Rapid Communication

Synthesis of new hydantoins as intermediates for diamino acids

S Thennarasu & P T Perumal*
Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India
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An efficient and convenient procedure involving microwave and ultrasound conditions for the synthesis of 5,5-disubstituted hydantoins is reported. The combined use of microwave and ultrasound reduces the reaction time significantly. In the presence of potassium cyanide and ammonium carbonate, the acetyl ester bond is hydrolysed under both ultrasonic and reflux conditions.

Hydantoins, well known for their CNS activity\(^1\),\(^2\), have been reported to possess a variety of pharmacological properties. A number of 2,4-imidazolidinedione derivatives have been shown to act as inhibitors of metalloproteins\(^3\) and exhibit antifungal\(^5\) activities. Recently, 5,5-disubstituted hydantoins have been reported to possess potent inhibitory activity towards HIV protease\(^6\),\(^7\) and act as sodium channel blockers\(^8\),\(^9\). A survey of recent literature reveals that hydantoins are attractive substrates for the synthesis of amino acids\(^10\)–\(^15\) and that hydantoins are obtained economically from aldehydes and ketones by Bucherer-Bergs reaction\(^16\). In continuation of our endeavour to design small antimicrobial peptides, synthesis and study of 5,5-disubstituted hydantoins as intermediates for diamino acids were undertaken.

Evidence from the recent literature shows that several organic reactions are promoted and accelerated by microwave\(^17\)–\(^20\) and ultrasonic irradiations\(^21\),\(^23\). The required starting compounds, 3-acetamido ketones were prepared by Dakin-West reaction\(^24\) \textit{albeit} under microwave irradiation condition. Under the influence of microwaves, the formation of 3-acetamido ketones is complete in less than two minutes, and the pure ketones were obtained in good to excellent yields (72-90%). The physical and spectral data of the 3-acetamido ketones are in complete agreement with the assigned structures (Scheme 1). Thus, microwave irradiation obviates the use of conventional refluxing in a solvent for several hours.

In the present investigation, 5,5-disubstituted hydantoins were obtained by reacting, under ultrasonic irradiation, the 3-acetamido ketones with potassium cyanide and commercial ammonium carbonate-ammonium carbamate mixture in aqueous ethanol. The products formed were characterized as 2,4-imidazolidinediones on the basis of elemental analysis and spectral data. The results are presented in Table 1. The efficacy of this ultrasonic method was evaluated by conducting the reaction in refluxing aqueous ethanol. Under ultrasonic conditions, hydantoins were isolated in good yields within 3 hr, whereas at reflux the reaction yielded products only after refluxing for 9-24 hr. Thus, the combined use of microwave and ultrasound appears to offer the obvious advantage of time and a simple protocol that allows the isolation of pure products.

The \(^1\)H and \(^13\)C NMR of 2c and 3c deserve a special mention. The amide and imide proton signals of hydantoins could be easily identified by deuterium exchange method. The OAc methyl protons of 2c which appear at \(\delta\) 2.24 as singlet are absent in 3c. Similarly, the \(^13\)C signals corresponding to OAc group of 2c which appear at \(\delta\) 21.0 and 169.3 are also absent in the spectrum of 3c. Also, the singlet at \(\delta\) 9.14 corresponding to the OH proton of 3c is absent in the \(^1\)H NMR spectrum of 2c. Thus, the hydroxy group in the aromatic ring of 1c is regenerated in 3c.

It has been reported in the literature\(^25\) that the amide and imide carbonyl resonances of unsubstituted 2,4-imidazolidinedione appear, respectively, at 173.7 and 158.2 ppm in DMSO-\(d_6\). However, the amide and imide carbonyls of the title 5,5-disubstituted hydantoins appear at \(\delta\) 177.3 and 156.6 ppm, respectively. The downfield shift of 3.6 ppm of amide carbonyls suggests that the 5,5-disubstitution make the amide bond in the hydantoin ring weaker and therefore more susceptible for hydrolysis\(^25\). The ramifications of this study as well as other subtle factors involved in the hydrolysis of hydantoins to diamino acids are being examined.

Experimental Section
General method of preparation of 3-acetamidoalkan-2-ones

The L-amino acid (2.0 g) was dissolved in a mixture of pyridine (8.0 mL) and acetic anhydride (8.0 mL) taken in a Erlenmeyer flask fitted with a
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H2N COOH M.W., 2 min.

HOC NH 3a-d

\( R = \text{isobutyl} \)
\( R = \text{benzyl} \)
\( R = \text{4-hydroxybenzyl} \)
\( R = \text{imidazolylmethyl} \)

\( (\text{NH}_3\text{CO}_3^-) \text{NH}_2\text{COON}^- \)

KCN.

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KCN.


Table I—Synthesis of acetamido ketones 2a-d and new hydantoins 3a-d.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>M.W. v(min)</th>
<th>Yield of 2a-d (%)*</th>
<th>m.p. of 2a-d (°C)**</th>
<th>Ketone</th>
<th>At reflux in ethanol (hr)</th>
<th>Yield of 3a-d (%)*</th>
<th>U.S. (°C)b</th>
<th>Yield of 3a-d (%)*</th>
<th>m.p. (°C)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2</td>
<td>78</td>
<td>Vis. liq.</td>
<td>2a</td>
<td>24</td>
<td>68</td>
<td>3</td>
<td>65</td>
<td>120-21</td>
</tr>
<tr>
<td>1b</td>
<td>2</td>
<td>84</td>
<td>98-99 (98-99)</td>
<td>2b</td>
<td>9</td>
<td>76</td>
<td>3</td>
<td>74</td>
<td>153-54</td>
</tr>
<tr>
<td>1c</td>
<td>2</td>
<td>88</td>
<td>121-22/ (123)</td>
<td>2c</td>
<td>9</td>
<td>72</td>
<td>3</td>
<td>73</td>
<td>160-61</td>
</tr>
<tr>
<td>1d</td>
<td>2</td>
<td>56</td>
<td>Vis. mass</td>
<td>2d</td>
<td>9</td>
<td>32</td>
<td>3</td>
<td>28</td>
<td>176-77</td>
</tr>
</tbody>
</table>

Scheme I

Table I—Synthesis of acetamido ketones 2a-d and new hydantoins 3a-d.

General method for the synthesis of 5,5-disubstituted hydantoins

The 3-acetamido ketone (0.03 mole), commercial ammonium carbonate-ammonium carbamate mixture (0.09 mole) and potassium cyanide (0.09 mole) were dissolved in aqueous ethanol, and the contents were refluxed on a water-bath or subjected to ultrasonic irradiation in a bath (Roop Telsonic Ultrasonix Ltd. TEC-40; 33 KHz; 150 Watts) at 45°C for the specified time. The reaction mixture was then concentrated and neutralised with 3N HCl. The precipitate formed was recrystallised from ethanol-3N HCl (3:7) mixture.

Spectral data for 3-acetamido-4-phenylbutan-2-one 2b: IR (KBr): 3323, 3060, 2969, 2162, 1718, 1637, 1541 cm⁻¹; ¹H NMR: δ 7.06 (m, 5H), 6.26 (d, 1H), 4.81 (dt, 1H), 3.03 (m, 2H), 2.14 (s, 3H), 1.92 (s, 3H); ¹³C NMR: δ 207.20, 169.62, 135.81, 129.42 (2C), 128.58 (2C), 127.05, 59.44, 37.05, 27.99, 22.97.

General method for the synthesis of 5,5-disubstituted hydantoins

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Spectral data for 5-(1-acetamido-2-phenyl)ethyl-5-methylimidazolidin-2,4-dione 3b: IR (KBr): 3487, 3334, 3231, 2745, 1731, 1660, 1547, 1419 cm⁻¹; ¹H NMR: δ 10.82 (s, 1H), 7.73 (s, 1H), 7.61 (d, 1H), 7.17 (m, 5H), 4.16 (dt, 1H), 2.55 (m, 2H), 1.68 (s, 3H), 1.23 (s, 3H); ¹³C NMR: δ 177.30, 169.27, 156.62, 132.17, 128.85 (2C), 128.06 (2C), 126.13, 65.72, 54.21, 34.89, 22.42, 21.04; MS: m/z 276 (M⁺, 0.2%), 166(7%), 162(28%), 142(8%), 120(100%), 91(24%), 43(52%). Anal. Calcd for C₁₄H₁₇N₃O₃: C, 60.8; H, 6.6; N, 15.2. Found: C, 61.09; H, 6.18; N, 15.27.

References

12 Hiroshi Y, Japan Pat 08,269,017, 1996; Chem Abstr, 126, 1997, 59950h.
16 (a) Bucherer H T & Steiner W, J Prakt Chem, 140, 1934, 291.