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ScienceDirect
Chinese Chemical Letters 20 (2009) 793–796
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

# Microwave-assisted synthesis of asymmetric thiocarbonohydrazones under solvent-free conditions

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Received 28 November 2008

**Abstract**

Six new asymmetric thiocarbonohydrazones **3a–3f** were synthesized from following steps: firstly hydrazine hydrate reacted with carbon disulfide to form thiocarbonohydrazide (**1**) under microwave irradiation. Then compound (**1**) reacted with ketone and different aldehydes step by step to give **3a–3f** with excellent yields under solvent-free conditions using microwave irradiation. Their structures have been determined by elemental analysis, IR, MS and $^1$H NMR data.


*Keywords:* Thiocarbonohydrazide; Asymmetric thiocarbonohydrazones; Microwave irradiation; Solvent-free; Organic synthesis

Thiocarbonohydrazones, a class of compounds possessing a wide spectrum of medicinal properties, have been studied for activity against tuberculosis [1], cancer [2], bacterial [3] and viral infections [4]. Meanwhile, thiosemicarbazones also have wide application to crystal engineering, superamolecular chemistry [5], optoelectronics [6] fields. So, particularly intense interest has been directed toward the synthesis and biochemical studies of those compounds.

In recent years, microwave dielectric heating technology combined with solvent-free conditions has been used in many organic reactions, leading to shorter reaction times, higher yields, cleaner reaction products and environmentally more benign conditions compared with the classical heating [7–9].

Although a lot of different structures thiocarbonohydrazones using conventional method and microwave irradiation method have been synthesized [10–14], very little is known about the asymmetric thiocarbonohydrazones [11], especially there is not one report about the synthesis of asymmetric thiocarbonohydrazones under solvent-free conditions using microwave irradiation. Recently, we have reported the synthesis of new $N^4$-[bi-(4-fluoro-phenyl)-methyl]-piperazine thiosemicarbazones under solvent-free conditions using microwave irradiation with excellent yields [14]. In order to search for a new class of compounds with broad spectrum of biological activities and to explore the relationship between their structures and biological activities, thiocarbohydrazide **1** was synthesized and reacted with acetophenone and different aldehydes to achieve six asymmetric thiocarbonohydrazones under solvent-free conditions using microwave technology in this paper. It proved to be more rapid and much easier to manipulate, and the excellent yields.

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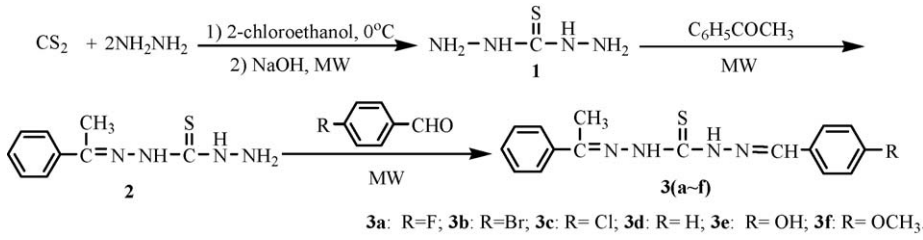
1001-8417/$ – see front matter 
doi:10.1016/j.cclet.2009.03.013




Scheme 1. Synthetic route of compounds **3a–3f**.

As shown in Scheme 1, thiocarbohydrazide **1** was prepared by reaction of the Hydrazine hydrate with carbon disulfide and 2-chloroethanol, followed by treatment with sodium hydroxide under microwave irradiation at 400 W for 15 min. The thiocarbohydrazide reacted with acetophenone and substituted aldehydes (2:1:1) step by step to afford compounds **3a–3f** in excellent yields (80–89%) under microwave irradiation without solvent at 350 W for 7–8 min (Scheme 1). The identities of compounds **3a–3f** were established by elemental analysis, IR, MS and $^1$H NMR data.

## 1. Experimental

Melting points were determined with an XRC-1 micro melting point apparatus and uncorrected. IR spectra were recorded on a FT-IR 16PC spectrophotometer (KBr disc). $^1$H NMR spectra were recorded using a Varian 400 MHz spectrometer in DMSO-$d_6$ with TMS as internal standard. Mass spectra were carried out on a Finnigan MAT-4510 spectrometer. Elemental analyses were performed on a PE-2400 elemental analyzer. All the products have been described. A Galanz domestic microwave oven equipped with a turntable and operating 2450 MHz was used at its full power, 750 W, for all the experiments. Other reagents were commercially available and used as received (Table 1).

### *1.1. Procedure for the preparation of thiocarbohydrazide **1***

Hydrazine hydrate (80%, 18 mL, 0.3 mol) and 2-chloroethanol (1 mL, 0.015 mol) were added to a three-neck flask. Then carbon disulfide (6 mL, 0.1 mol) was added dropwise under stirring with cooling using an ice-water bath, and yellow solid was formed. After adding NaOH (0.6 g, 0.015 mol), the reaction mixture was exposed to microwave irradiation at 400 W for 15 min. Then it was cooled to room temperature. The solid thus obtained was collected by filtration, washed by methanol and recrystallized from water. White granule crystal was obtained. m.p. 171–172 °C (lit. [15] m.p. 170 °C), yield 88%.

### *1.2. Synthesis of asymmetric thiocarbonohydrazones derivatives under MW irradiation*

Acetophenone (1.25 mmol) and **1** (2.5 mmol) were dissolved in $CH_2Cl_2$. $SiO_2$ was added and then the solvent was evaporated, and 2 drops of glacial acetic acid were added. Then the reaction mixture was irradiated for 5 min at 350 W under solvent-free conditions. The mixture was cooled and suspended in $CHCl_3$ (10 mL). The $SiO_2$ was removed by suction filtration and the filtrate was evaporated to give the crude product (**2**). The crude product was recrystallised from ethanol and water to give a pure product. Then mixture of **2** (1 mmol) and aldehyde (1 mmol) dissolved in $CH_2Cl_2$. $SiO_2$ was added and the solvent was evaporated under reduced pressure, and 2 drops of glacial acetic acid

Table 1
The antibacterial activity of the compounds **3a–3f** MIC's in μg/mL[a].

| Compds | 3a | 3b | 3c | 3d | 3e | 3f |
|---|---|---|---|---|---|---|
| *E. coli* | 20 | >20 | >20 | 16 | 8 | 16 |
| *S. cereus* | >20 | 20 | 16 | 20 | 16 | 8 |

[a] MIC: Minimum inhibitory concentration.

were added. Then the reaction mixture was irradiated for 2–3 min at 350 W under solvent-free conditions. The reaction mixture was cooled and suspended in $CHCl_3$ (10 mL). The solid was removed by suction filtration and the filtrate was evaporated to give the crude product (**3**). The crude product was washed with cold ethanol, then with water. The crude product was recrystallised from ethanol to give a pure product **3a–3f**.

*1-(4-Fluorobenzaldehyde)-3-acetophenone-thiocarbonohydrazone* (**3a**): 2 min, Yellow solid, yield 89%, m.p. 202–204 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.92 (s, 1H, NH), 11.65 (s, 1H, NH), 8.17 (s, 1H, CH), 7.33–7.62 (m, 9H, ArH), 1.58 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3332 (NH), 3122 (Ph-H), 1552 (C=N), 1234 (C=S), 1003 (F). MS: *m/z*, 315 ($M^+$+1), 177, 137. Anal. Calcd. for $C_{16}H_{15}FN_4S$: C 61.13, H 4.81, N 17.82; Found: C 61.26, H 4.97, N 17.68.

*1-(4-Bromobenzaldehyde)-3-acetophenone-thiocarbonohydrazone* (**3b**): 2.5 min, Yellow solid, yield 87%, m.p. 215–216 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.91 (s, 1H, NH), 11. 63 (s, 1H, NH), 8.16 (s, 1H, CH), 7.33–7.63 (m, 9H, ArH), 1.58 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3329 (NH), 3125 (Ph-H), 1554 (C=N), 1226 (C=S), 783 (Br). MS: *m/z*, 375 ($M^+$+1), 197,177. Anal. Calcd. for $C_{16}H_{15}BrN_4S$: C 51.21, H 4.03, N 14.93; Found: C 51.36, H 4.17, N 14.72.

*1-(4-Chlorobenzaldehyde)-3-acetophenone-thiocarbonohydrazone* (**3c**): 2.5 min, Yellow solid, yield 86%, m.p. 201–202 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.93 (s, 1H, NH), 11.67 (s, 1H, NH), 8.17 (s, 1H, CH), 7.32–7.61 (m, 9H, ArH), 1.59 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3332 (NH), 3121 (Ph-H), 1552 (C=N), 1269 (C=S), 823 (Cl). MS: *m/z*, 331 ($M^+$+1), 177, 153. Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C 58.09, H 4.57, N 16.93; Found: C 58.36, H 4.37, N 16.72.

*1-Benzaldehyde-3-acetophenone-thiocarbonohydrazone* (**3d**): 2.5 min, Yellow solid, yield 89%, m.p. 195–197 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.95 (s, 1H, NH), 11.71 (s, 1H, NH), 8.20 (s, 1H, CH=N), 7.31–7.60 (m, 10H, ArH), 1.58 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3331 (NH), 3125 (Ph-H), 1556 (C=N), 1252 (C=S). MS: *m/z*, 297 ($M^+$+1), 177, 119. Anal. Calcd. for $C_{16}H_{16}N_4S$: C 64.84, H 5.44, N 18.90; Found: C 64.46, H 5.37, N 18.92.

*1-(4-Hydroxybenzaldehyde)-3-acetophenone-thiocarbonohydrazone* (**3e**): 3 min, Yellow solid, yield 80%, m.p. 203–205 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.88 (s, 1H, NH), 11.61 (s, 1H, NH), 9.93 (s, 1H, OH), 8.19 (s, 1H, CH=N), 7.11–7.61 (m, 9H, ArH), 1.57 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3329 (NH), 3122 (Ph-H), 1543 (C=N), 1263 (C=S). MS: *m/z*, 313 ($M^+$+1), 177, 135. Anal. Calcd. for $C_{16}H_{16}N_4OS$: C 61.52, H 5.16, N 17.93; Found: C 61.76, H 5.37, N 18.11.

*1-(4-Methoxybenzaldehyde)-3-acetophenone-thiocarbonohydrazone* (**3f**): 3 min, Yellow solid, yield 80%, m.p. 209–211 °C. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 11.82 (s, 1H, NH), 11.62 (s, 1H, NH), 8.21 (s, 1H, CH=N), 6.93–7.57 (m, 9H, ArH), 3.71 (s, 3H, $OCH_3$), 1.57 (s, 3H, $CH_3$). IR (KBr, $\nu$, cm$^{-1}$): 3343 (NH), 3132 (Ph-H), 1548 (C=N), 1261 (C=S). MS: *m/z*, 327 ($M^+$+1), 295, 177, 149. Anal. Calcd. for $C_{17}H_{18}N_4OS$: C 62.55, H 5.56, N 17.16; Found: C 62.71, H 5.37, N 17.04.

## 2. Results and discussion

The microwave method used in this work has the advantage of short reaction time, high reaction yield and easy manipulation compared to the conventional method. The reaction of liquid aromatic aldehydes with compound **1** is faster than that of solid aromatic aldehydes. The IR spectra of compounds **3a–3f** exhibit a characteristic strong absorption at 1200–1270 cm$^{-1}$ attributable to the C=S, the strong absorption bands falling within the range of 3300–3400 cm$^{-1}$ are assigned to the N–H stretching vibration. The strong bands between 1540 and 1550 cm$^{-1}$ indicate the absorption of C=N. In the $^1$H NMR spectra, the multiple peaks between $\delta$ 11.60–11.93 ppm should be assigned to the protons in the =N–NH–C=S, a singlet peaks at $\delta$ 8.16–8.21 ppm due to the CH=N group.

The preliminary antibacterial activities of the compounds were evaluated with *E. coli* and *S. aureus in vitro* using agar microdilution method. The results indicated that the compounds **3e** and **3f** exhibited good inhibition effect to *S. aureus* and *E. coli*.

In conclusion, from our experimental results it is evident that the use of microwave for the synthesis of asymmetric thiocarbonohydrazones under solvent-free condition proved to be an efficient, safe and environmentally benign technique with significant decreases in reactions times, comparably high chemical yields, and easy manipulation. It is thus a rapid and convenient method for the preparation of compounds of type **3a–3f**.

## Acknowledgment

We thank the Natural Science Foundation of Southwest University for Nationalities (No. 08NQZ002) for financial support.

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