Microwave-assisted rapid synthesis of thiosemicarbazide derivatives

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Rapid and highly efficient synthesis of thiosemicarbazides by the coupling of isothiocyanate and carboxylic acid hydrazides in small amount of a polar solvent is achieved under microwave irradiation by using a domestic microwave oven. The reaction proceeds rapidly and is completed within 2-4 min giving a series of thiosemicarbazides derivatives 4, 5 in high yields. All of the compounds have been characterized by FT-IR, ¹H-NMR, and mass spectroscopy.

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Thiosemicarbazides are important compounds because of their reported industrial and biological activities like anticonvulsant¹, antifungal², plant growth promoting³ and antibacterial⁴ activity. Thiosemicarbazides are also used as intermediates for the synthesis of heterocyclic compounds, such as 1,2,4-triazoles⁵, 1,3,4-thiadiazoles⁶ and 1,3,4-oxadiazoles⁷ derivatives. A general method for the synthesis of thiosemicarbazides is the condensation of isothiocyanate and derivatives of the carboxylic acid hydrazides in ethanol as solvent under reflux⁸,⁹. In recent years, microwave irradiation using commercial domestic ovens has been rapidly increased for optimization and acceleration of organic synthesis under solvent free condition¹⁰-¹⁴. It has been reported for the variety of reactions such as synthesis of heterocycles¹⁵ and more recently for synthesis of polymers¹⁶, because of advantages such as reduction in reaction time, improved energy utilization, potential for lower processing temperature and improved product uniformity.

In connection with our interest in the use of microwave¹⁷ to evaluate the synergy between dry media and microwave irradiation in the synthesis of thiosemicarbazides, we report herein the synthesis of several thiosemicarbazide derivatives 4a-c and 5a-c under solvent free conditions and microwave irradiation.

The condensation of derivatives of isothiocyanates 3 and pyridine carboxylic acid hydrazides 2a-c under microwave irradiation was carried out according to Scheme 1 and reaction conditions are given in Table I.

From a series of initial solvent free experiments it was observed that the yield of the reaction was very low. As a result of some more experiments, the small amount of ethanol was selected to prepare homogeneous system.

In the conventional heating, this condensation required longer reaction times (0.5-7.45 hr). In contrast, under microwave irradiation, the reactions are completed within 2-4 minutes, and in most of the cases afford the product in high yields. The products were characterized on the basis of their IR, ¹H NMR, mass spectroscopic data and their melting points. In the IR spectra absence of the NCS absorption bands at 2050-2070 cm⁻¹ and presence of the absorption band at 1236-1390 cm⁻¹ due to C=S bond are in accordance with the structure of the reaction products. Furthermore, in all the ¹H NMR spectra of the compounds 4a-c the benzylic -CH₂ group appeared around δ 4.73 – 4.75 as a singlet. In the ¹H NMR spectra of compounds 5a-c the methyl group was observed around δ 2.2 – 2.3 as a singlet. All the other

\[
\begin{align*}
\text{R-C-NHNH}_2 + \text{R'-NCS} &\xrightarrow{\text{MW}} \text{R-C-NHNHC-NHR'} \\
\text{R=a 2-Pyridyl} & \\
\text{b 3-Pyridyl} & \\
\text{c 4-Pyridyl} & \\
\end{align*}
\]

Scheme I
required protons in compounds 4-5(a-c) were observed at appropriate chemical shifts. Further evidence for characterization of the synthesized compounds has been obtained from their mass spectral data. For compounds 4-5(a-c) the molecular ion peak was observed at m/z 286 in all compounds.

In conclusion, we have developed a general and rapid method for the synthesis of thiosemicarbazide derivatives in moderate to high yield, under microwave irradiation.

**Experimental Section**

Melting points were obtained from an electrothermal digital melting point apparatus and are uncorrected. FT-IR spectra were recorded on a UNICAM Galaxy Series FTIR 5000 spectrometer as KBr discs. 'H NMR spectra were determined on a Varian 500 MHz instrument. The EIMS were obtained from a MAT-112-s-machine. A domestic microwave oven (Samsung) at 2450 MHz (90% power, 900 W) was used in all experiments for carrying out the reactions. The isothiocyanates were prepared according to the reported procedure.

**General Procedure.** 20 mg pyridine carboxylic acid hydrazide (1.3 x 10^-3 mole) and isothiocyanate (1.8 x 10^-3 mole) were mixed thoroughly in a mortar. Then two drops of ethanol were added and the reaction mixture irradiated with microwave for 2-4 min. The progress of the reaction was monitored by TLC. The solid obtained was purified by recrystallization from ethanol.

<table>
<thead>
<tr>
<th>Compd R' R</th>
<th>Conventional heating</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% yield</td>
<td>Time (hr)</td>
</tr>
<tr>
<td>4a Ph-CH₂</td>
<td>2-pyridyl</td>
<td>84</td>
</tr>
<tr>
<td>4b Ph-CH₂</td>
<td>3-pyridyl</td>
<td>88</td>
</tr>
<tr>
<td>4c Ph-CH₂</td>
<td>4-pyridyl</td>
<td>88</td>
</tr>
<tr>
<td>5a 2-CH₂,Ph</td>
<td>2-pyridyl</td>
<td>83</td>
</tr>
<tr>
<td>5b 2-CH₂,Ph</td>
<td>3-pyridyl</td>
<td>83</td>
</tr>
<tr>
<td>5c 2-CH₂,Ph</td>
<td>4-pyridyl</td>
<td>96</td>
</tr>
</tbody>
</table>

*All reported yields refer to isolated product.*
1H, Ar-H), 8.75-8.79 (d, 1H, Ar-H), 9.09 (s, 1H, Ar-H), 9.67, 9.76, 10.89 (s, 3H, 3NH); MS: m/z(%) 286 (100, M+), 179 (60), 149 (99), 106(99), 78(99).

References