A convenient one-pot preparation of \(N\)-substituted thioamides

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A convenient one-pot preparation of \(N\)-substituted thioamides from acyl halides, amines and \(\text{H}_2\text{O/PSCl}_3/\text{Et}_3\text{N}\) in good to excellent yield has been reported through a solvent-free, microwave assisted method.

**Keywords**: Thionation, PSCl\(_3\), solvent-free, microwave, acyl halides, amines

\(N\)-substituted thioamides are valuable organic compounds and have wide applications\(^1,2\). Preparation of \(N\)-substituted thioamides starting from acyl halides and amines is an attractive method as it allows an easy introduction of diverse building blocks for constructing desired thioamides. This is a two step procedure. For avoiding a lengthy separation process and purification of intermediate, one-pot preparation techniques are highly preferred. The potential of one-pot procedure is enhanced if applied with microwave heating under solvent-free condition\(^3\). Herein, is reported a very convenient microwave assisted, solvent-free, one-pot procedure for the preparation of a variety of \(N\)-substituted thioamides from acyl halides and amines using \(\text{H}_2\text{O/PSCl}_3/\text{Et}_3\text{N}\) thionating system (Scheme I).

![Scheme I — Synthesis of \(N\)-substituted thioamides](image)

**Results and Discussion**

Condensation of acyl halide with amine to generate amide is usually carried out by reacting substrates in the presence of a base under solvent condition\(^4\). In search for an easy and convenient synthesis, microwave irradiation under solvent-free condition was tried out. Diethyl amine, benzoyl chloride, and TEA were mixed in 1:1:1.5 molar ratio and irradiated with microwave. A very rapid reaction occurred and the reaction was completed within minutes with excellent conversion. For the next step, a recently developed thionating system\(^5\) \(\text{H}_2\text{O/PSCl}_3/\text{Et}_3\text{N}\) was employed, which gave satisfactory results.

After having optimized the reaction conditions it was now important to determine the generality of this methodology by applying to a variety of acyl halides and amines. The result of formation of several thioamides is summarized in Table I. Excellent result was obtained in most cases. Primary and secondary amines underwent smooth amide formation and thionation.

Substituted aromatic acyl halides bearing an electron-withdrawing or electron-donating group also reacted efficiently (compounds 5, 9, 10).

In conclusion, a simple and practical approach has been developed for the preparation of \(N\)-substituted thioamides.

**Experimental Section**

**Materials and Methods**

All reagents were obtained from commercial suppliers and were used as received. Solvents were purified by standard procedures. Analytical TLC was performed on Merck 25 DC-Alufolien Kieselgel 60F\(_{254}\) aluminium-backed plates and visualization of the spots on TLC was achieved either by exposure to I\(_2\) vapors or UV light. \(^1\)H NMR spectra were recorded on a Bruker 400 MHz spectrometer using TMS as an internal standard and CDCl\(_3\) as a solvent. Chemical shift (\(\delta\)) are expressed in ppm, and coupling constants (\(J\)) are given in Hz. GC-MS spectra were recorded on a Thermo Finnigan TRACE GC mass spectrometer in
electron ionization mode. All reactions were run in an open vessel in unmodified household microwave (Samsung CE2977N) operating at 2450 MHz. The melting points were recorded in open capillary tubes and are uncorrected. Elemental analysis was performed on a Perkin-Elmer analyzer and results were found to be within 0.4% of the calculated values.

**General procedure for the synthesis of N-substituted thioamides**

Amine (5 mmole) was added slowly to the pre-cooled acyl halide (5 mmole), taken in a test tube. Triethyl amine (TEA, 7.5 mmole) was added to this mixture drop-wise with constant mixing. The temperature of the reaction-mixture was maintained at 50-60°C. Contents were mixed thoroughly and microwaved for the time specified in **Table 1**. On completion of amide formation (monitored by GC and TLC), water (7.5 mmole) was added with mixing. This was followed by slow addition of PSCl3 (7.5 mmole) and TEA (11 mmole). After the addition was over, reaction-mixture was again subjected to microwave irradiation. Throughout the reaction, microwave exposure was intermittent with 30 s break. Contents were gently mixed with the help of glass thermometer which also indicated the temperature of reaction-mixture. Depending upon the substrates, reaction temperature was found to vary from 70-100°C. On completion of the reaction, contents were adsorbed on silica gel and loaded on a column of silica gel and eluted with hexane/ethyl acetate mixture. After removal of the solvent in vacuo, the pure compound was obtained.

**Table 1 — Preparation of N-substituted thioamides**

<table>
<thead>
<tr>
<th>Compd</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Conversion [Yield]</th>
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<tr>
<td>1</td>
<td>C6H5</td>
<td>C2H5</td>
<td>C2H5</td>
<td>2+5</td>
<td>85-100</td>
<td>98[88]</td>
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<tr>
<td>2</td>
<td>CH3</td>
<td>C2H5</td>
<td>C2H5</td>
<td>2+5</td>
<td>80-90</td>
<td>95[79]</td>
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<tr>
<td>3</td>
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<td>c-C6H11</td>
<td>H</td>
<td>4+8</td>
<td>85-95</td>
<td>95[84]</td>
</tr>
<tr>
<td>4</td>
<td>C6H5</td>
<td>n-C6H7</td>
<td>H</td>
<td>4+5</td>
<td>70-85</td>
<td>97[83]</td>
</tr>
<tr>
<td>5</td>
<td>Cl-C6H4</td>
<td>n-C6H7</td>
<td>H</td>
<td>3+5</td>
<td>75-95</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
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<td>C6H6CH2</td>
<td>H</td>
<td>3+6</td>
<td>85-100</td>
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</tr>
<tr>
<td>7</td>
<td>Cl-CH2</td>
<td>n-C6H7</td>
<td>H</td>
<td>3+4</td>
<td>75-95</td>
<td>93</td>
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<tr>
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<td>C2H5</td>
<td>4+6</td>
<td>80-90</td>
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<tr>
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<td>C2H5</td>
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<td>iso-C3H7</td>
<td>H</td>
<td>3+4</td>
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<td>C6H6CH2CH2</td>
<td>H</td>
<td>2+4</td>
<td>70-90</td>
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<tr>
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<td>-</td>
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<td>H</td>
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<td>H</td>
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<tr>
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<td>-</td>
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<tr>
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<td>H</td>
<td>3+5</td>
<td>80-85</td>
<td>95[89]</td>
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</table>

All reactions were carried out at 180 W under solvent-free condition. Microwave exposure was intermittent (1 min duration) with 30 s break. A-time for amide formation and B-time for thionation. GC conversions and identification by their MS data. Isolated yield after column purification and determined from single experiment. Silica gel column chromatography (5-20% EtOAc in hexane). Formation of 2-phenyl-2,5-dihydrothiazole was observed instead of N-(2-bromoethyl)-thiobenzamide.
N, N-Diethyl-thiobenzamide, 1b

Pale yellow solid, m.p. 41-42°C. 1H NMR (400 MHz, CDCl3): δ 1.12 (t, J=7.1 Hz, 3H), 1.37 (t, J=7.0 Hz, 3H), 3.41 (q, J=7.1 Hz, 2H), 4.10 (q, J=7.1 Hz, 2H), 7.20-7.22 (m, 2H), 7.27-7.31 (m, 3H); MS(EI): m/z 193(M⁺), 192, 176, 164, 132, 121, 104, 77, 61, 51. Anal. Calcd for C13H13NS: C, 68.35; H, 7.82; N, 7.25; S, 16.59. Found: C, 68.51; H, 7.90; N, 7.32; S, 16.26%.

N, N-Diethyl-thioacetamide, 2b

Pale yellow liquid. 1H NMR (400 MHz, CDCl3): δ 1.21 (t, J=7.1 Hz, 3H), 2.59 (s, 6H), 3.53 (q, J=7.2 Hz, 2H), 3.93 (q, J=7.1 Hz, 2H); MS(EI): m/z 131(M⁺), 102, 70, 59, 42. Anal. Calcd for C6H13NS: C, 54.91; H, 9.98; N, 10.67; S, 24.43. Found: C, 55.01; H, 10.08; N, 10.75; S, 24.15%.

N-Cyclohexyl-thiobenzamide, 3b

Pale yellow solid, m.p. 85-86°C. 1H NMR (400 MHz, CDCl3): δ 1.24-1.46 (m, 5H), 1.73-1.78 (m, 3H), 2.16-2.19 (m, 2H), 3.40-3.62 (m, 4H), 7.66-7.70 (m, 2H); MS(EI): m/z 219(M⁺), 186, 162, 138, 121, 104, 77, 55, 41. Anal. Calcd for C13H13NS: C, 70.20; H, 7.36; N, 6.82; S, 15.62. Found: C, 71.26; H, 7.95; N, 6.47; S, 14.31%.

N-Propyl-thiobenzamide, 4b

Pale yellow liquid. 1H NMR (400 MHz, CDCl3): δ 0.97 (t, J=7.3 Hz, 3H), 1.68-1.77 (m, 2H), 3.72 (dd, J1=6.9 Hz, J2=6.0 Hz, 2H), 7.28-7.38 (m, 3H), 7.82 (s, br, 1H, NH); MS(EI): m/z 179(M⁺), 150, 121, 104, 77, 58, 51. Anal. Calcd for C13H13NS: C, 66.99; H, 7.31; N, 7.81; S, 17.89. Found: C, 67.11; H, 7.45; N, 7.88; S, 17.54%.

N-Benzyl-thiobenzamide, 6b

Pale yellow solid, m.p. 78-79°C. 1H NMR (400 MHz, CDCl3): δ 4.96 (d, J=5.1 Hz, 2H), 7.32-7.44 (m, 8H), 7.69 (s, br, 1H, NH), 7.73-7.77 (m, 2H); MS(EI): m/z 227 (M⁺), 211, 194, 165, 121, 103, 91, 77, 65, 51. Anal. Calcd for C13H13NS: C, 73.97; H, 5.76; N, 6.16; S, 14.11. Found C, 74.06; H, 5.88; N, 6.24; S, 13.81%.

N-Phenyl-thioacetamide, 8b

Light yellowish solid, m.p. 76-78°C. 1H NMR (400 MHz, CDCl3): δ 2.52 (s, 2H), 2.73 (s, 2.6H), 7.15-7.18 (m, 2H), 7.27-7.42 (m, 3H), 7.64-7.67 (m, 1.4H), 8.86 (br, s, 1H, NH); MS(EI): m/z 151 (M⁺), 150, 118, 110, 93, 77, 59. Anal. Calcd for C11H13NS: C, 63.54; H, 6.00; N, 9.26; S, 21.20. Found C, 63.68; H, 5.88; N, 9.14; S, 21.28%.

N, N-Diethyl-3-methyl-thiobenzamide, 9b

Light yellowish solid, m.p. 80-81°C. 1H NMR (400 MHz, CDCl3): δ 1.14 (t, J=3.1 Hz, 3H), 1.39 (t, J=7.0 Hz, 3H), 2.32 (s, 3H), 3.42 (q, J=7.0 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 7.13 (m, 4H); MS(EI): m/z 207 (M⁺), 207, 192, 173, 146, 135, 118, 91, 61. Anal. Calcd for C15H17NS: C, 69.51; H, 8.26; N, 6.76; S, 15.47. Found: C, 69.69; H, 8.17; N, 6.82; S, 15.30%.

N-Isopropyl-thiobenzamide, 11b

Pale yellow solid, m.p. 57-58°C. 1H NMR (400 MHz, CDCl3): δ 1.32 (d, J=6.5 Hz, 6H), 4.73-4.77 (m, 1H), 7.29-7.39 (m, 4H), 7.62-7.64 (m, 2H); MS(EI): m/z 179(M⁺), 178, 150, 146, 121, 104, 77, 76, 58, 51. Anal. Calcd for C10H13NS: C, 66.99; H, 7.31; N, 7.81; S, 17.89. Found: C, 67.12; H, 7.25; N, 7.88; S, 17.74%.

N-Phenethyl-thiobenzamide, 12b

Pale yellow solid, m.p. 88-89°C. 1H NMR (400 MHz, CDCl3): δ 3.02 (t, J=6.9 Hz, 2H), 4.05 (dd, J1=6.9 Hz, J2=5.8 Hz, 2H), 7.19-7.30 (m, 8H), 7.36 (s, br, 1H, NH), 7.55-7.57 (m, 2H); MS(EI): m/z 241(M⁺), 162, 136, 127, 121, 104, 91, 77, 65, 51. Anal. Calcd for C15H19NS: C, 74.65; H, 6.26; N, 5.80; S, 13.29. Found: C, 74.78; H, 6.33; N, 5.86; S, 13.01%.

Phenyl-piperidin-1-yl-methanethione, 13b

Pale yellow solid, m.p. 64-66°C. 1H NMR (400 MHz, CDCl3): δ 1.48-1.52 (m, 2H), 1.66-1.76 (m, 4H), 3.44 (t, J=5.6 Hz, 2H), 4.29 (t, J=5.4 Hz, 2H), 7.18-7.27 (m, 5H); MS(EI): m/z 205(M⁺), 204, 188, 172, 144, 121, 104, 77, 69, 51. Anal. Calcd for C13H17NS: C, 70.20; H, 7.36; N, 6.82; S, 15.62. Found: C, 70.34; H, 7.26; N, 6.89; S, 15.50%.

N-Phenyl-thiobenzamide, 14b

Pale yellow solid, m.p. 100°C. 1H NMR (400 MHz, CDCl3): δ 7.18-7.88 (m, 10H), 9.09 (s, br, 1H, NH); MS(EI): m/z 213(M⁺), 197, 180, 121, 110, 77, 51. Anal. Calcd for C13H13NS: C, 73.20; H, 5.20; N, 6.57; S, 15.03. Found: C, 73.38; H, 5.12; N, 6.63; S, 14.86%.
2-Phenyl-1-piperidin-1-yl-ethanethione, 16b

Pale yellow solid, m.p. 72-73°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.28-1.34 (m, 2H), 1.60-1.72 (m, 4H), 3.60 (t, $J$=5.8 Hz, 2H), 4.30 (t, $J$=5.6 Hz, 2H), 4.38 (s, 2H), 7.26-7.37 (m, 5H); MS(EI): m/z 219(M$^+$), 186, 128, 91, 69. Anal. Calcd for C$_{13}$H$_{17}$NS: C, 71.18; H, 7.81; N, 6.39; S, 14.62. Found: C, 71.30; H, 7.73; N, 6.47; S, 14.49%.

N-Isobutyl-thiobenzamide, 17b

Pale yellow solid, m.p. 58-59°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.97 (d, $J$=6.7 Hz, 6H), 2.03-2.09 (m, 1H), 3.57-3.60 (m, 2H), 6.15 (s, br, 1H, NH), 7.28-7.39 (m, 3H), 7.64-7.66 (m, 2H); MS(EI): m/z 193(M$^+$), 150, 138, 121, 77, 57, 51. Anal. Calcd for C$_{11}$H$_{15}$NS: C, 68.35; H, 7.82; N, 7.25; S, 16.59. Found: C, 68.51; H, 7.90; N, 7.32; S, 16.25%.

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References


