A Novel Microwave Synthesis of Unsubstituted Cyclic Imides

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Abstract: A number of unsubstituted cyclic imides were synthesized from cyclic anhydrides, hydroxylamine hydrochloride NH₂OH (HCl), and 4-N,N-dimethylaminopyridine (DMAP) under microwave irradiation in a mono-mode microwave. This synthesis gave the unsubstituted cyclic imides in high yields (61-81%) instead of the predicted N-hydroxy cyclic imides which were found to be the minor products.

Keywords: Hydroxylamine (HCl), Unsubstituted Cyclic Imides, DMAP, Microwave.

Introduction

Unsubstituted cyclic imides are important functionalities which are found to maintain biologically activity [1, 2, 3]. The synthesis of imides either under conventional or microwave suffer harsh conditions thereby increasing byproduct formation [4]. Currently there are several conventional and microwave synthetic techniques of unsubstituted cyclic imides. These conventional syntheses use the condensation of liquid and/or gaseous ammonia with cyclic anhydrides, the cyclization of an amide-acid with 1,1’ carbonyldiimidazole (CDI) and DMAP, the reaction of diacid chlorides with lithium nitride, the reaction of a primary and a secondary amide with AlCl₃, and the reaction of anhydrides with urea, and formamide [5, 6, 7, 8, 9]. Additionally, microwave syntheses have used the reaction of cyclic anhydrides with urea or thiourea, formamide, benzonitrile, cyanate, thiocyanate, DMAP/ammonium chloride and ammonium acetate [10, 11, 12, 13, 14, 15]. The use of microwave technology in many organic reactions has been found to increase the reaction yields, decrease reaction times, and promote reactions under solventless conditions [16, 17, 18, 19]. In view of the applications of microwave technology for the synthesis of important functionalities, we wish to report a novel microwave synthesis of unsubstituted cyclic imides using generic cyclic anhydrides, NH₂OH (HCl), and DMAP instead the predicted N-hydroxy cyclic imides in good yields.
Results and Discussion

Microwave Synthesis

The synthesis of \( \text{N}-\text{hydroxy cyclic imides} \) was attempted under microwave irradiation using an array of cyclic anhydrides, hydroxylamine (HCl), and DMAP yielding the corresponding unsubstituted cyclic imide as the major product, instead of the \( \text{N}-\text{hydroxy cyclic imide} \) (Scheme 1). Although variations of several parameters gave moderate yields of the \( \text{N}-\text{hydroxy cyclic imide} \) (~30 percent), repeated studies found only the unsubstituted cyclic imide as the major product. Increased \( \text{N}-\text{hydroxy cyclic imide} \) was found at lower temperatures and shorter reaction times. Although this work contradicts the work of Sugamoto et.al. whose work found that \( \text{N}-\text{hydroxy cyclic imides} \) were synthesized in high yield under microwave conditions, previous work by Consonni found that cyclic \( \text{N}-\text{hydroxyimides} \) can be converted to unsubstituted cyclic imides under basic conditions [20, 21].

Scheme 1. The Synthesis of Unsubstituted Cyclic Imides

Although this synthesis was found to produce the unsubstituted cyclic imides no definite mechanism has been determined. One possible mechanism for unsubstituted cyclic imide formation is the breakdown of hydroxylamine (HCl) into ammonia and water (Scheme 2). The production of ammonia then promotes unsubstituted cyclic imide formation. A second possibility is the conversion of cyclic \( \text{N}-\text{hydroximide} \) into the unsubstituted cyclic imide. The production of unsubstituted cyclic imides appeared to be enhanced by the addition of a base catalyst and additional heating.

Scheme 2. Alternate Mechanisms for the Hydroxylamine and Cyclic Anhydride
We were able to use this technique to synthesize unsubstituted imides using hydroxylamine as a source for nitrogen, DMAP, and cyclic anhydrides for the cyclic carbon backbone. The microwave synthesis found between 61 and 81 isolated percent yields. N-hydroxy cyclic imides were formed as the minor product in low yields. This technique may be applied for the construction of the unsubstituted cyclic imide moiety of many biologically important molecules including streptimidone, a glutarimide antibiotic [22].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imides</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<td>150</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Imide 2" /></td>
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<td>150</td>
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<tr>
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<td><img src="image3.png" alt="Imide 3" /></td>
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<td>150</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Imide 4" /></td>
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<td>150</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Imide 5" /></td>
<td>5</td>
<td>150</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Imide 6" /></td>
<td>5</td>
<td>150</td>
<td>81</td>
</tr>
</tbody>
</table>

**Experimental Section**

**General:** The monomode microwave reactions were carried out in a CEM Discover Microwave. All Gas Chromatograph Mass Spectrometry (GC-MS) were performed using a Shimadzu GC-17A and GCMS-QP5050A labsolutions system. All reagents were purchased from Aldrich Chemical Company and were used without further purification.
**General Synthesis:** Phthalic anhydride (0.20 g, 1.35 mmol), hydroxylamine hydrochloride (0.9 g, 1.35 mmol), and DMAP (0.04 g, 0.34 mmol) were thoroughly mixed in a CEM-sealed vial with a magnetic stirrer. The mixture was capped and heated in a CEM Discover microwave for 5 minutes at 150 °C. The sample was rapidly cooled to room temperature yielding a dark brown solid. The sample was dissolved in 4 ml of ethyl acetate and was washed with (2x) 2ml of aq. NaHCO₃ solution. The organic layer was dried to afford a white solid (0.14 g, 70%) MS m/z 147 (M +) 104, 76, 50.

Only the GCMS is given, however additional unsubstituted cyclic imides data matched data reported earlier [15].

**Succinimide:** MS m/z 99 (M +) 56.

**Glutarimide:** MS m/z 113 (M +) 70, 42.

**cis-1,2-Cyclobutanedicarboximide:** MS m/z 125 (M +) 82, 54.

**3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione:** MS m/z 153 (M +) 125, 99, 82, 67, 54, 41.

**3a,4,7,7a-Tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione:** MS m/z 177 (M +) 149, 99, 78, 51.

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**References and Notes**


