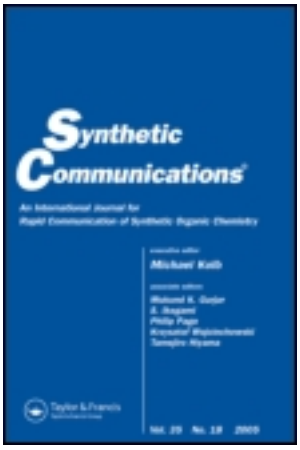


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# Microwave-Assisted Solid-State Synthesis and Characterization of Thiohydantoin Derivatives

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# Microwave-Assisted Solid-State Synthesis and Characterization of Thiohydantoin Derivatives

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**Abstract:** A new and efficient solid-state method for the preparation of thiohydantoins is reported. With this method, twelve thiohydantoin compounds have been synthesized in good to excellent yields (81–92%). In addition, this method has the advantages of high yields, a cleaner reaction, simple methodology, and short reaction times.

**Keywords:** Microwave activation, solid-state synthesis, thiohydantoin derivatives

In recent years, the use of microwave technology in organic synthesis has received considerable attention.[1–3] It has many advantages, such as high efficiency and selectivity, easy separation and purification, and environmental acceptability.[4–6] All these merits are in accord with the green production's requests of energy-savings and high efficiency. Today, it has been widely used in a variety of organic reactions.[7–10] However, the solvent-free synthesis of thiohydantoins by the reaction of arylisothiocyanates with free amino acids has not been reported.

It is well known that thiohydantion derivatives display a wide range of biological properties, including anticonvulsant,[11] antiviral,[12] and antitumor[13] activities, and can act as herbicidal and fungicidal regeants.[14] Meanwhile, some were used to synthesize novel optically active poly(amide-imide)s using microwave irradiation.[15] Therefore, particularly

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intense interest has been directed toward the synthesis of them.[16–18] Generally, these reactions were carried out in solution. All these methods have their merits. However, they also have drawbacks, such as using large amounts of volatile and poisonous solvents and needing a long reaction time.

To overcome these disadvantages, avoid the use of a solvent, and synthesize these valuable compounds rapidly and with a high efficiently, a new, rapid, solvent-free synthesis of thiohydantoins with microwave activation was studied. It was found that the addition reaction of aryl isothiocyanates and DL-amino acid in the presence of sodium hydroxide and the cyclizative condensation of adduct in the presence of sodium hydrogen sulphate in a microwave oven takes place quickly. In the reaction, we have found that the substrates containing electron-withdrawing groups can make the reaction time shorter. However, there is no inevitable relationship between the yields and the electron-withdrawing and electron-donating groups in the substrates. It was also worthy of note that the thiohydantoins were formed via a condensation reaction in which the amino acids underwent nucleophilic addition followed by ring closure, and the asymmetric center of amino acid was not involved in the reaction and the configuration had not been changed in this Microwave irradiation (MWI) reaction.

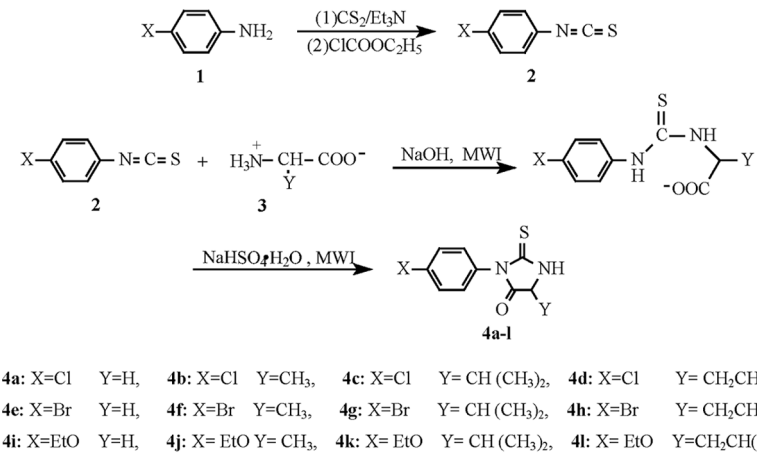
Using this new method, we synthesized twelve thiohydantoins in excellent yield (81–92%). This method has significant advantages, such as operational simplicity, shorter reaction time, higher yields, and environmental acceptability. The structures of the products were characterized by IR, MS, $^{1}$H NMR, $^{13}$C NMR, and elemental analysis. And more detailed work about the application of the thiohydantoins in analytical chemistry and physiological activitiy is in progress in our laboratory.

## EXPERIMENTAL

Melting points were determined with a Kofler micro melting point apparatus and are uncorrected. IR spectra were recorded on a FTS-40 spectrophotometer using KBr pellets. $^{1}$H NMR and $^{13}$C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard and $CDCl_3$ or DMSO-$d_6$ as solvent. Chemical shifts ($\delta$) were expressed in ppm downfield from internal standard TMS and coupling constants $J$ are given in Hz. Mass spectra were recorded on a HP-5 6890/5973 GC-MS spectrometer. Elemental analyses were performed on PE-2400 CHN elemental analyzer. We used a Galanz microwave oven (750 W).

### General Procedure for the Preparation of Thiohydantoins (4a-l)

Synthesis of the aryl isothiocyanates (**2**) were described in detail elsewhere (Scheme 1).[19]




**4a:** X=Cl Y=H, **4b:** X=Cl Y=$CH_3$, **4c:** X=Cl Y= $CH(CH_3)_2$, **4d:** X=Cl Y= $CH_2CH(CH_3)_2$,
**4e:** X=Br Y=H, **4f:** X=Br Y=$CH_3$, **4g:** X=Br Y= $CH(CH_3)_2$, **4h:** X=Br Y= $CH_2CH(CH_3)_2$,
**4i:** X=EtO Y=H, **4j:** X= EtO Y= $CH_3$, **4k:** X= EtO Y= $CH(CH_3)_2$, **4l:** X= EtO Y=$CH_2CH(CH_3)_2$.

***Scheme 1.*** Synthesis of aryl thiohydantoins (4a-1).

Aryl isothiocyanate (1 mmol), DL-amino acid (1 mmol), and sodium hydroxide (1 mmol) were mixed well in a mortar, then irradiated in a microwave oven with 495 W for the specified time, 6–10 min, under solvent-free conditions. Then sodium hydrogen sulphate (1 mmol) was added and mixed well, and irradiated again with 495 W for 2 min. The reaction was traced with TLC. After the reaction was completed, the mixture was cooled to room temperature. A small amount of ethanol was dropped into the mortar and then cool water was poured into the mortar slowly, and the precipitate was filtrated and the filtrate was condensed. The crude products were collected, dried and recrystallized from ethanol. Drying in vacuum gave the pure products. All the compounds gave satisfactory analytical and spectra data.

## Physical and Spectra Data of Compounds 4a-l

3-(*p*-Chlorophenyl)-2-thiohydantoin **4a**: Yellow crystals. Yields: 87%; Mp 229.5–231°C IR (KBr): 3214 (N-H), 3051, 2955, 2900, 1756 (C═O), 1598, 1530, 1276 (C═S), 827 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.13 (s, 1H, N-H), 7.57 (d, 2H, $J = 8.4$ Hz, ArH), 7.34 (d, 2H, $J = 8.4$ Hz, ArH), 4.29 (s, 2H, N-$CH_2$). Anal. calcd. for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.80; H, 3.02; N, 12.44.

5-Methyl-3-(*p*-chlorophenyl)-2-thiohydantoin **4b**: White crystals. Yields: 86%; Mp 209–210.5°C; IR (KBr): 3175 (N-H), 3077, 2940, 1757 (C═O), 1530, 1497, 1264 (C═S), 821 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.71 (s, 1H, N-H), 7.51 (d, 2H, $J = 8.2$ Hz, ArH), 7.33 (d, 2H,

$J = 8.2$ Hz, ArH), 4.38 (q, 1H, $J = 7.0$ Hz, N-CH), 1.63 (d, 3H, $J = 7.0$ Hz, $CH_3$); MS ($m/z$): 240 ($M^+$),169 (B), 111, 86, 75, 28. Anal. calcd. for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 49.88; H, 3.69; N, 11.72.

5-Isopropyl-3-(*p*-chlorophenyl)-2-thiohydantoin **4c**: White crystals. Yields: 88%; Mp 192–193.5°C; IR (KBr): 3177 (N-H), 3076, 966, 2873, 1759 (C═O), 1520, 1496, 1268 (C═S), 830 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.81 (s, 1H, N-H), 7.50 (d, 2H, $J = 8.8$ Hz, ArH), 7.28 (d, 2H, $J = 8.8$ Hz, ArH), 4.21 (d, 1H, $J = 3.6$ Hz, N-CH), 2.41 (m, 1H, CH), 1.16 (d, 3H, $J = 6.8$ Hz, $CH_3$), 1.06 (d, 3H, $J = 6.8$ Hz, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$):$\delta$ 184.38 (C═S), 173.24 (C═O), 135.86, 131.58, 130.13, 130.03, 65.58 (N-CH), 31.77, 19.33, 16.82; MS ($m/z$): 268 ($M^+$,B), 226, 169, 111, 75. Anal. calcd. for $C_{12}H_{13}ClN_2OS$: C, 53.53; H, 4.88; N, 10.42. Found: C, 53.59; H, 4.78; N, 10.47.

5-Isobutyl-3-(*p*-chlorophenyl)-2-thiohydantoin **4d**: White crystals. Yields: 85%; Mp 173–174 °C; IR (KBr): 3166 (N-H), 3031, 2956, 2872, 1760 (C═O), 1603, 1539, 1280 (C═S), 825 $m^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.00 (s, 1H, N-H), 7.49 (d, 2H, $J = 8.8$ Hz, ArH), 7.29 (d, 2H, $J = 8.8$ Hz, ArH), 4.33 (dd, 1H, $J = 2.8$, 9.2 Hz, N-CH), 1.90 (m, 2H, $CH_2$), 1.74 (m, 1H, CH), 1.03 (t, 6H, $J = 6.4$ Hz, $2CH_3$); $^{13}C$ NMR(100 MHz, $CDCl_3$): $\delta$ 183.85 (C═S), 174.19 (C═O), 135.83, 131.58, 130.13, 130.03, 59.02 (N-CH), 25.79, 41.01, 23.60, 22.09; MS ($m/z$): 282 ($M^+$), 253, 226, 169 (B), 111, 75. Anal. calcd. for $C_{13}H_{15}ClN_2OS$: C, 55.21; H, 5.35; N, 9.91. Found: C, 55.30; H, 5.20; N, 9.95.

3-(*p*-Bromophenyl)-2-thiohydantoin **4e**: Yellow crystals. Yields: 91%; Mp 247–249 °C; IR (KBr): 141 (N-H), 3041, 2928, 1765 (C═O), 1590, 1517, 1269 (C═S), 821 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$10.40 (s, 1H, N-H), 7.71 (d, 2H, $J = 8.8$ Hz, ArH), 7.28 (d, 2H, $J = 8.8$ Hz, ArH), 4.30 (s, 2H, N-$CH_2$). Anal. calcd. for $C_9H_7BrN_2OS$: C, 39.87; H, 2.60; N, 10.33. Found: C, 39.98; H, 2.50; N, 10.49.

5-Methyl-3-(*p*-bromophenyl)-2-thiohydantoin **4f**: White crystals. Yields: 88%; Mp 210–212°C; IR (KBr): 174 (N-H), 3075, 2938, 1758 (C = O), 1597, 1529, 1275 (C═S), 823 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.77 (s, 1H, N-H), 7.66 (d, 2H, $J = 8.4$ Hz, ArH), 7.24 (d, 2H, $J = 8.4$ Hz, ArH), 4.38 (q, 1H, $J = 7.2$ Hz, N-CH), 1.62 (d, 3H, $J = 7.2$ Hz, $CH_3$); MS ($m/z$): 286 ($M^+ + 2$), 215 (B), 157, 86; Anal. calcd. for $C_{10}H_9BrN_2OS$: C, 42.12; H, 3.18; N, 9.82. Found: C, 42.28; H, 3.25; N, 9.97.

5-Isopropyl-3-(*p*-bromophenyl)-2-thiohydantoin **4g**: White crystals, Yields: 81%; Mp 205–206.5°C; IR (KBr): 3180 (N-H), 3083, 2966, 2873, 1762 (C═O), 1560, 1521, 1270 (C = S), 830 $cm^{-1}$; $^1H$ NMR(400 MHz, $CDCl_3$): $\delta$ 7.99 (s, 1H, N-H), 7.64 (d, 2H, $J = 8.8$ Hz, ArH), 7.20 (d, 2H, $J = 8.8$ Hz, ArH), 4.20 (d, 1H, $J = 3.6$ Hz, N-CH), 2.41 (m, 1H, CH), 1.17 (d, 3H, $J = 6.8$ Hz, $CH_3$), 1.07 (d, 3H, $J = 6.8$ Hz, $CH_3$); MS ($m/z$): 312

($M^+$,B), 272, 213, 184, 155, 28. Anal. calcd. for $C_{12}H_{13}BrN_2OS$: C, 46.02; H, 4.18; N, 8.94. Found: C, 46.14; H, 4.20; N, 8.90.

5-Isobutyl-3-(*p*-promophenyl)-2-thiohydantoin **4h**: White crystals. Yields: 91%; Mp 192–193.5°C; IR (KBr): 3256 (N-H), 3060, 2957, 2871, 1758 (C═O), 1587, 1528, 1280 (C═S), 825 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.03 (s, 1H, N-H), 7.64 (d, 2H, $J = 8.4$ Hz, ArH), 7.22 (d, 2H, $J = 8.4$ Hz, ArH), 4.33 (dd, 1H, $J = 3.2$, 9.2 Hz, N-CH), 1.91 (m, 2H, $CH_2$), 1.76 (m, 1H, CH), 1.04 (t, 6H, $J = 6.4$ Hz, $2CH_3$); MS ($m/z$): 328 ($M^+ + 2$,B), 270, 215, 175, 155, 134, 86, 43. Anal. calcd. for $C_{13}H_{15}BrN_2OS$: C, 47.71; H, 4.62; N, 8.56. Found: C, 47.55; H, 4.64; N, 8.66.

3-(*p*-Ethoxylphenyl)-2-thiohydantoin **4i**: Yellow crystals. Yields: 90%; Mp 202–204°C; IR (KBr): 3160 (N-H), 3079, 2986, 2888, 1770 (C═O), 1600, 1580, 1281 (C═S), 842 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.31 (s, 1H, N-H), 7.22 (d, 2H, $J = 8.8$ Hz, ArH), 7.01 (d, 2H, $J = 8.8$ Hz, ArH), 4.26 (s, 2H, N-CH), 4.08 (q, 2H, $J = 6.8$ Hz, $CH_2$), 1.44 (t, 3H, $J = 6.8$ Hz, $CH_3$); Anal. calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 56.04; H, 5.08; N, 11.75.

5-Methyl-3-(*p*-bromophenyl)-2-thiohydantoin **4j**: White crystals. Yields: 89%; Mp 192.5–194°C; IR (KBr): 3220 (N-H), 3061, 2990, 2878, 1720 (C═O), 1608, 1597, 1285 (C═S), 843 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.81 (s, 1H, N-H), 7.24 (d, 2H, $J = 8.8$ Hz, ArH), 7.02 (d, 2H, $J = 8.8$ Hz, ArH), 4.35 (q, 1H, $J = 6.8$ Hz, N-CH), 4.10 (q, 2H, $J = 6.8$ Hz, $CH_2$), 1.61 (d, 3H, $J = 6.8$ Hz, $CH_3$), 1.45 (d, 3H, $J = 6.8$ Hz, $CH_3$); MS ($m/z$): 250 ($M^+$, B), 179, 151, 122. Anal. calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.75; H, 5.58; N, 11.25.

5-Isopropyl-3-*(p*-ethoxylphenyl)-2-thiohydantoin **4k**: White crystals. Yields: 90%; Mp 201–203°C; IR (KBr): 3175 (N-H), 3059, 2988, 2877, 1763 (C═O), 1606, 1590, 1272 (C═S), 845 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.02 (s, 1H, N-H), 7.22 (d, 2H, $J = 8.8$ Hz, ArH), 7.02 (d, 2H, $J = 8.8$ Hz, ArH), 4.19 (d, 1H, $J = 3.6$ Hz, N-CH), 4.10 (q, 2H, $J = 6.8$ Hz, $CH_2$), 2.40 (m, 1H, CH), 1.46 (t, 3H, $J = 6.8$ Hz, $CH_3$), 1.15 (d, 3H, $J = 6.8$ Hz, $CH_3$), 1.05 (d, 3H, $J = 6.8$ Hz, $CH_3$); MS ($m/z$): 278 ($M^+$, B), 235, 179, 151, 122. Anal. calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.61; H, 6.45; N, 10.00.

5-Isobutyl-3-(*p*-ethoxylphenyl)-2-thiohydantoin **4l**: White crystals. Yields: 92%; Mp 168.5–170°C; IR(KBr): 3176 (N-H), 3075, 2969, 2873, 1764 (C═O), 1612, 1525, 1281 (C═S), 827 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$):$\delta$ 7.90 (s, 1H, N-H), 7.22 (d, 2H, $J = 8.8$ Hz, ArH), 7.02 (d, 2H, $J = 8.8$ Hz, ArH), 4.31 (dd, 1H, $J = 2.8$, 9.2 Hz, N-CH), 4.09 (q, 2H, $J = 6.4$ Hz, $CH_2$), 1.91 (m, 2H, $CH_2$), 1.75 (m, 2H, $CH_2$), 1.45 (t, 3H, $J = 6.8$ Hz, $CH_3$), 1.04 (t, 6H, $J = 6.4$ Hz, $2CH_3$); MS ($m/z$): 292 ($M^+$, B), 263, 236, 179, 151. Anal. calcd. for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.83; H, 6.85; N, 9.64.

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