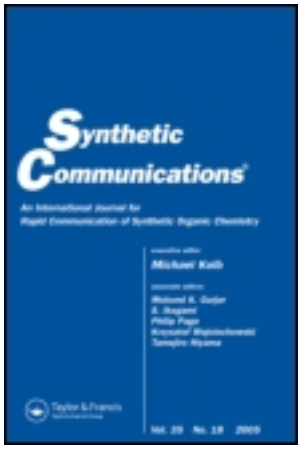


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# Microwave-Assisted Solid-Phase Synthesis of 4,5-Dihydroxy-1,3-dialkyl-4,5-diarylimidazolidine-2-thione and Thiohydantoins

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# MICROWAVE-ASSISTED SOLID-PHASE SYNTHESIS OF 4,5-DIHYDROXY-1,3-DIALKYL-4,5-DIARYLIMIDAZOLIDINE-2-THIONE AND THIOHYDANTOINS

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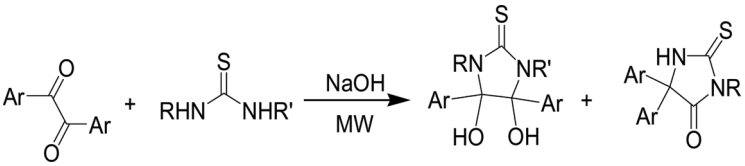
## GRAPHICAL ABSTRACT




**Abstract** *4,5-Dihydroxy-1,3-dialkyl-4,5-diarylimidazolidine-2-thione are obtained in good yields from the 1:1 addition reaction between benzil derivatives and thiourea derivatives in the solid phase. These compounds undergo smooth rearrangement followed by a hydrogen shift to produce thiohydantoins in excellent yields.*

**Keywords** 5-5-Diarylthiohydantoin; 4,5-dihydroxy-1,3-dialkyl-4,5-diarylimidazolidine-2-thione; microwave; solid phase

## INTRODUCTION

Thiohydantoins and their derivatives represent an important class of biologically active molecules having broad medicinal and agrochemical applications. Furthermore, many thiohydantoins are responsible for inhibition of fatty acid hydrolases, glycogen phosphorylases, amylases, and serine proteases.[1–3]

Applications of microwave irradiation in a variety of organic reactions have rapidly increased as a result of short reaction time and operational simplicity.[4–8] As part of our current studies on the development of new routes in heterocyclic

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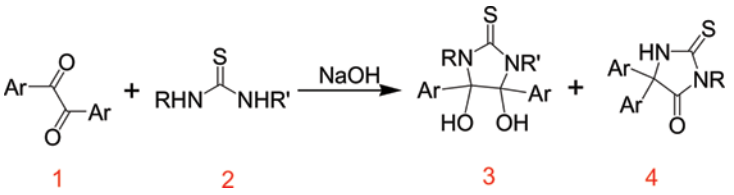



**Scheme 1.** Synthesis of compounds **3** and **4**.

**Table 1.** Solid-phase synthesis of 4,5-dihydroxy-1,3-dialkyl-4,5-diarylimidazolidine-2-thione and thiohydantoins

| Product | Ar | R | R′ | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | Me | Me | 95 | 146–147 |
| **3b** | 4-$MeC_6H_4$ | Me | Me | 92 | 132–133 |
| **3c** | $C_6H_5$ | Et | Et | 85 | 108–110 |
| **4a** | $C_6H_5$ | H | H | 98 | 229–231 |
| **4b** | 4-$MeC_6H_4$ | H | H | 97 | 94–96 |
| **4c** | 2-$ClC_6H_4$ | H | H | 93 | 135–137 |
| **4d** | 4-$ClC_6H_4$ | H | H | 96 | 234–236 |
| **4e** | 2-$NO_2C_6H_4$ | H | H | 95 | 168–170 |
| **4f** | 4-$NO_2C_6H_4$ | H | H | 98 | 265–266 |
| **4g** | $C_6H_5$ | Me | H | 90 | 181–182 |
| **4h** | 4-$MeC_6H_4$ | Me | H | 87 | 152–153 |
| **4i** | 4-$ClC_6H_4$ | Me | H | 88 | 183–184 |

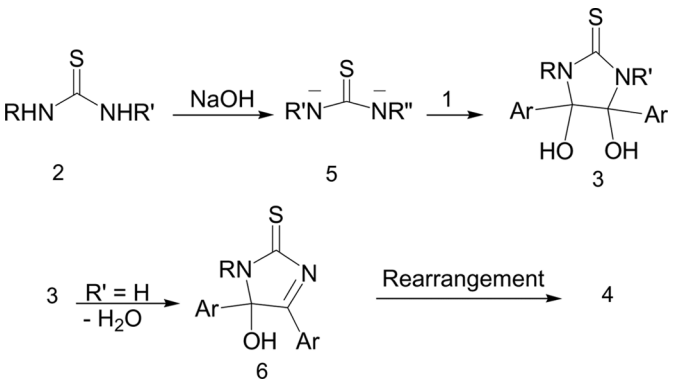
systems,[9–11] we report an efficient synthesis of 4,5-dihydroxy-1,3-dialkyl-4,5-diarylimidazoliodine-2-thiones **3** and thiohydantoins **4**.

The reaction of benzils **1** and thioureas **2** in the presence of sodium hydroxide (NaOH) leads to dioles **3**, which undergo intramolecular reaction in microwave irradiation to produce **4** in excellent yields (Scheme 1 and Table 1).

## RESULTS AND DISCUSSION

The reaction of the benzils **1** with the alkyl thioureas **2** under microwave irradiation (100 W) in the presence of the sodium hydroxide in the solid phase proceeded smoothly to afford the target compounds **3** and **4** in 78–98% yield (Scheme 1). The structures of compounds **3** were confirmed by elemental analyses and infrared (IR), $^1$H and $^{13}$C NMR, and mass spectral data. Thus, the $^1$H NMR spectrum of each of the isolated dioles **3** exhibited OH protons signal at about 3.0–4.5 ppm. Further evidence was obtained from the $^{13}$C NMR spectra, which displayed N(C)OH carbon resonances at about 90–100 ppm. The mass spectra of **3** displayed the molecular ion peaks at appropriate $m/z$ values.

Dioles **3** undergo a smooth reaction to produce thiohydantoins **4** (Scheme 1). Structure **4** was assigned to the isolated products on the basis of their elemental analyses and IR, $^1$H and $^{13}$C NMR, and mass spectral data. Thus, the $^1$H NMR spectrum of each of the isolated products exhibited a NH proton signal(s) at about




**Scheme 2.** Plausible mechanism for the formation of compounds **3** and **4**.



9.0–12.5 ppm. Further evidence was obtained from the $^{13}C$ NMR spectra, which displayed a C=O carbon signal at about 162–175 ppm and C=S carbon signal at about 180–184 ppm.

Although we have not yet established the mechanism of formation of **3** and **4** in an experimental manner, a possible explanation is proposed in Scheme 2.[12] Presumably, the ionic intermediate **5**, formed from the sodium hydroxide and the thioureas, is attacked by **1** to produce 5-dihydroxy-1,3-dialkyl-4,5-diarylimidazolidine-2-thione **3**. Dioles **3** eliminate water to produce the intermediates **6**, which apparently under goes rearrangement followed by a hydrogen shift to produce the final products **4** in excellent yields.

In summary, we have prepared novel thiohydantoins via a one-pot reaction between benzils and thioureas in the presence of a strong base such as sodium hydroxide. Finally, the proposed procedure for the preparation of thiohydantoin derivatives is advantageous because of its experimental simplicity, short reaction time, and excellent yields.

## EXPERIMENTAL

Thioureas **2** and sodium hydroxide were obtained from Fluka and were used without further purification. Benzil **1** was prepared by known methods.[13–15] The microwave oven used for this work was an ETHOS-MR (800 W, 180 °C) operating at 2450 MHz. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N, and S were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. $^1H$ and $^{13}C$ NMR spectra ($CDCl_3$) were measured with a Bruker DRX-500 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

### General Procedure for the Preparation of Dioles 3

A mixture of 1 mmol of **1** and 2 mmol of **2** was placed into an open glass container, 0.080 g (2 mmol) of sodium hydroxide was added, and the mixture was

irradiated in a microwave oven at a power of 100 W over a period of 1.5 min. The hot mixture was then poured into ice water, and the precipitate was filtered off. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate of **3** was filtered off, dried for 2 days in a desiccator over calcium chloride, and recrystallized from ethanol.

### Selected Data

**4,5-Dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (3a).** White powder; mp 146–147.5 °C; yield: 0.30 g (95%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3333 (OH), 1520 (C=C). Anal. calcd. (%) for $C_{17}H_{18}N_2O_2S$ (314.40): C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 65.10; H, 5.56; N, 8.61; S, 10.51. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.13$ (6 H, s, 2 Me), 4.17 (2 H, s, 2 OH), 6.94–7.18 (10 H, m, CH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 30.9$ (2 Me), 96.0 (2C), 127.2 (4 CH), 128.4 (4 CH), 129.0 (2 CH), 136.1 (2 C), 184.8 (C=S).

**4,5-Dihydroxy-1,3-dimethyl-4,5-dip-tolylimidazolidine-2-thione (3b).** White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 3335 (OH), 1524 (C=C). Anal. calcd. (%) for $C_{17}H_{18}N_2O_2S$ (314.4): C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 64.90; H, 5.87; N, 8.86; S, 10.40. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (6 H, s, 2 Me), 3.12 (6 H, s, 2 Me), 4.15 (2 H, s, 2 OH), 7.30–7.73 (8 H, m, CH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 21.5$ (2 Me), 30.9 (2 Me), 96.0 (2C), 128.2 (4 CH), 129.4 (4 CH), 135.0 (2 C), 137.1 (2 C), 184.8 (C=S).

**4,5-Dihydroxy-1,3-diethyl-4,5-diphenylimidazolidine-2-thione (3c).** White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 3330 (OH), 1515 (C=C). Anal. calcd. (%) for $C_{19}H_{22}N_2O_2S$ (342.46): C, 66.64; H, 6.48; N, 8.18; S, 9.36. Found: C, 66.10; H, 6.56; N, 8.31; S, 9.71. EIMS: $m/z$ (%) 342 ($M^+$, 4), 324 (64), 265 (100), 189 (67), 165 (38), 77 (33). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (6 H, t, $^3J_{HH} = 6.9$ Hz, 2 Me), 3.33 (2 H, dt,$^3J_{HH} = 6.9$ Hz, $^2J_{HH} = 12.2$ Hz, $CH_2$), 3.92 (2 H, dt, $^3J_{HH} = 6.9$ Hz, $^2J_{HH} = 12.2$ Hz, $CH_2$), 4.33 (2 H, s, 2 OH), 6.89–7.52 (10 H, m, CH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 15.4$ (2 Me), 40.2 (2 $CH_2$), 96.8 (2C), 127.5 (4 CH), 128.2 (4 CH), 128.7 (2 CH), 136.4 (2 C), 184.0 (C=S).

### General Procedure for the Preparation of 4

A mixture of 1 mmol of **1** and 0.152 g (2 mmol) of thiourea was placed into an open glass container, 0.080 g (2 mmol) of sodium hydroxide was added, and the mixture was irradiated in a microwave oven at a power of 100 W over a period of 1.5 min. The hot mixture was then poured into ice water, and the precipitate was filtered off. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate of **4** was filtered off, dried for 2 days in a desiccator over calcium chloride, and recrystallized from ethanol.

### Selected Data

**5,5-Diphenyl-2-thioxoimidazolidin-4-one (4a, $C_{15}H_{12}N_2OS$).** White powder; mp 229–231 °C; yield: 0.26 g (98%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3250 (NH), 1735

(C=O), 1524 (C=C). EIMS: $m/z$ (%). 268 ($M^+$, 100), 239 (62), 180 (98), 104 (69), 77 (70). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 6.91–7.82$ (10 H, m, CH), 11.10 (1 H, s, NH), 11.82 (1 H, s, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 74.2$ (C), 127.7 (2CH), 127.9 (4 CH), 129.5 (4 CH), 131.4 (2 C), 162.6 (C=O), 180.5 (C=S).

**2-Thioxo-5,5-dip-tolylimidazolidin-4-one (4b).** White powder; mp 94–96 °C; yield: 0.29 g (97%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3244 (NH), 1760 (C=O), 1520 (C=C). Anal. calcd. (%) for $C_{17}H_{16}N_2OS$ (296.10): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.97; H, 5.36; N, 9.61; S, 10.51. EIMS: $m/z$ (%) 296 ($M^+$, 100), 253 (80), 211 (40), 194 (90), 91 (73), 65 (38). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.22$ (6 H, s, 2 Me), 6.80–7.73 (8 H, m, CH), 11.28 (1 H, s, NH), 12.10 (1 H, s, NH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (2 Me), 74.2 (C), 127.9 (4 CH), 129.5 (4 CH), 135.4 (2 C), 137.7 (2 C), 162.6 (C=O), 180.5 (C=S).

**5,5-Bis(2-chlorophenyl)-2-thioxoimidazolidin-4-one (4c, $C_{15}H_{10}N_2OSCl_2$).** Yellow powder; mp 135–137 °C; yield: 0.31 g (93%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3150 (NH), 1750 (C=O), 1524 (C=C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.27–7.80$ (8 H, m, CH), 11.30 (1 H, s, NH), 12.20 (1 H, s, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 74.6$ (C), 127.8 (2 CH), 127.9 (2 CH), 129.5 (2 CH), 129.9 (2 CH), 133.4 (2 C), 141.4 (2 C), 162.6 (C=O), 180.5 (C=S).

**5,5-Bis(4-chlorophenyl)-2-thioxoimidazolidin-4-one (4d, $C_{15}H_{10}N_2OSCl_2$).** White powder; mp 234–236 °C; yield: 0.32 g (96%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3150 (NH), 1690 (C=O), 1524 (C=C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.27–7.90$ (8 H, m, CH), 11.40 (1 H, s, NH), 12.32 (1 H, s, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 77.4$ (C), 129.3 (4 CH), 129.9 (4 CH), 131.5 (2 C), 138.4 (2 C), 162.6 (C=O), 180.8 (C=S).

**5,5-Bis(2-nitrophenyl)-2-thioxoimidazolidin-4-one (4e).** Brown powder; mp 168–170 °C; yield: 0.34 g (95%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3050 (NH), 1690 (C=O), 1524 (C=C). Anal. calcd. (%) for $C_{16}H_{12}N_4O_5S$ (372.36): C, 51.61; H, 3.25; N, 15.05; S, 8.61. Found: C, 50.92; H, 3.38; N, 15.21; S, 9.11. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.20–7.90$ (8 H, m, CH), 9.20 (1 H, s, NH), 11.91 (1 H, s, NH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 74.0$ (C), 127.2 (2 CH), 129.9 (2 CH), 135.5 (2 CH), 138.4 (2 C), 148.5 (2 C), 172.6 (C=O), 181.5 (C=S).

**5,5-Bis(4-nitrophenyl)-2-thioxoimidazolidin-4-one (4f).** Brown powder; mp 265–266 °C; yield: 0.35 g (98%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3150 (NH), 1700 (C=O), 1520 (C=C). Anal. calcd. (%) for $C_{16}H_{12}N_4O_5S$ (372.36): C, 51.61; H, 3.25; N, 15.05; S, 8.61. Found: C, 48.98; H, 3.36; N, 15.61; S, 8.41. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.27–7.80$ (8 H, m, CH), 9.30 (1 H, s, NH), 11.89 (1 H, s, NH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 74.2$ (C), 121.7 (4 CH), 129.9 (4 CH), 145.5 (2 C), 146.4 (2 C), 174.6 (C=O), 181.9 (C=S).

**3-Methyl-5,5-diphenyl-2-thioxoimidazolidin-4-one (4g).** White powder; mp 94–96 °C; yield: 0.25 g (90%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3286 (NH), 1711 (C=O), 1499 (C=C). Anal. calcd. (%) for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 67.90; H, 5.06; N, 9.82; S, 11.41. EIMS: $m/z$ (%) 282 ($M^+$, 100), 225 (8), 193 (3), 180 (54), 167 (37), 105 (32), 77 (30). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.14$ (3 H, s, Me), 7.07–7.19 (10 H, m, CH), 7.90 (1 H, s,

NH).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 27.6$ (Me), 71.9 (C), 127.0 (2 CH), 128.1 (4 CH), 128.7 (4 CH), 138.5 (2 C), 167.6 (C=O), 181.5 (C=S).

**3-Methyl-2-thioxo-5,5-dip-tolylimidazolidin-4-one (4h).** White powder; mp 94–96 °C; yield: 0.27 g (87%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3278 (NH), 1682 (C=O), 1501 (C=C). Anal. calcd. (%) for $C_{18}H_{18}N_2OS$ (310.41): C, 65.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 66.90; H, 5.46; N, 8.61; S, 9.81. EIMS: $m/z$ (%) 310 ($M^+$, 100), 295 (2), 281 (8), 267 (11), 253 (11), 219 (23), 91 (27). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.36$ (6 H, s, 2 Me), 3.33 (3 H, s, Me), 7.07–7.25 (8 H, m, CH), 8.20 (1 H, s, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 22.2$ (2 Me), 28.3 (Me), 72.5 (C), 127.1 (2 CH), 130.0 (4 CH), 130.7 (4 CH), 138.5 (2 C), 172.0 (C=O), 183.1 (C=S).

**5,5-Bis(4-chlorophenyl)-3-methyl-2-thioxoimidazolidin-4-one (4i).** White powder; mp 148–150 °C; yield: 0.31 g (88%); IR (KBr) ($\nu_{max}/cm^{-1}$): 3280 (NH), 1690 (C=O), 1490 (C=C). Anal. calcd. (%) for $C_{16}H_{12}N_2OSCl_2$ (351.25): C, 54.71; H, 3.44; N, 7.98; S, 9.13. Found: C, 55.90; H, 3.26; N, 7.61; S, 9.81. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.35$ (3 H, s, Me), 7.02–7.24 (8 H, m, CH), 8.27 (1 H, s, NH). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 28.8$ (Me), 77.0 (C), 129.3 (4 CH), 129.9 (4 CH), 131.5 (2 C), 138.4 (2 C), 162.6 (C=O), 181.8 (C=S).

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