Solvent-free synthesis of acyl thiosemicarbazides with microwave activation

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A new and rapid synthesis of acyl thiosemicarbazides has been reported for the first time using domestic microwave oven. Comparing with the conventional methods, this process has advantages such as shorter reaction time, higher yields and environmental acceptability.

In recent years, the solvent-free organic reaction assisted by microwaves have gained special attention. The use of microwave activation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time. Moreover, the solvent-free reaction avoids organic solvents during the reaction in organic synthesis, leads to a clean, efficient and economical technology. This methodology has widely been used in a variety of organic reactions. However, the solvent-free synthesis of acyl thiosemicarbazides has not been reported so far.

The synthesis of acyl thiosemicarbazides is useful because of various biological activities such as antiviral, antifungal, insecticides, herbicides and plant-growth regulator, antituberculosis and restraining central nerve. Therefore, many methods of synthesis of acyl thiosemicarbazides have been explored. Generally, these reactions were carried out in solution and have drawbacks such as using large amounts of volatile and poisonous solvent, with high reaction time.

In order to find an environmentally benign procedure, we investigated a new method for the synthesis of acyl thiosemicarbazides, namely, solvent-free synthesis with microwave activation (Scheme I). By this way, we have synthesized eight new acyl thiosemicarbazides in short reaction period. The yields are excellent, the safety is largely increased, the work is considerably simplified and the cost is reduced. The structures of the products were confirmed by IR, 1H NMR, MS and elemental analysis.

At the same temperature of microwave reactions, we have done these experiments in solution. As a result, most of the reaction periods are more than 30 min, and the yields are less than 80% in conventional methods. Similarly, on comparing the reactions in solid state without microwave, with those assisted by microwave, we find that the reaction periods are longer and the yields are lower in the former case. Hence the reactions carried out with microwave technique are superior to the reactions using conventional methods in our experiments.

**Experimental Section**

**General.** Melting points were determined in a Kofler micromelting point apparatus and are uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer in KBr. 1H NMR spectra were measured on a FT-80A spectrometer using TMS as internal standard and (CD3)2CO as solvent. Elemental analyses were performed on Carlo-Erba 1102 elemental analyzer. Mass spectra were obtained on a KRTOSEI-MS50(U.K) Galanz Microwave oven(750w).

**General procedure for the preparation of 3a-h.** Aryl isothiocyanate (1mmole) and acylhydrazine

![Scheme I](image-url)
adjustor of the microwave oven to proper temperature (about 50 °C), and irradiated the reaction mixture in microwave oven for the specified time (2–6 min) under solventless conditions. After the reaction was complete, the crude products were recrystallized from ethanol and dried in vacuum to yield the pure products. All the compounds gave satisfactory analytical and spectral data.

1-Benzoyl-4-(p-chlorophenyl) thiosemicarbazide 3a: White-tabular, yield 89.8%, m.p. 188-90°C; IR(KBr)/cm⁻¹: 3357, 3187, 3031, 3001, 1673, 1600, 1509, 1400, 1255, 833, 779, 690; ¹H NMR: δ 7.297-8.000 (m, 9H, ArH), 8.944 (s, 1H, NH), 9.601 (s, 1H, NH), 9.835 (s, 1H, NH); Anal. Calculated for C₁₉H₁₆ClN₃O₅S: C, 54.99; H, 3.93; N, 13.75. Found: C, 54.78; H, 3.61; N, 13.57.

1-(m-Chlorobenzoyl)-4-(p-chlorophenyl) thiosemicarbazide 3b: White-tabular, yield 88.3%, m.p. 186.5-87.5°C; IR(KBr)/cm⁻¹: 3318, 3215, 3153, 3033, 1671, 1638, 1620, 1546, 1209, 822, 735, 673; ¹H NMR: δ 7.315-7.986 (m, 8H, ArH), 8.978 (s, 1H, NH), 9.607 (s, 1H, NH), 9.962 (s, 1H, NH); Anal. Calculated for C₁₉H₁₆Cl₂N₄O₅S: C, 49.41; H, 3.24; N, 12.35. Found: C, 49.78; H, 3.61; N, 12.67%; MS: m/z 341(M⁺), 171, 169(B), 139, 117, 75.

1-(m-Chlorobenzoyl)-4-(p-bromophenyl) thiosemicarbazide 3c: White-stick, yield 89.5%, m.p. 190-91°C; IR(KBr)/cm⁻¹: 3317, 3213, 3151, 3075, 1671, 1638, 1622, 1546, 1211, 819, 770, 673; ¹H NMR: δ 7.456-7.984 (m, 8H, ArH), 8.991 (s, 1H, NH), 9.605 (s, 1H, NH), 9.966 (s, 1H, NH); Anal. Calculated for C₁₉H₁₅BrCl₂N₄O₅S: C, 43.69; H, 2.86; N, 10.92. Found: C, 43.78; H, 2.61; N, 10.77%.

1-(1-Naphthoacetyl)-4-(p-ethoxyphenyl) thiosemicarbazide 3f: White-tabular, yield 92.3%, m.p. 177-79°C; IR(KBr)/cm⁻¹: 3272, 3190, 3046, 3013, 2981, 2929, 1670, 1654, 1600, 1538, 1243, 820, 782; ¹H NMR: δ 1.340 (t, 3H, CH₃), 4.011 (q, 2H, CH₂), 4.131 (s, 2H, CH₂), 6.821-7.181 (m, 11H, ArH), 8.703 (s, 1H, NH), 8.999 (s, 1H, NH), 9.404 (s, 1H, NH); Anal. Calculated for C₂₃H₂₁N₄O₅S: C, 66.49; H, 5.54; N, 11.08. Found: C, 66.31; H, 5.50; N, 11.29%; MS: m/z 380(M⁺), 179, 150(B), 141, 115, 65.

1-(1-Naphthoacetyl)-4-(p-ethoxyphenyl) thiosemicarbazide 3g: White-needle, yield 87.7%, m.p. 181-83°C; IR(KBr)/cm⁻¹: 3265, 3200, 3099, 2944, 1701, 1597, 1543, 1223, 825, 756, 689; ¹H NMR: δ 4.657 (s, 2H, CH₂), 6.973-7.573 (m, 9H, ArH), 8.917 (s, 1H, NH), 9.369 (s, 1H, NH), 9.744 (s, 1H, NH); Anal. Calculated for C₁₂H₁₅BrCl₂N₂O₂S: C, 53.65; H, 4.17; N, 12.52. Found: C, 53.31; H, 4.50; N, 12.09%; MS: m/z 335(M⁺), 171, 169(B), 127, 111, 94, 77, 75.

1-(Phenoxacylacetyl)-4-(p-chlorophenyl) thiosemicarbazide 3h: White-needle, yield 86.4%, m.p. 188.5-190°C; IR(KBr)/cm⁻¹: 3264, 3210, 3094, 2998, 2941, 1701, 1596, 1543, 1222, 836, 756, 689; ¹H NMR: δ 4.653 (s, 2H, CH₂), 6.791-7.503 (m, 9H, ArH), 8.919 (s, 1H, NH), 9.395 (s, 1H, NH), 9.747 (s, 1H, NH); Anal. Calculated for C₁₂H₁₅BrCl₂N₄O₂S: C, 47.37; H, 3.68; N, 11.05. Found: C, 47.31; H, 3.50; N, 11.39%.

References
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