), 91 (99%), 92 (11%), 106 (31%), 132 (24%), 165 [M^+] (100%); Anal. Calcd for $C_9H_{11}NS$. C, 65.41; H, 6.71; N, 8.48; S, 19.40. Found C, 65.21; H, 6.65; N, 8.34; S, 19.80.

N-Propyl-thionicotinamide(6): Light yellow solid mp 96°C; ^{1}H NMR (400MHz, $CDCl_3$): δ 8.88(d, 1H, *J*= 3.6), 8.69 (dd, 1H , J_1= 9.6, J_2=2.4), 8.15-8.12(m, 1H), 7.75 (br, S , 1H),7.38-7.28 (m, 1H), 3.85-3.81 (m,2H), 1.86-1.81 (m, 2H), 1.08 (t,3H, *J*=7.2 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 196.35, 151.62,146.16, 137.84, 135.38, 123.36, 48.66, 21.45, 11.55; EIMS: m/z 69 (9%), 78 (22%), 105 (85%), 119 (11%), 121 (94%), 123 (17%), 151 (15%), 179 (62%), 180 [M^+] (100%), 181 (14%); Anal. Calcd for $C_9H_{12}N_2S$. C, 59.96; H, 6.71; N, 15.54; S, 17.79. Found C, 59.82; H, 6.79; N, 15.42; S, 17.86

Phenyl-Pyrrolidine-1-yl methane thione (7): Solid mp 73-75 °C[1e;] ^{1}H NMR (400MHz, $CDCl_3$): δ 7.36-7.33 (m,5H), 3.98 (t,2H, *J*=6.8), 3.47 (t,2H, *J*=6.8 Hz), 2.12-2.05 (m,2H), 2.00-1.94 (m,2H);

EIMS: m/z 70 (25%), 77 (27%), 104 (32%), 121 (65%), 122 (19%), 130 (83%), 131 (9%), 158 (21%), 190 (40%), 191 [M^+](100%); Anal. Calcd for $C_{11}H_{13}NS$. C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found

C, 69.12; H, 6.89; N, 7.28; S, 16.81

N-Phenethyl-thiobenzamide (8): Solid mp 98 °C[1f]; ^{1}H NMR (600MHz, $CDCl_3$): δ 7.66-7.28 (m,1H), 4.17-4.12 (m,2H), 3.12 (t, 2H, *J*=10.2 Hz);EIMS: m/z 77 (18%), 104 (100%), 121 (35%), 241 [M^+](36%); Anal. Calcd for $C_{15}H_{15}NS$. C, 74.65; H, 6.26; N, 5.80; S, 13.29. Found . C, 74.95; H, 6.20; N, 5.75; S, 13.10.

1-Pyrrolidin-1-yl-pentane-1-thione (9): Oil; ^{1}H NMR (400MHz, $CDCl_3$): δ 3.86 (t, 2H, J=6.8), 3.63(t, 2H,J=6.8), 2.70 (t, 2H,J=8), 2.09-2.06 (m,2H), 1.99-1.96 (m,2H), 1.76-1.74 (m,2H), 1.44-1.38 (m,2H), 0.94 (t,3H,J=7.2Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$) 200.87, 53.82, 50.52, 44.01, 31.06, 26.42, 24.35, 22.55, 13.89; EIMS: m/z 55(14%), 68 (27%), 70 (92%), 72 (19%), 96 (66%), 110 (17%), 128 (22%), 129 (75%), 138 (23%), 142 (19%), 171 [M^+] (100%), 172 (11%); Anal. Calcd for $C_9H_{17}NS$. C, 63.10; H, 10.00; N, 8.18; S, 18.72. Found C, 62.97; H, 10.14; N, 8.11; S, 18.78.

N-(2-Hydroxy-ethyl)-thiobenzamide (10): Light yellow Solid mp 96 °C[1g] ; ^{1}H NMR (600MHz, $CDCl_3$): δ 8.08(br, s, 1H), 7.81-7.80 (m, 2H), 7.50-- 7.41 (m, 3H), 4.09-4.01 (m,4H), 1.99 (s, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 203.51, 141.72, 131.24, 128.55, 126.74, 60.63, 48.50; EIMS: m/z 51 (12%), 77 (46%), 105 (100%), 117 (18%), 122 (33%), 134 (10%), 147 (11%), 181[M^+](10 %). (Anal. Calcd for $C_9H_{11}NOS$. C, 59.64; H, 6.12; N, 7.73; O, 8.83; S, 17.69. Found C, 65.86; H, 6.12; N, 7.72; O, 8.81; S, 17.61

1-Morpholin-4-yl-ethanethione (11): Solid mp 89-91 °C[1h]; ^{1}H NMR (400MHz, $CDCl_3$): δ 4.34 (t,2H, J=4.8 Hz), 3.79 (t, 2H, J=4.8 Hz), 3.75 (s,4H), 2.67 (s,3H); EIMS: m/z 59 (12%), 65 (15%), 91 (99%), 92 (11%), 106 (31%), 132 (24%), 165 [M^+] (100%), 166 (11%); Anal. Calcd for $C_6H_{11}NOS$. C, 49.62; H, 7.63; N, 9.64; O, 11.02; S, 22.08. Found C, 49.48; H, 7.63; N, 9.59; O, 11.12; S, 22.18.

1-Piperidin-1-yl-ethanethione (12): Solid mp 55-56 °C ; ^{1}H NMR (400MHz, $CDCl_3$): δ 4.28-4.27 (m, 2H), 3.68 (t, 2H, J=5.2 Hz), 2.66 (s, 3H), 1.72-1.66 (m,6H) EIMS: m/z 55 (9%), 56 (11%), 59 (32%), 68 (14%), 69 (29%), 82 (16%), 84(37%), 110 (30%), 143 [M^+] (100%), 144 (9%).

N-(2-Piperazin-1-yl-ethyl)-thiobenzamide (13): Yellow viscous liquid; ^{1}H NMR (600MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.78 (d, 2H. *J*= 6.0 Hz), 7.49 (t, 1H, *J*=6.0 Hz), 7.42 (t, 2H, *J*=6.0 Hz) 3.93 -3,90 (m, 2H), 3.14-3.13 (m, 4H), 2.81 (t, 2H, *J*=6.0 Hz) 2.76 (S, 4H);^{13}C NMR (150.9 MHz, $CDCl_3$) δ 198.88, 141.41, 131.24, 128.60, 128.52, 127.55, 126.73, 55.14, 50.61, 43.98, 42.73; EIMS: m/z 56 (39%), 57 (11%), 58 (17%), 60 (12%), 70 (48%), 77 (22%), 84 (12%), 85 (10%), 97 (11%), 99 (100%), 103 (21%), 104 (20%), 112 (94%), 121 (38%), 164 (13%), 249[M^+] (5%)Anal. Calcd for $C_{13}H_{19}N_3S$. C, 62.61; H, 7.68; N, 16.85; S, 12.86. Found $C_{13}H_{19}N_3S$. C, 62.65; H, 7.66; N, 16.72; S, 12.97.

2-Phenyl-4,5-dihydro-thiazole (14): Yellow oil[2a]; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.9-7.8 (m, 2H), 7.4-7.3 (m, 3H), 4.45 (t, 2H, *J*=8.4 Hz), 3.40 (t, 2H, *J*=8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.69, 132.87, 130.68, 128.06, 127.97, 64.85, 33.82; EIMS: m/z 59 (18%), 60 (76%), 77(21%), 103(10%), 104(22%), 117(22%),163 [M^+] (100%); Anal. Calcd for C_9H_9NS. C, 66.22; H, 5.56; N, 8.58; S, 19.64. Found C, 66.34; H, 5.51; N, 8.55; S, 19.60.

2-(4-Tolyl)-4, 5-dihydro-[1, 3]-thiazole(15): Yellow solid (m.p: 41-42°C)[2b]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 2H, *J*=8.0 Hz), 7.17 (d, 2H, *J*=8.0 Hz), 4.41 (t, 2H, *J*=8.4 Hz), 3.36 (t, 2H, *J*=8.4 Hz), 2.35 (s, 3H); EIMS: m/z 59 (15%), 60 (79%), 89(14%), 91(15%), 116(19%), 117(31%), 118(35%), 131(225), 177[M^+](100%). Anal. Calcd for C_{10} $H_{11}NS$. C, 67.75; H, 6.25; N, 7.90; S, 18.09. Found C, 67.69; H, 6.28; N, 7.88; S, 18.14

2-(4-Methoxy-phenyl)-4,5-dihydro-thiazole (16): Solid mp 43-44 °C[2b]; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.78 (d, 2H *J*= 8 Hz), 6.91 (d, 2H, *J*= 8 Hz), 4.42 (t,2H,*J*=8 Hz), 3.84 (s, 3H), 3.39 (t, 2H, *J*= 8 Hz); EIMS: m/z 60 (8%), 90 (10%), 103 (10%), 133 (100%), 134 (16%), 147 (10%), 193[M^+] (41%).
Anal. Calcd for $C_{10}H_{11}NOS$. C, 62.15; H, 5.74; N, 7.25; O, 8.28; S, 16.59. Found C, 62.14; H, 5.76; N, 7.22; O, 8.23; S, 16.65.

2-(4-Bromo-phenyl)-4,5-dihydro-thiazole (17): Solid mp 90-92 °C[2c]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.71 (m, 2H), 7.61-7.54 (m, 2H), 4.44 (t, 2H, *J*=8.4 Hz), 3.47 (t, 2H, *J*=8.4 Hz); EIMS: m/z 77,60, 104,117, 163 [M; Anal. Calcd for C_9H_8BrNS. C, 44.64; H, 3.33; Br, 33.00; N, 5.78; S, 13.24. Found C, 44.54; H, 3.35; Br, 33.14; N, 5.77; S, 13.20.

References-

1. (a) R. C. Moreau, P. Loiseau; *Annales Pharmaceutiques Francaises*, 1978, 36, 269. (b) E. Schaumann, S. Scheiblich, U. Wriede, G. Adiwidjaja, *Chemische Berichte,* 1988, 6, 1165. (c S. Yamada, A.M. M. E. Omar, T.Hino; *Chemical & Pharmaceutical Bulletin,* 1964, **2**, 244. (d) Maurice J. Schlatter, *J. Am. Chem. Soc.*, 1942, 64, 2722. (e) K. Shiosaki, G. Fels, H. Rapoport, *J. Org. Chem.*, 1981, 16, 3230. (f) W. F. Russell, *Journal of the Chemical Society, Transactions,* 1910, 953. (g) Alan A. Goldberg, W. Kelly, J. *Chem. Soc*., 1948, 1919. (h) Neal O. Brace, *J. Am. Chem. Soc*., 1953, 75, 357. (i) C. S. Marvel, P. de Radzitzky, James J. Brader, *J. Am. Chem. Soc*., 1955, 5997.

2. (a) Y. Kodama, M. Ori, T. Nishio, *Helvetica Chimica Acta*, 2005, Vol. 88, 187. (b) I. Mohammadpoor-Baltrok, M. Moghadam, S. Tangestaninejad, V. Mirkhani, S. F. Hojati, *Cat. Comm.*, 2008, 9, 1153. (c) Y. Robbe, J. P. Fernandez, J. P. Chapat, H. S. Roumanou, M. Fatome, G. Subra, *Eur. J. Med. Chem. Chim-Ther*., 1985, 20, 16. (d) A. R. Katritzky, C. Cai, K. Suzuki, S. K. Singh, *J. Org. Chem*. 2004, 69, 811. (e) A. Zhou, Charles U. Pittman, *Tetrahedron Lett*., 2004, 48, 8899

4. Selected copies of ^{1}H NMR and ^{13}C NMR

(i) **^{1}H NMR spectra of N-Propyl-thionicotinamide(6)**

(ii) **^{13}C NMR spectra of N-Propyl-thionicotinamide(6)**

(iii) **^{1}H NMR spectra of 1-Pyrrolidin-1-yl-pentane-1-thione (9)**

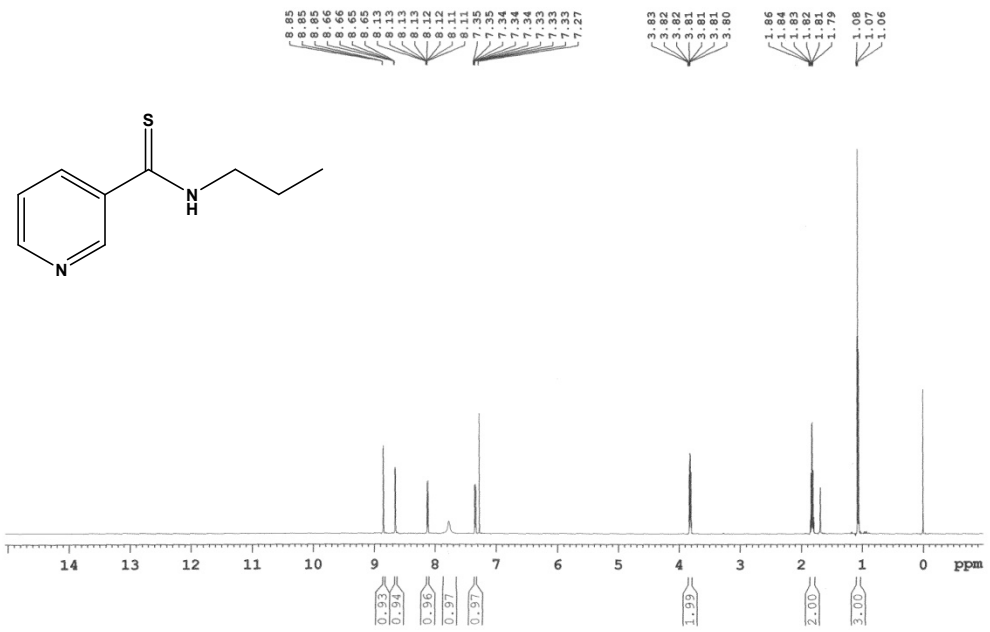
(iv) **^{13}C NMR spectra of 1-Pyrrolidin-1-yl-pentane-1-thione (9)**

(v) **^{1}H NMR spectra of N-(2-Hydroxy-ethyl)-thiobenzamide (10)**

(vi) **^{13}C NMR spectra of N-(2-Hydroxy-ethyl)-thiobenzamide (10)**

(vii) **^{1}H NMR spectra N-(2-Piperazin-1-yl-ethyl)-thiobenzamide (13)**

(viii) **^{13}C NMR spectra of N-(2-Piperazin-1-yl-ethyl)-thiobenzamide (13)**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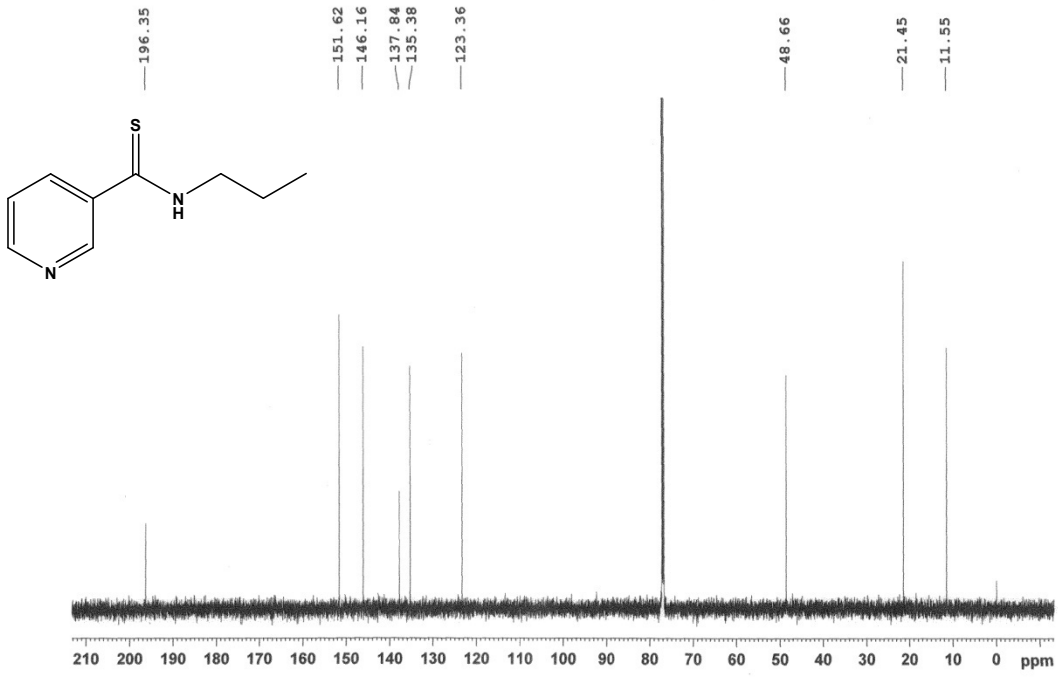
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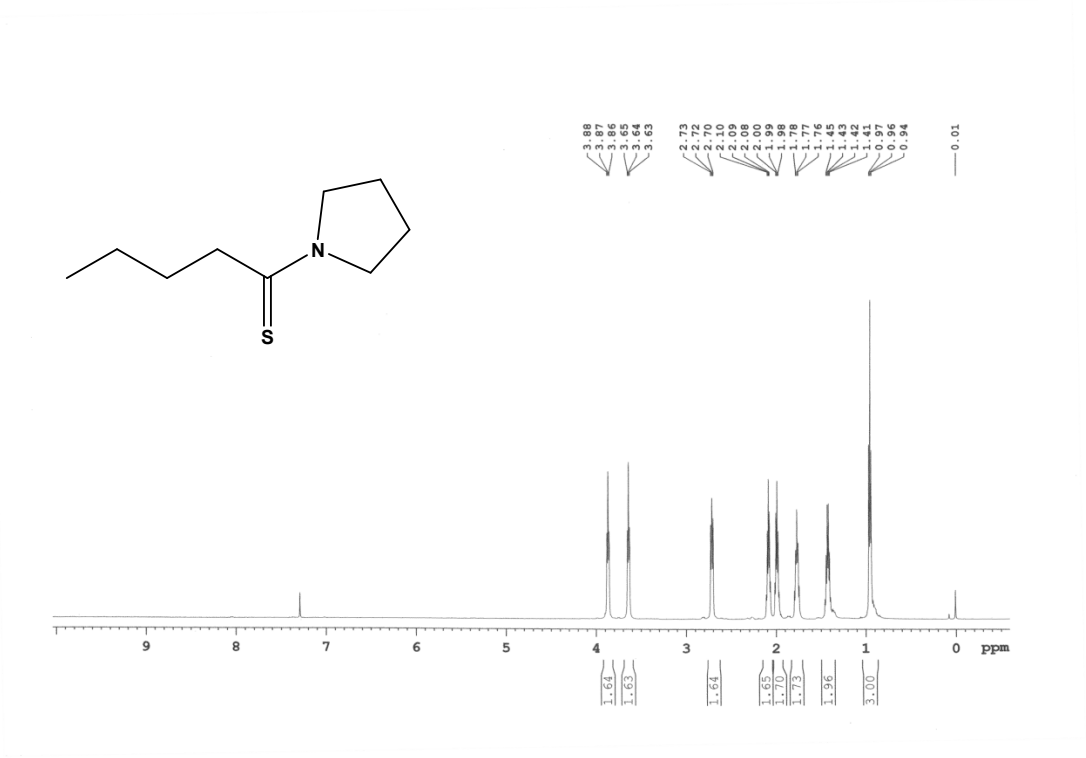
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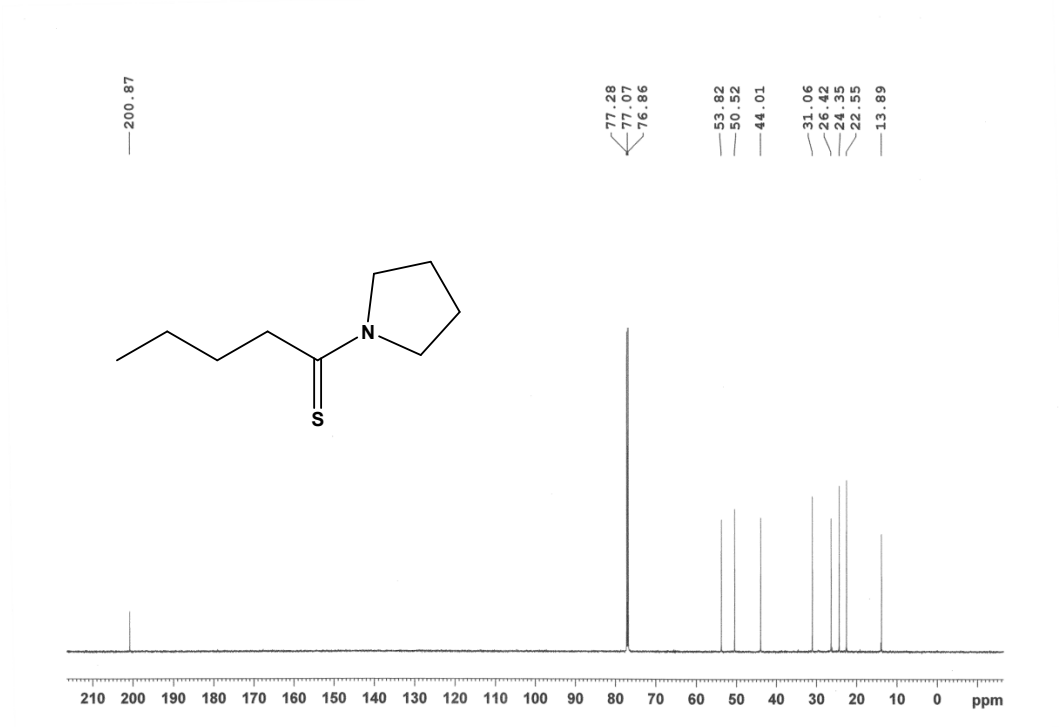
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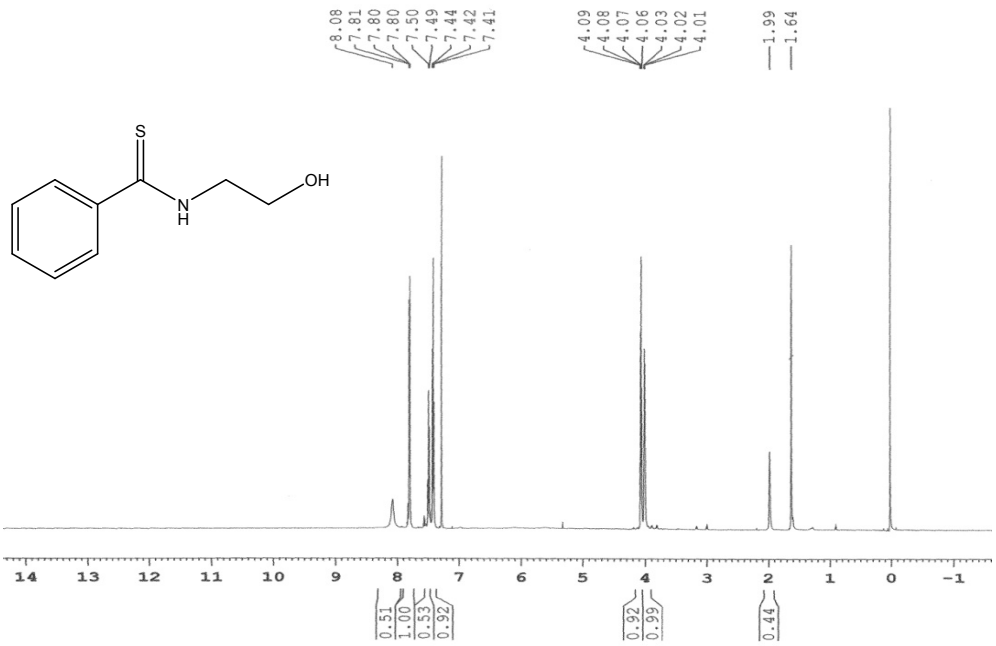
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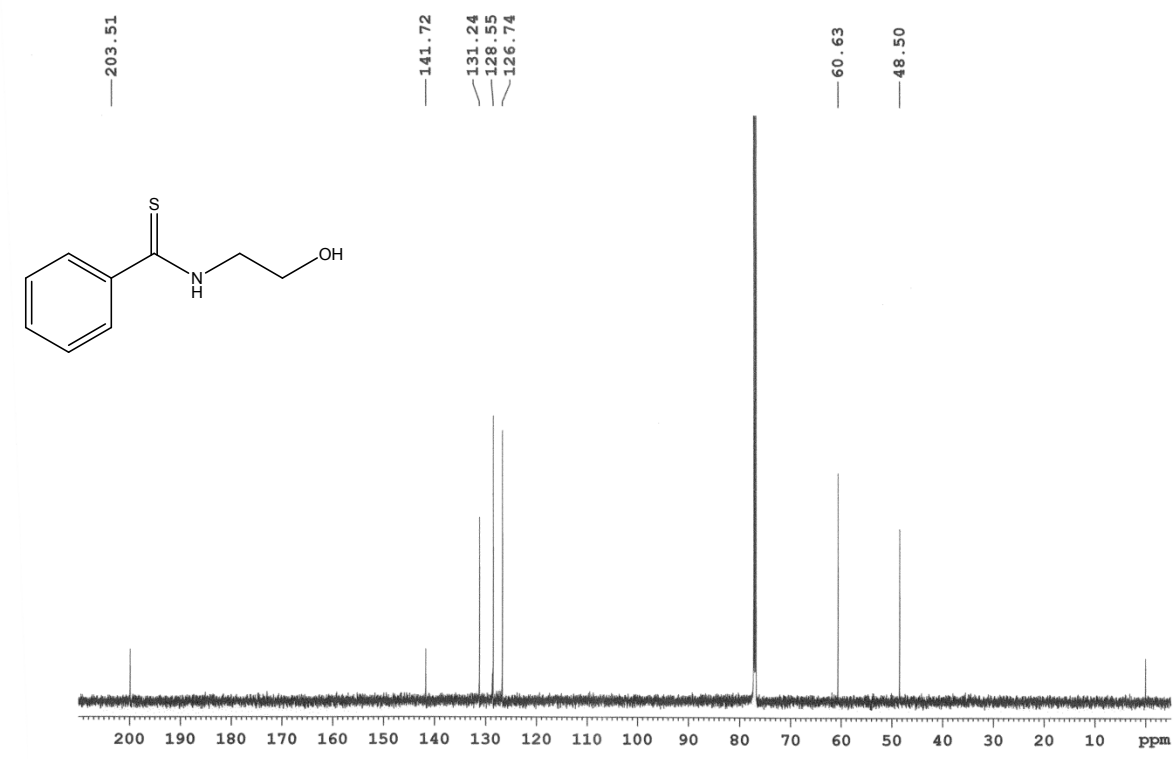
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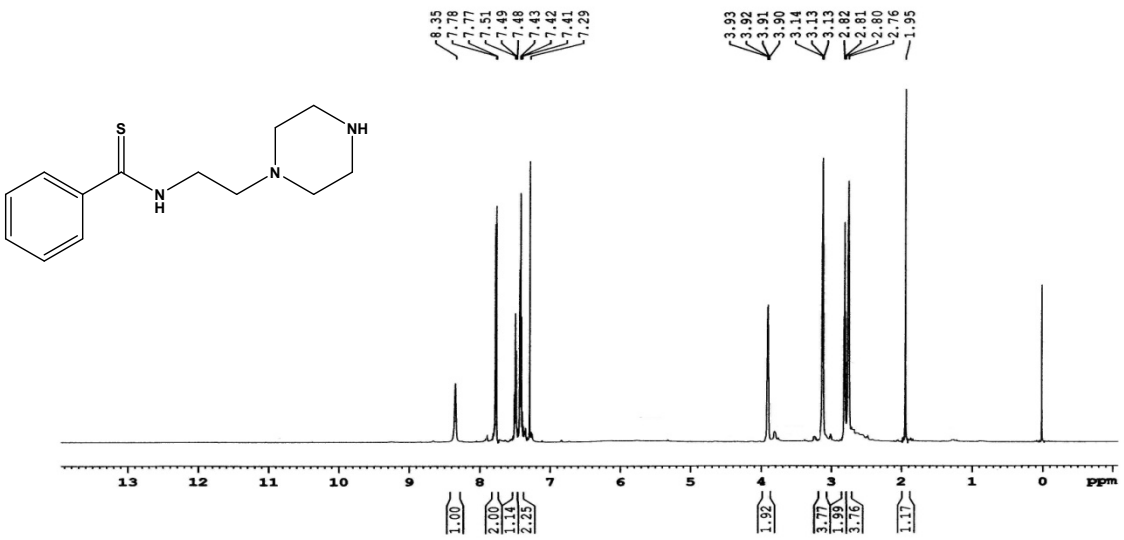
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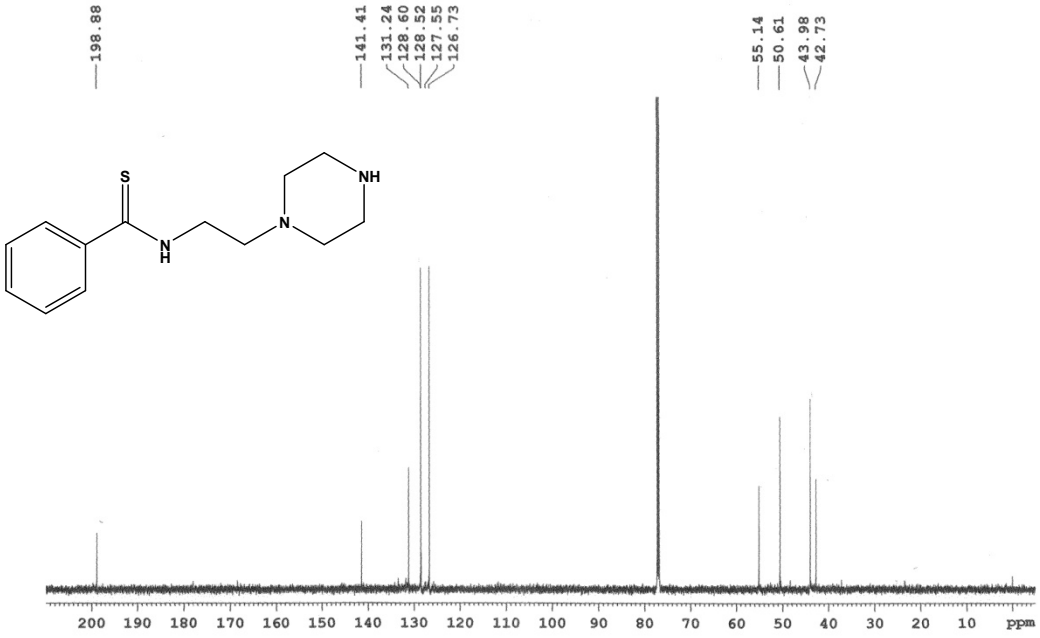
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