Microwave-Promoted Facile and Rapid Synthesis Procedure for the Efficient Synthesis of 5,5-Disubstituted Hydantoin

Javad Safari \(^a\), Soheila Gandomi-Ravandi \(^a\) & Leila Javadian \(^a\)

\(^a\) Laboratory of Organic Chemistry Research, Department of Chemistry, College of Chemistry, University of Kashan, Kashan, Iran

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MICROWAVE-PROMOTED FACILE AND RAPID SYNTHESIS PROCEDURE FOR THE EFFICIENT SYNTHESIS OF 5,5-DISUBSTITUTED HYDANTOINS

Javad Safari, Soheila Gandomi-Ravandi, and Leila Javadian
Laboratory of Organic Chemistry Research, Department of Chemistry, College of Chemistry, University of Kashan, Kashan, Iran

GRAPHICAL ABSTRACT

Abstract A fast, general, environmentally friendly, and facile method for preparation of 5,5-disubstituted hydantoins from the reaction between ketone (or aldehyde) derivatives with KCN and ammonium carbonate under microwave irradiation is presented. The microwaves remarkably accelerated this reaction, the reaction times decreased dramatically, the reaction conditions were milder, and the yields were also greater. Also a comparative study of microwave versus classical conditions has been done. All the products were characterized by infrared, NMR, and CHN analysis, and their melting points are identical to those of the known compounds reported in the literature. This method might be useful in the future for the preparation of similar derivatives.

Keywords Bucherer–Bergs reaction; hydantoin; microwave irradiation; multi-component reaction

INTRODUCTION

Imidazolidine-2,4-diones (or hydantoins) are well-known compounds since their discovery, more than a century ago. The discovery of hydantoin and the prospects of developing novel hydantoin-based drugs for the treatment of tumors, convulsions, diabetes, viruses, and arrhythmia has generated worldwide interest.

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Address correspondence to Javad Safari, Laboratory of Organic Chemistry Research, Department of Chemistry, College of Chemistry, University of Kashan, Kashan, P.O. Box 87317-51167, Iran. E-mail: Safari@kashanu.ac.ir
among researchers.[2] Hydantoins also serve as useful intermediates for the preparation of synthetic amino acids via chemical or enzymatic hydrolysis.[3] Phenytoin (5,5-diphenylhydantoin, PHE) is one of the oldest reportedly nonsedative anticonvulsant drugs, being employed in the control of tonic–clonic seizures, some forms of partial seizures, or a combination of these.[4] Realizing the importance of hydantoin in organic and medicinal chemistry, various methods have been developed[5] that have essentially constructed the hydantoin ring substituted at different positions. Therefore, the synthesis of hydantoins is a very active research field.[6] Of existing methods to hydantoins, the Bucherer–Bergs synthesis[7] and the Reed synthesis[8] are the most commonly used protocols. There is a need to develop a method that can produce a variety of hydantoin derivatives with substituents at the desired positions. Poor yields, difficult reaction conditions, expensive substrates, and environmental concern are still the most relevant aspects, which encourage chemists to develop a better and practical method for hydantoin synthesis. Researchers have developed new methods/techniques that include the use of solid-phase synthesis,[9] microwave synthesis,[10] and typical catalyst/synthetic strategy.[11]

Improving the substrate reactivity and product formation efficiency by energizing the reactions with microwave irradiation is another development in organic green chemical synthesis. Microwave irradiation has been known as an alternative to conventional heating in organic synthesis.[12] Additionally, the microwave-accelerated synthesis has been recognized in constituting ecofriendly protocols as it offers several advantages such as high efficiency, short reaction times, minimum energy consumption, good yields, and better purity of the products.[13] The acceleration of a chemical reaction under microwaves depends on the dielectric properties of the solvent. Solvents able to directly absorb microwaves increase the reaction rate of the dissolved reagents. Solvents, such as hydrocarbons, that cannot absorb microwaves themselves can be indirectly heated under microwaves, only when in the presence of materials able to interact with the radiation. Polar solvents of low molecular weight and high dielectric constant irradiated by microwaves increase their temperature very rapidly, reaching boiling point in a short time: In this class of solvents, the rate of a given reaction is enhanced.[14]

To quickly generate large libraries of 5,5-disubstituted hydantoins, we expected that the application of the microwave technology will be useful for the development of efficient methodologies for the production of hydantoin scaffolds (Scheme 1). Use of the microwave energy/heating would be the most facile and efficient route in terms of reaction time, green chemistry, product purity, and yield that can be achieved.

Scheme 1. Synthesis of 5,5-disubstituted hydantoins.
RESULTS AND DISCUSSION

In this work, 5,5-disubstituted hydantoins are obtained in good yield from the reaction of carbonyl derivatives in the presence of potassium cyanide, ammonium carbonate, in the presence of EtOH/H₂O under microwave irradiation. All of the products were obtained in good yields. Their yields varied from 83 to 99%. The optimum period of reaction time (irradiation time) was 2–13 min; shorter irradiation times provided a poor yield of hydantoin derivatives while longer irradiation times caused degradation. These results indicate shorter reaction times than in the conventional heating method. Also the yields of reaction are relatively increased in this way (Table 1).

From the results in Table 1, it seemed that the aldehydes (or ketones) containing electron-withdrawing groups were found to be more reactive and could react with KCN and ammonium carbonate rapidly. In contrast, the aldehydes (or ketones) containing electron-donating groups have shown lower reactivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Thermal</th>
<th>MW</th>
<th>Mp</th>
<th>Rep.</th>
<th>Lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H</td>
<td>C₆H₅</td>
<td>1.5/82</td>
<td>2/93</td>
<td>184–185</td>
<td>185&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>H</td>
<td>4-CH₃C₆H₅</td>
<td>1.2/79</td>
<td>6/88</td>
<td>183–184</td>
<td>182.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>H</td>
<td>4-OCH₃C₆H₅</td>
<td>2/85</td>
<td>3/94</td>
<td>193–197</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>i-Bu</td>
<td>CH₃</td>
<td>3.5/92</td>
<td>7/99</td>
<td>148–150</td>
<td>148&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>3.4/91</td>
<td>7/98</td>
<td>219–221</td>
<td>220&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>4/76</td>
<td>5/86</td>
<td>199–201</td>
<td>198–199&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>p-ClC₆H₄</td>
<td>CH₃</td>
<td>3.2/84</td>
<td>4/96</td>
<td>261–262</td>
<td>260&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>m-CH₃C₆H₄</td>
<td>CH₃</td>
<td>6/85</td>
<td>9/97</td>
<td>180–182</td>
<td>175–180&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>7/73</td>
<td>10/84</td>
<td>295–296</td>
<td>297–298&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td></td>
<td></td>
<td>10/71</td>
<td>13/83</td>
<td>&lt;300</td>
<td>324–325&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Ref. 19.
<sup>b</sup>Ref. 20.
<sup>c</sup>Ref. 21.
<sup>d</sup>Ref. 22.
<sup>e</sup>Ref. 23.
<sup>f</sup>Ref. 24.
<sup>g</sup>Ref. 25.

Table 2. Effect of polarity of solvent on the yield of reaction under microwave irradiation

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Unreacted ketone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Methanol</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>DMSO</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Ethanol–H₂O (1:1)</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>69</td>
<td>31</td>
</tr>
</tbody>
</table>
We considered the effect of solvent on the yield of reaction. The results in Table 2 show the most yields of reaction were achieved at EtOH to H2O ratio of 1:1 (mL). When other solvents were used, no significant improvement in the yield was observed. In the microwave-assisted procedure, ethanol was chosen because of solvating power and H2O was added for better solvation of KCN and (NH4)2CO3 (Table 2).

EXPERIMENTAL

In a typical procedure chemicals were purchased from Merck chemical company. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 Avance spectrometer. Tetramethylsilane (TMS) was used as an internal reference. Infrared (IR) spectra were obtained on a Magna-550 Nicolet instrument. Vibrational transition frequencies were reported as wave numbers (cm−1), and band intensities were designated as week (w), medium (m), and strong (s). Ultraviolet (UV) spectra were recorded on a Hitachi 200-20 spectrometer using spectrophotometric grade ethanol (Baker). Melting points were obtained with a micromelting-point apparatus (Electrothermal, MK3) and are uncorrected. Microwave synthesis was carried out on an Ethos 1600, Milestone microwave reactor.

General Procedure for Synthesis of 5,5-Disubstituted Hydantoins
Under Conventional Heating Conditions

All of 5,5-disubstituted hydantions were synthesized by the method of Bucherer–Bergs shown in Scheme 1. Following this procedure, 5 mmol of aldehyde or ketone was dissolved in 7 mL of 50% ethanol. The freshly powdered ammonium carbonate (2.40 g) and 0.42 g of potassium cyanide (6.5 mmol) were dissolved in 7 mL H2O. The mixture was placed in a round-bottomed flask. The reactants were mixed and irradiated at microwave oven for the period as indicated in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC, ethyl acetate/petroleum ether = 1:1.3 v/v). After the completion, the reaction mixture was chilled in an ice bath. The solution was neutralized with diluted hydrochloric acid. The solvent was removed under reduced pressure. The product was collected by filtration and washed with EtOH/H2O (1:1). The product was dried and recrystallized from 95% ethanol. The products were identified by comparing their physical and spectral data with those of authentic samples.

5-(4-Methoxyphenyl)-imidazolidine-2,4-dione (C10H10N2O3, 2c)

White needles; UV (CH3OH) λmax: 280 nm; 1H NMR (DMSO-d6, 400 MHz) δ: 9.3 (s, 1H, N3-H), 8.34 (s, 1H, N1-H), 7.21 (d, J = 7.7 Hz, 2H), 6.94 (d, J = 7.7 Hz, 2H), 5.08 (s, 1H), 3.74 (s, 3H); 13C NMR (DMSO-d6) δ: 166.71 (C=O), 160.04 (C=O), 158.37 (C), 127.12 (2CH), 120.03 (2CH), 113.63 (C), 61.04 (Cspiro), 55.20 (C-H); IR (KBr cm−1) ν: 3350 (N-H, m), 3215 (N-H, s), 1779 (C=O, s), 1732 (C=O, s), 1610 (C=C, w), 1515 (C=C, w), 1246 (C-O, m), Anal. calcd. for C10H10N2O3 (206.166): C, 58.25; H, 4.88; N, 13.58; O, 23.2. Found: C, 58.27; H, 4.84; N, 13.61; O, 23.27. MS (m/z): 206 (M+, 51), 163 (23), 134 (100), 119 (92).
CONCLUSIONS

In summary, we describe a facile, ecofriendly, and green procedure for synthesis of 5,5-disubstituted hydantoins via condensation of representative aldehydes (or ketones) with KCN and ammonium carbonate in the presence of EtOH/H_{2}O under microwave irradiation and conventional heating conditions. The method has several advantages, for example, excellent yields, shorter reaction time, and no by-products.

ACKNOWLEDGMENT

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