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MICROWAVE-ASSISTED SYNTHESIS OF 3,5-DISUBSTITUTED THIOHYDANTOINS USING FUNCTIONAL IONIC LIQUID AS SOLUBLE SUPPORT

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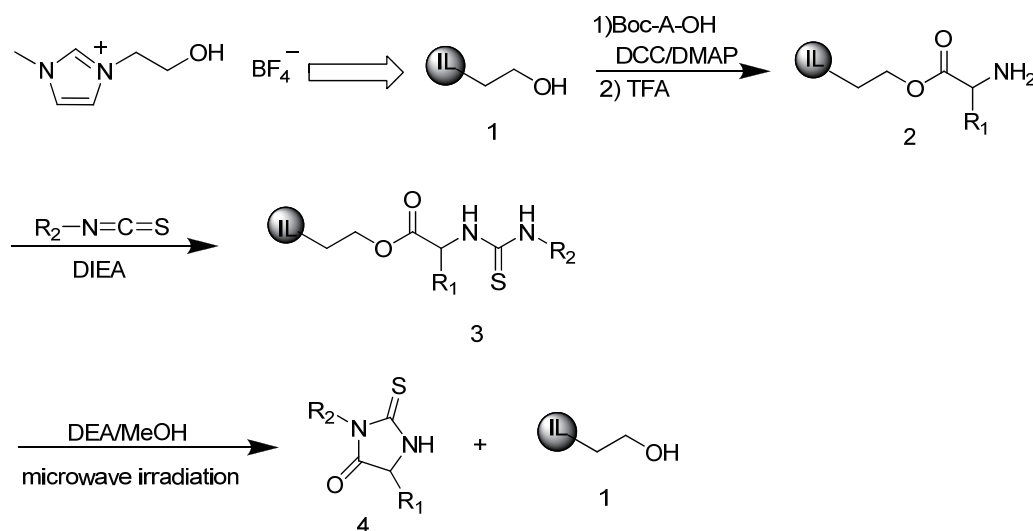
Abstract – A new approach for the syntheses of 3,5-disubstituted thiohydantoin was described using functionalized ionic liquid as soluble support. The products were obtained in good yields and purities after cyclization-cleavage from the ionic-liquid-supported under microwave irradiation, the ionic-liquid-supported species can there be purified from the reaction mixture by simple washing, and no chromatographic purification were needed during the synthesis.

Organic synthesis using insoluble solid polymer resin as support was first proposed by Merrifield more than four decades ago¹ and has since been applied extensively in numerous areas.^{2,3} However, the solid phase synthesis approach suffers from some disadvantages. This has led to alternative methodologies with the aim of restoring homogeneous reaction conditions. Recently, more attentions in ionic liquids (ILs) research has been paid on the functionalized ionic liquids with special task, which have been introduced as soluble supports in liquid-phase organic synthesis.⁴ Substrates anchored on ionic liquids are expected to retain their reactivities, and allow the use of conventional spectroscopic analysis during the synthetic process. Finally the products could be cleaved from the ionic liquid support. Recent reports from several groups have successfully demonstrated the efficiency of ionic liquid supported synthesis for small molecules⁵ and peptides.⁶ Microwave irradiation⁵ has become an established tool in organic synthesis. Hoffmann *et al.* reported ionic liquids could efficiently absorb microwave energy by which the reaction

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rate could be accelerated remarkably.⁷

3,5-Disubstituted thiohydantoin s have been identified to possess a wide range of biological activities.⁸ As a part of our ongoing efforts in using ionic liquid as eco-friendly medium in condensation reaction,⁹ we report herein a new synthetic approach of 3,5-disubstituted thiohydantoin s under microwave irradiation using the functionalized ionic liquid (1) as soluble supports, which incorporate both the thiourea and imidazole functionalities (Scheme 1).



Scheme 1

For this study, 1-(2-hydroxyethyl)-1-methylimidazolium tetrafluoroborate **1** was prepared according to the literature.^{10,11} As shown in Scheme 1, the functionalized ionic liquid **1** dissolved in acetonitrile was coupled with a *t*-Botoxycarbonyl (BOC) amino acid under dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) activation at room temperature for 18 hours. Ionic-liquid-supported Boc-amino acid was removed the Boc group using trifluoroacetic acid (TFA) in dichloromethane to yield **2**, which was reacted with an isothiocyanate to provide the ionic-liquid-supported thiourea **3**. The reaction was conveniently monitored via the ninhydrin test.¹² The desired 3,5-disubstituted thiohydantoin s **4** was obtained via intramolecular cyclization with concomitant cleavage from IL support using diethylamine (DEA) under microwave irradiation for 45 min.

To establish the scope of this reaction, various amino acids and isothiocyanates were investigated. The results were summarized in Table 1, all the products were characterized by ¹H NMR, IR spectrum and ESI-MS. The method was found to be generally applicable, all the products were obtained in good to excellent yields.

In summary, we have successfully performed the microwave-assisted synthesis of 3,5-disubstituted thiohydantoin using hydroxyl-functionalized ionic liquids as soluble support. Our method represents an attractive alternative to the classical solid- and fluorous-phase synthesis strategies including being environmentally more benign, the isolation and purification of intermediates more easy, the shorter reaction times, the higher yields, no need for the use of large molar excess of reagents, without the need for chromatographic purification. It is well believed that this methodology constitutes an attractive avenue for the rapid synthesis of heterocyclic products.

Table 1. Synthesis of 3, 5-disubstituted thiohydantoin using ionic liquid as soluble support

Entry	Product	R ₁	R ₂	Yield ^a (%)
1	4a	PhCH ₂	Ph	87
2	4b	PhCH ₂	3-MePh	82
3	4c	PhCH ₂	n-Bu	79
4	4d	(Me) ₂ CH	Ph	80
5	4e	(Me) ₂ CH	3-MePh	76
6	4f	(Me) ₂ CH	n-Bu	70
7	4g	(Me) ₂ CHCH ₂	Ph	79
8	4h	(Me) ₂ CHCH ₂	3-MePh	75
9	4i	(Me) ₂ CHCH ₂	n-Bu	69
10	4j	H	Ph	85
11	4k	H	3-MePh	80

^a Isolated yield based on 2.

EXPERIMENTAL

The ¹H NMR spectra were recorded on Bruker Avance DMX-500 MHz instrument with CDCl₃ or dimethyl sulfoxide (DMSO-d₆) as solvent and tetramethylsilane (TMS) as the internal standard, and the chemical shifts are expressed in parts per million (ppm). Electrospray ionization-mass spectrometry (ESI-MS) data were recorded on a Bruker Esquire 3000t spectrometer. The infrared (IR) spectra were recorded on a Bruker Vector 200 spectrophotometer (KBr film). Elemental analyses were performed on a Carlo Erba EA 1106 instrument. The microwave irradiation was performed in a 5 mL flask equipped with mechanical stirrer in a Biotage Initiator 8 microwave oven.

General procedure for the synthesis of the 3,5-disubstituted thiohydantoin **4**:

Esterification (Loading) Step: Dicyclohexylcarbodiimide (DCC, 1 M in CH₂Cl₂, 10 mL, 10 mmol) was

added to a mixture of ionic liquid (1.07 g, 5 mmol), Boc-amino acid (10 mmol), and (dimethylamino)pyridine (0.25 g, 2 mmol) in dry MeCN (25 mL). The mixture was stirred vigorously for 18 h at room temperature under nitrogen and filtrated through a plug of Celite. The Celite plug was rinsed with MeCN, and the combined organic phase was concentrated in vacuum. The crude residue was washed first with Et₂O (20 mL×3) and then dissolved in CH₂Cl₂ and washed with 2 M HCl (10 mL×3). The organic phase was dried over Na₂SO₄ and concentrated to afford 1.95 g (91%) of ionic-liquid-supported Boc-amino acid as a pale yellow oil.

Forming Step (Deprotection and Coupling): TFA (10 mL) was added to a solution of ionic-liquid-supported Boc-amino acid (2 mmol) in CH₂Cl₂ (10 mL). The reaction was stirred at room temperature under nitrogen for 0.5 h. Upon concentration under reduced pressure, the residue was washed twice with Et₂O and dried on a vacuum line to yield the deprotected ionic-liquid-supported amino acid **2** as a TFA salt. The ionic-liquid-supported Boc-amino acid was then dissolved together with isothiocyanate (3 mmol, 1.5 eq) and *N,N*-diisopropylethylamine (DIEA) (3 mmol, 1.5 eq) in dry MeCN, and the resulting reaction mixture was stirred at 35 °C under nitrogen atmosphere for 8 h. Completeness of the coupling was verified by the ninhydrin test. The solvent was removed under vacuum, and the residue was washed with Et₂O (20 mL×3) to afford the ionic-liquid-supported thiourea **3** as yellow oil.

Cyclization/Cleavage Step: A mixture of the ionic-liquid-supported thiourea (1 mmol) from the previous step and commercial diethylamine (2 mmol, 2 eq) was dissolved in MeOH (5 mL). The resulting solution was placed in a cylindrical quartz reactor. Then reactor was introduced into a Biotage Initiator 8 microwave oven. The liquid mixture was stirred mechanically and was irradiated at 120 °C for a reaction time ranging 45 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at 25 °C. The resulting solution was concentrated by rotary evaporation and the crude solution was extracted with Et₂O (20 mL ×3). Concentration of the combined Et₂O extracts under reduced pressure afforded the desired 3,5-disubstituted thiohydantoins **4**.

5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (4a). ¹H NMR (CDCl₃): δ = 7.46 (m, 2H), 7.38 (m, 3H), 7.33(m, 3H), 7.05 (m, 2H), 4.55 (q, 1H, J = 4 Hz, J = 7.51 Hz), 3.38 (m, 1H), 3.14 (m, 1H). IR (neat): 3166.53, 1750.66, 1512.92, 1403.19, 1333.59, 1262.06, 1187.65, 1097.07 cm⁻¹. ESIMS, m/z: 283 (MH⁺). Anal. Calcd for C₁₆H₁₄N₂OS: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.15; H, 5.09; N, 9.81.

5-Benzyl-2-thioxo-3-(*m*-tolyl)imidazolidin-4-one (4b). ¹H NMR (CDCl₃): δ = 7.41 (m, 7H), 7.02 (m, 2H), 4.52 (m, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 2.37 (s, 3H). IR (neat): 3415.75, 2923.17, 1740.49, 1648.89, 1496.01, 1392.65, 1258.01, 1191.04, 735.08cm⁻¹. ESIMS, m/z: 297 (MH⁺). Anal. Calcd for

C₁₇H₁₆N₂OS: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.78; H, 5.53; N, 9.36.

5-Benzyl-3-butyl-2-thioxoimidazolidin-4-one (4c). ¹H NMR (CDCl₃): δ = 9.16 (s, 1H), 7.30 (m, 5H), 5.30 (s, 1H), 3.48 (s, 2H), 3.02 (d, 2H, J = 6 Hz), 1.33 (m, 7H). IR (neat): 3446.12, 2925.06, 2856.66, 1680.08, 1457.49, 1391.21, 1201.59 cm⁻¹. ESIMS, m/z: 263 (MH⁺). Anal. Calcd for C₁₄H₁₈N₂OS: C, 64.09; H, 6.91; N, 10.68. Found: C, 64.21; H, 7.02; N, 10.59.

5-Isopropyl-3-phenyl-2-thioxoimidazolidin-4-one (4d). ¹H NMR (CDCl₃): δ = 7.38 (brs, 1H), 7.38 (m, 3H), 7.31 (m, 2H), 4.71 (d, 1H, J = 4 Hz), 2.38 (m, 1H), 1.15 (d, 3H, J = 7 Hz), 1.12 (3H, d, J = 7 Hz). IR (neat): 3178.90, 2964.12, 1756.58, 1681.85, 1513.73, 1404.83, 1348.02, 1266.60, 1183.70, 759.03cm⁻¹. ESIMS, m/z: 235 (MH⁺). Anal. Calcd for C₁₂H₁₄N₂OS: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.58; H, 6.09; N, 11.85.

5-Isopropyl-2-thioxo-3-(*m*-tolyl)imidazolidin-4-one (4e). ¹H NMR (CDCl₃): δ = 7.50 (brs, 1H), 7.37 (m, 1H), 7.27 (s, 1H), 7.11 (m, 2H), 4.16 (d, 1H, J = 4 Hz), 2.40 (s, 3H), 2.33 (m, 1H), 1.22 (d, 3H, J = 6.8 Hz), 1.03–1.05 (d, 3H, J = 6.8 Hz). IR (neat): 3178.90, 2964.12, 1756.58, 1681.85, 1513.73, 1404.83, 1348.02, 1266.60, 1183.70, 759.03cm⁻¹. ESIMS, m/z: 249 (MH⁺). Anal. Calcd for C₁₃H₁₆N₂OS: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.95; H, 6.58; N, 11.21.

3-Butyl-5-isopropyl-2-thioxoimidazolidin-4-one (4f). ¹H NMR (CDCl₃): δ = 7.50 (brs, 1H), 7.26 (m, 2H), 7.27 (s, 1H), 7.11 (m, 2H), 4.16 (d, 1H, J = 4 Hz), 2.40 (s, 3H), 2.33 (m, 1H), 1.22 (d, 3H, J = 6.8 Hz), 1.03–1.05 (d, 3H, J = 6.8 Hz). IR (neat): 3441.09, 2966.12, 2864.59, 2510.67, 1681.83, 1464.29, 1200.35, 1135.50, 1060.51, 794.61cm⁻¹. ESIMS, m/z: 215 (MH⁺). Anal. Calcd for C₁₀H₁₈N₂OS: C, 56.04; H, 8.47; N, 13.07. Found: C, 56.01; H, 8.56; N, 13.01.

5-Isobutyl-3-phenyl-2-thioxoimidazolidin-4-one (4g). ¹H NMR (CDCl₃): δ = 7.28 (m, 3H), 3.48 (s, 1H), 3.40 (m, 2H), 3.24 (m, 1H), 1.74 (m, 1H), 1.58 (m, 2H), 1.11 (d, 6H, J = 7 Hz). IR (neat): 3428.07, 2928.40, 1635.83, 1528.44, 1447.63, 1405.18, 1352.36, 1316.54, 1262.23, 756.86cm⁻¹. ESIMS, m/z: 249 (MH⁺). Anal. Calcd for C₁₃H₁₆N₂OS: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.76; H, 6.56; N, 11.22.

5-Isobutyl-2-thioxo-3-(*m*-tolyl)imidazolidin-4-one (4h). ¹H NMR (CDCl₃): δ = 7.26 (m, 1H), 7.10 (m, 4H), 3.48 (m, 1H), 2.40 (s, 3H), 1.71 (m, 2H), 1.67 (m, 1H), 1.09 (d, 6H, J = 7 Hz). IR (neat): 3332.47, 2927.12, 2856.43, 1752.57, 1708.84, 1618.62, 1526.48, 1451.97, 1273.72, 1087.35cm⁻¹. ESIMS, m/z: 263 (MH⁺). Anal. Calcd for C₁₄H₁₈N₂OS: C, 64.09; H, 6.91; N, 10.68. Found: C, 64.08; H, 6.95; N, 10.58.

3-Butyl-5-isobutyl-2-thioxoimidazolidin-4-one (4i). ¹H NMR (CDCl₃): δ = 4.12 (t, 2H, J = 7 Hz), 3.73 (m, 1H), 2.02 (m, 2H), 1.62 (m, 1H), 1.43 (m, 2H), 1.33 (m, 2H), 1.25 (m, 3H), 0.97 (d, 6H, J = 7 Hz). IR

(neat): 3448.12, 2959.02, 2861.73, 1684.66, 1459.49, 1399.47, 1201.82, 1138.24, 837.82, 754.35 cm^{-1} . ESIMS, m/z : 229 (MH^+). Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_2\text{OS}$: C, 57.86; H, 8.83; N, 12.27. Found: C, 57.93; H, 8.91; N, 12.17.

3-Phenyl-2-thioxoimidazolidin-4-one (4j). ^1H NMR (CDCl_3): δ = 7.38 (m, 5H), 7.01 (m, 1H), 3.79 (s, 2H). IR (neat): 3032.50, 2972.59, 2927.55, 1715.14, 1526.43, 1404.32, 1319.61, 1256.09, 1133.83 cm^{-1} . ESIMS, m/z : 193 (MH^+). Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{OS}$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.13; H, 4.21; N, 14.47.

2-Thioxo-3-*m*-(tolyl)imidazolidin-4-one (4k). ^1H NMR (CDCl_3): δ = 7.39 (m, 1H), 7.26 (m, 2H), 7.12 (m, 2H), 3.77 (s, 2H), 2.40 (s, 3H). IR (neat): 3374.31, 2960.61, 1746.93, 1605.41, 1492.70, 1392.90, 1355.74, 1268.56, 1235.06 cm^{-1} . ESIMS, m/z : 207 (MH^+). Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{OS}$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.33; H, 4.89; N, 13.49.

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