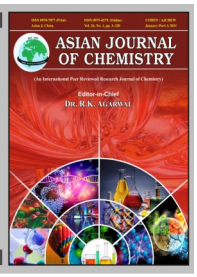
Asian Journal of Chemistry; Vol. 26, No. 4 (2014), 1171-1173

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16119



# An Efficient Method for Synthesis of Thiohydantoins with α-Amino Esters Under Microwave Irradiation

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*Received*: 30 July 2013; *Accepted*: 6 October 2013; *Published online*: 15 February 2014; AJC-14722

An efficient and simple way for synthesis of thiohydantoins is reported. In the absence of any additional catalysts, a series of thiohydantoins were synthesized with amino esters and isothiocyanates in aqueous medium under microwave irradiation. Excellent isolated yields (up to 98 %) were obtained under mild conditions.

**Keywords: Thiohydantoin, Microwave irradiation, Amino esters, Isothiocyanates.**

## INTRODUCTION

Thiohydantoins are the ultimate reaction products of the Edman degradation for peptide sequencing while their derivatives have been found to exist in many nature products and medicines[1,2]. Recent research results showed that thiohydantoins and their derivatives have a wide range of biological activities such as antiviral, antitumor, anticancer, anticonvulsant, antiulcer and antibacterial activities[3-9]. In addition, thiohydantoins are traditionally being considered as useful intermediates in peptide and heterocycles synthesis. For this reason, the synthesis of thiohydantoins is valuable for drug discovery and lots of efficient methods have been reported[9-20]. However, the present methods suffer from drawbacks such as long reaction times, use of corrosive reagents and tedious work-up procedures. Therefore, the development of a simple and efficient method for synthesis of thiohydantoins is still necessary. Herein, we reported a fast and simple way for synthesis of thiohydantoins with α-amino esters and isothiocyanates in aqueous medium under the microwave irradiation.

## EXPERIMENTAL

All starting materials were of the commercially available (analytical grade) and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92. Melting poits were measured with SGW X-4 melting point apparatus. $^1$H and $^{13}$C NMR (300 or 600 and 75 or 150 Hz, respectively) spectra were recorded in $CDCl_3$. $^1$H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). $^{13}$C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). IR spectra were recorded on NICONET-380 spectrophotometer using KBr pellets. ESIMS spectra were recorded on BioTOF Q.

**General procedure for the synthesis of thiohydantoins :** A mixture of isothiocyanate (2 mmol) and DL-amino ester (2 mmol) were stirred under microwave (400 w) at 400 °C in DMF/ $H_2O$ (3:1) (8 mL). After 5 min, the solvent was removed under reduced pressure and the residue purified through column chromatography on silica gel (hexane/EtOAc) to give pure product thiohydantoins.

**Spectral data of the products:** 5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (**3a**): White solid; yield: 98 %; m.p. 189-190 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.06-3.14 (m, 1H), 3.32-3.38 (m, 1H), 4.51-4.54 (m, 1H), 7.07 (d, *J* = 9.60 Hz, 2H), 7.25-7.51 (m, 8H), 7.52 (brs, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 37.7, 60.8, 127.9, 128.1, 129.1, 129.3, 132.5, 134.3, 172.5, 183.7; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3172, 1754, 1518, 1408, 1337, 1269, 1189, 1108; ESI HRMS exact mass calcd. for $(C_{16}H_{14}N_2OS + Na)^+$ requires *m/z* 305.0719, found *m/z* 305.0719.

**5-Benzyl-3-(4-chlorophenyl)-2-thioxoimidazolidin-4-one (3b):** White solid; yield: 89 %; m.p. 225-227 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.06-3.13 (m, 1H), 3.35-3.38 (m, 1H), 4.50-4.54 (m, 1H), 7.01 (d, *J* = 7.23 Hz, 2H), 7.26 - 7.43 (m, 8H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 37.7, 60.8, 127.9, 129.1, 129.3, 129.4, 129.5, 130.9, 134.1, 135.3, 172.2, 183.2; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3167, 1754, 1516, 1494, 1409,

1273, 1188, 1092; ESI HRMS exact mass calcd. for $(C_{16}H_{13}N_2OSCl + Na)^+$ requires *m/z* 339.0329, found *m/z* 339.0341.

**5-Benzyl-3-(4-methoxyphenyl)-2-thioxoimidazolidin-4-one (3c):** White solid; yield: 90 %; m.p. 216-218 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.04-3.12 (m, 1H), 3.33-3.38 (m, 1H), 3.82 (s, 3H), 4.50-4.54 (m, 1H), 6.93-7.00 (m, 4H), 7.26-7.28 (m, 3H), 7.34-7.40 (m, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 37.7, 55.4, 60.8, 125.0, 127.8, 129.1, 129.3, 129.4, 134.3, 172.8, 184.1; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3182, 1754, 1516, 1408, 1350, 1252, 1172, 1110; ESI HRMS exact mass calcd. for $(C_{17}H_{16}N_2O_2S + Na)^+$ requires *m/z* 335.0825, found *m/z* 335.0826.

**5-Benzyl-2-thioxo-3-*p*-tolylimidazolidin-4-one (3d):** White solid; yield: 94 %; m.p. 214-215 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.07-3.11 (m, 1H), 3.31-3. 33 (m, 1H), 4.49-4.51 (m, 1H), 6.93 (d, *J* = 8.16 Hz, 2H), 7.24-7.37 (m, 7H), 7.62 (brs, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 21.3, 37.6, 60.8, 127.8, 127.9, 129.0, 129.4, 129.9, 134.2, 139.4, 172.7, 183.9; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3175, 1753, 1518, 1408, 1347, 1269, 1189, 1112; ESI HRMS exact mass calcd. for $(C_{17}H_{16}N_2OS\text{-}H)^+$ requires *m/z* 295.3901, found *m/z* 295.0906.

**5-Benzyl-3-methyl-2-thioxoimidazolidin-4-one (3e):** White solid; yield: 84 %; m.p. 130-132 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.27-2.86 (m, 1H), 3.20 (s, 3H), 3.31-3.37 (m, 1H), 4.28-4.33 (m, 1H), 7.10 (brs, 1H), 7.20 (d, *J* = 6.24 Hz, 2H), 7.31-7.38 (m, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 27.5, 37.6, 60.7, 127.4, 129.0, 129.2, 134.9, 173.2, 184.1; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3201, 1743, 1519, 1446, 1337, 1298, 1126, 1103; ESI MS $(M + H)^+$ 221.1.

**5-(4-Hydroxybenzyl)-3-methyl-2-thioxoimidazolidin-4-one (3f):** White solid; yield: 91 %; m.p. 178-179 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.77-2.81 (m, 1H), 3.20 (s, 3H), 3.20-3.24 (m,1H), 4.08-4.26 (m, 1H), 5.30 (brs, 1H), 6.80 (d, *J* = 8.46 Hz, 2H), 6.91 (brs, 1H), 7.07 (d, *J* = 8.40 Hz, 2H),; $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 27.5, 36.8, 60.8, 126.8, 130.3, 155.2, 173.2, 184.2; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3186, 1736, 1518, 1438, 1338, 1267, 1094; ESI HRMS exact mass calcd. for $(C_{11}H_{12}N_2O_2S + H)^+$ requires *m/z* 237.0692, found *m/z* 237.0703.

**3-Methyl-5-phenyl-2-thioxoimidazolidin-4-one (3g):** White solid; yield: 88 %; m.p. 157-159 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 3H), 5.11 (s, 1H), 7.16 (brs, 1H), 7.31-7.33 (m, 2H), 7.40-7.43 (m, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 27.8, 62.8, 126.6, 129.3, 129.5, 133.0, 172.3, 184.7; IR (KBr): 3184, 1758, 1520, 1497, 1273, 1247, 1173, 1108; ESI HRMS exact mass calcd. for $(C_{10}H_{11}N_2O_2S + H)^+$ requires *m/z* 207.0587, found *m/z* 207.0585.

**3,5-Diphenyl-2-thioxoimidazolidin-4-one (3h):** White solid; yield: 96 %; m.p. 236-237 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.30 (s, 1H), 7.32-7.52 (m, 10H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 63.1, 126.6, 128.3, 128.8, 129.2, 129.3, 129.5, 129.6, 130.9, 133.2, 171.5, 184.2; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3148, 1758, 1520, 1404, 1273, 1183, 1105; ESI HRMS exact mass calcd. for $(C_{15}H_{12}N_2OS + Na)^+$ requires *m/z* 291.0563, found *m/z* 291.0565.

**5-Isopropyl-3-phenyl-2-thioxoimidazolidin-4-one (3i):** White solid; yield: 91 %; m.p. 211-212 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.80 Hz, 3H), 1.14 (d, *J* = 6.99 Hz, 3H), 2.36-2.40 (m, 1H), 4.11-4.17 (m, 1H) 7.25-7.30 (m, 2H) 7.46-7.54 (m, 3H), 7.82 (brs, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 16.2, 18.7, 31.6, 64.9, 128.3, 129.2, 129.3, 132.7, 172.9, 184.3; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3192, 1759, 1517, 1409, 1349, 1271, 1195, 1108; ESI HRMS exact mass calcd. for $(C_{12}H_{14}N_2OS + Na)^+$ requires *m/z* 257.0719, found *m/z* 257.0732.

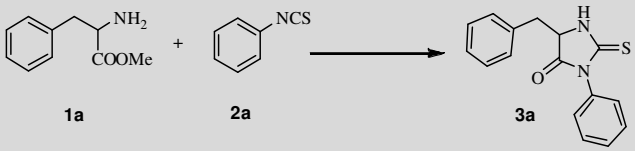
## RESULTS AND DISCUSSION

The classical method for the synthesis of thiohydantoins is the reaction of isothiocyanates with amino acids. Generally, thiourea was firstly produced and then cyclized to thiohydantoins. For entirely cyclization, acidic or basic conditions are usually required. However, this is not suitable for the synthesis of thiohydantoins with a pH-sensitive group. As part of our program to seek effective, economical and green reactions[21-23], we wish to synthesize thiohydantoins with amino esters and isothiocyanates in the absence of acid and base. Firstly, we took the reaction of methyl 2-amino-3-phenylpropanoate (**1a**) and phenyl isothiocyanate (**2a**) as a model reaction to develop the optimum reaction conditions. When the reaction went through two days in dichloromethane at 40 °C, the yield of **3a** was only 16 %. The main product was the thiourea. At the same reaction conditions, we tried other solvents such as toluene, water ($H_2O$) and N,N-dimethylformamide (DMF). There was only trace product in toluene. The yield of 3a were higher in $H_2O$ and DMF. So we considered use of the mixture of DMF and $H_2O$ as the solvent. To our surprise, the yield of **3a** enhanced to 92 % after two days when DMF/$H_2O$ (3:1) was used. Considering the microwave technology has been blossomed into a useful technique in synthetic chemistry due to the fast reaction rate and high yields[24-26], we used it to increase the efficiency. Much to our surprise, the product yield was enhanced to 98 % in DMF/$H_2O$ (3:1) at 40 °C after only 5 min with the power of 400 W. And then, the power of microwave irradiation was studied. When the power was 300 W, the yield of product was decreased to 91 % (entry 7, Table-1). Further enhancing the power to 600 W has little effect on the yield (entries 8-9, Table-1). We also investigated the effects of temperature. The results showed that the effects of temperature is the same as the power. Lower temperature disadvantaged the yield and higher temperature has little effect on the yield (entries 10-12, Table-1).

Having established the optimal reaction conditions, we next examined the generality of this microwave-assisted protocol. Various amino esters and isothiocyanates were tested under assistant of microwave irradiation (400 W) at 40 °C in the absence of catalysts with DMF/ $H_2O$ (3:1) as the solvents. As shown in **Scheme-I**, the methyl 2-amino-3-phenylpropanoate, methyl 2-amino-3-(4-hydroxy-phenyl)propanoate, methyl 2-amino-2-phenylacetate and methyl 2-amino-3-methylbutanoate all cyclized to thiohydantions with phenyl isothiocyanate, 4-chloro-phenyl isothiocyanate,4-methoxyphenyl isothiocyanate, 4-methyl-phenyl isothiocyanate and methyl isothiocyanate to afford the desired thiohydantoins in excellent yields (84-98 %, **Scheme-I**).

In summary, we have developed a highly efficient catalyst-free method for the synthesis of thiohydantions. With this protocol, a set of thiohydantions can be synthesized with

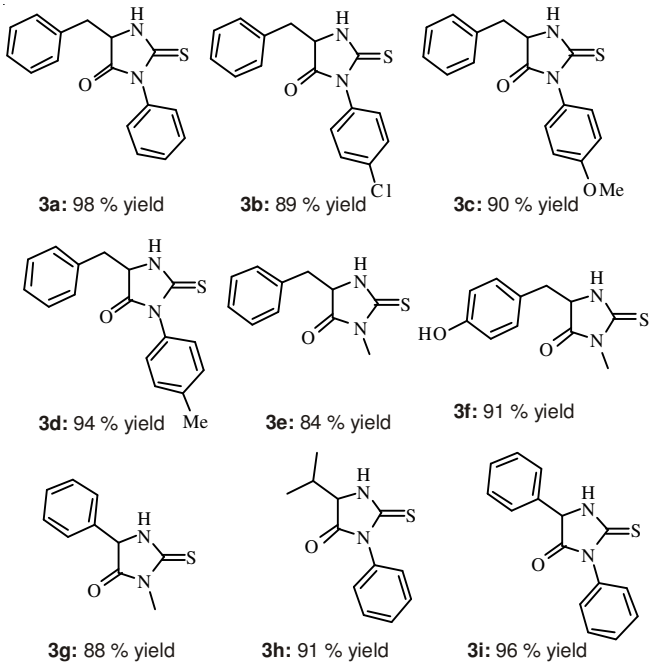
TABLE-1
EFFECTS OF REACTION CONDITIONS ON THE SYNTHESIS OF THIOHYDANTOIN[a]




1a 2a 3a

| Entry | Solvent | Temp. (°C) | Power (W) | Time | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 | - | 2d | 16 |
| 2 | Toluene | 40 | - | 2d | Trace |
| 3 | $H_2O$ | 40 | - | 2d | 35 |
| 4 | DMF | 40 | - | 2d | 21 |
| 5 | DMF/$H_2O$ (1/3) | 40 | - | 2d | 92 |
| 6 | DMF/$H_2O$ (1/3) | 40 | 400 | 5 min | 98 |
| 7 | DMF/$H_2O$ (1/3) | 40 | 300 | 5 min | 91 |
| 8 | DMF/$H_2O$ (1/3) | 40 | 500 | 5 min | 97 |
| 9 | DMF/$H_2O$ (1/3) | 40 | 600 | 5 min | 97 |
| 10 | DMF/$H_2O$ (1/3) | 20 | 400 | 5 min | 75 |
| 11 | DMF/$H_2O$ (1/3) | 60 | 400 | 5 min | 97 |
| 12 | DMF/$H_2O$ (1/3) | 80 | 400 | 5 min | 97 |

[a]Unless specified otherwise, the reaction was performed at 2 mmol scale in 8 mL solvent, [b]Isolated yield




**Scheme-I**

excellent yields in absence of any additional catalyst under microwave irradiation.

## ACKNOWLEDGEMENTS

The authors are grateful for the financial supports from the National Natural Science Foundation of China (21102115), the Open Fund of the Key Laboratory of Sichuan Province (Szjj2011-005) and the National Undergraduate Innovation and Entrepreneurship Training Programs of China (201210623009).

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