

[e007]

A Novel Microwave Synthesis of Unsubstituted Cyclic Imides

Ellis Benjamin ^{1,*}, Yousef Hijji ²

1 Department of Chemistry and Physics, Arkansas State University, AR 72467, USA

E-mail: ellisbenjamin@astate.edu

2 Department of Chemistry, Morgan State University, Baltimore, MD 21251, USA

E-mail: yhiiji@morgan.edu

* Author to whom correspondence should be addressed. (ellisbenjamin@astate.edu)

Received: / Accepted: / Published:

Abstract: A number of unsubstituted cyclic imides were synthesized from cyclic anhydrides, hydroxylamine hydrochloride NH_2OH (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.

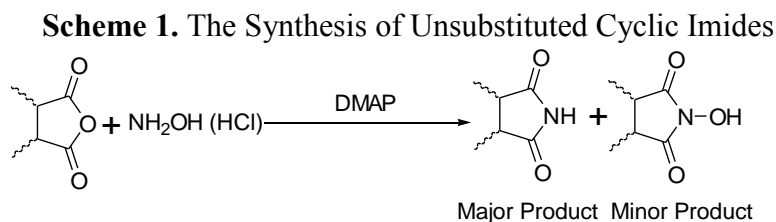
Introduction

Unsubstituted cyclic imides are important functionalities which are found to maintain biological 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 AlCl_3 , 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, NH_2OH (HCl), and DMAP instead the predicted *N*-hydroxy cyclic imides in good yields.

Results and Discussion

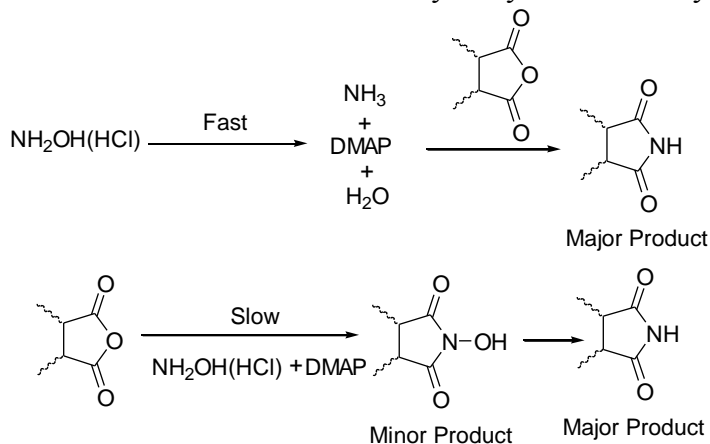
Microwave Synthesis

The synthesis of *N*-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 *N*-hydroxy cyclic imide (Scheme 1). Although variations of several parameters gave moderate yields of the *N*-hydroxy cyclic imide (~30 percent), repeated studies found only the unsubstituted cyclic imide as the major product. Increased *N*-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 *N*-hydroxy cyclic imides were synthesized in high yield under microwave conditions, previous work by Consonni found that cyclic *N*-hydroxyimides can be converted to unsubstituted cyclic imides under basic conditions [20, 21].

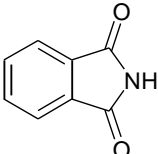
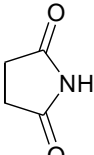
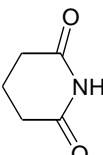
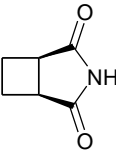
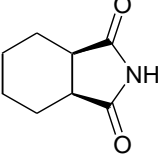
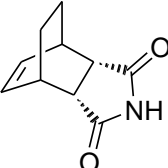


Although this synthesis was found to produce the unsubstituted cyclic imides no definite mechanism has been determined. One possible mechanism for unsubstituted cyclic imide formation is the breakdown of hydroxylamine (HCl) into ammonia and water (Scheme 2). The production of ammonia then promotes unsubstituted cyclic imide formation. A second possibility is the conversion of cyclic *N*-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].

NH ₂ OH(HCl)/ DMAP (CEM Discover)				
Entry	Imides	Time (min)	Temp (°C)	Yield (%)
1		5	150	70
2		5	150	71
3		5	150	61
4		5	150	61
5		5	150	61
6		5	150	81

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.

Acknowledgements

The author would like to thank Earl Benjamin for his editorial work.

References and Notes

1. Rennison, D.; Bova, S.; Cavalli, M.; Ricchelli, F.; Zulian, A.; Hopkins, B.; Brimble, M. A. Synthesis and activity studies of analogues of the rat selective toxicant norbormide. *Bioorganic & Medicinal Chemistry*, **2007**, *15*, 2963-2974.
2. Shoji, A.; Kuwahara, M.; Ozaki, H.; Sawki, H. Modified DNA aptamer that binds the (R)-isomer of a thalidomide derivative with high enantioselectivity. *Journal of the American Chemical Society*, **2007**, *129*, 1456-1464.
3. Nakae, K.; Nishimura, Y.; Ohba, S.; Akamatsu, Y. Migastatin acts as a muscarinic acetylcholine receptor antagonist. *Journal of Antibiotics*, **2006**, *59*, 685-692.
4. Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. Lewis Acid and Hexamethyldisilazane-Promoted Efficient Synthesis of N-Alkyl- and N-Arylimide Derivatives *Journal of Organic Chemistry*, **1997**, *62*, 2652-2654.
5. Polonaski, T.; Milewska, M. J.; Gdaniec, M. Synthesis, structure and chiroptical spectra of the bicyclic α -diketones, imides and dithioimides related to santenone. *Tetrahedron: Asymmetry*, **2000**, *11*, 3113-3122.
6. Muller, G. W.; Konnecke, W. E.; Smith, A. M.; Khetani, V. D. A Concise Two-Step Synthesis of Thalidomide. *Org. Process Res. Dev.*, **1999**, *3*, 139-140.

7. Gordon, A. J.; Ehrenkauffer, R. L. E. Chemistry of imides. II. Cyclic imides and some unusual products from some diacid chlorides and lithium nitride *Journal of Organic Chemistry*, **1971**, *36*, 44-45.
8. Bon, E.; Reau, R.; Bertand, G.; Bigg, D. C. H. Aluminum trichloride-promoted aminolysis of cyclic imides and oxazolidinones *Tetrahedron Letters.*, **1996**, *37*, 1217-1220.
9. Handley, G. J.; Nelson, E. R.; Somers, T. C. Compounds derived from β -substituted glutaric acids: glutarimides, glutaramic acids, 1,5-pentanediois. *Australian Journal of Chemistry*, **1960**, *13*, 127-144.
10. Seijas, J. A.; Vázquez-Tato, M. P.; González-Bande, C.; Martínez, M. M.; Pacios-López, B. Microwave Promoted Synthesis of a Rehabilitated Drug: Thalidomide. *Synthesis*, **2001**, *7*, 999-1000.
11. Peng, Y.; Song, G.; Qian, X. Imidation of cyclic carboxylic anhydrides under microwave irradiation. *Synth. Commun.*, **2001**, *31*, 1927-1931.
12. Kacprzak, K. Rapid and convenient microwave-assisted synthesis of aromatic imides and *N*-(hydroxymethyl)imides. *Synth. Commun.*, **2003**, *33*, 1499-1507.
13. Bratulescu, G. Reaction of benzonitrile with dicarboxylic acids. *Revista de Chimie (Bucharest)*, **2000**, *51*, 167-168.
14. Nikpour, F.; Kazemi, S.; Sheikh, D. A facile and convenient synthesis of 1H-Isoindole-1,3(2H)-diones. *Heterocycles*, **2006**, *68*, 1559-1564.
15. Hijji, Y. M.; Benjamin, E. Efficient microwave assisted syntheses of unsubstituted cyclic imides. *Heterocycles*, **2006**, *68*, 2259-2267.
16. Assem, Y.; Greiner, A.; Agarwal, S. Microwave-assisted controlled ring-closing cyclopolymerization of diallyldimethylammonium chloride via the RAFT process. *Macromolecular Rapid Communications*, **2007**, *28*, 1923-1928.
17. Lin, Y.-L.; Cheng, J.-Y.; Chu, Y.-H. Microwave-accelerated Claisen rearrangement in bicyclic imidazolium [β -3C-im][NTf₂] ionic liquid. *Tetrahedron*, **2007**, *63*, 10949-10957.
18. Khene, S.; Ogunsipe, A.; Antunes, E.; Nyokong, T. Microwave synthesis and photophysics of new tetrasulfonated tin(II) macrocycles. *Journal of Porphyrins and Phthalocyanines*, **2007**, *11*, 109-117.
19. Pal, S. K.; Kumar, S. Microwave-assisted synthesis of novel imidazolium-based ionic liquid crystalline dimers. *Tetrahedron Letters*, **2006**, *47*, 8993-8997.
20. Sugamoto, K.; Matsushita, Y.-I.; Kameda, Y.-H.; Suzuki, M.; Matsui, T. Microwave-assisted synthesis of *N*-hydroxyphthalimide derivatives. *Synthetic Communications*, **2005**, *35*, 67-70.
21. Consonni, P.; Favara, D.; Omodei-Salé, A.; Bartolini, G.; Ricci, A. Reactivity of *N*-phenacyloxycarbamates and related systems in the presence of bases: study of a new [1,2] anionic rearrangement. *J. Chem. Soc., Perkin Trans. 2*, 1983, 967 – 973.
22. Kim, B. S.; Moon, S. S.; Hwang, B. K. Isolation, antifungal activity, and structure elucidation of the glutarimide antibiotic, streptimidone, produced by *Micromonospora coerulea*. *J. Agric. Food Chem.*, **1999**, *47*, 3372 -3380.