International Journal of Engineering Technology Science and Research
IJETSR
www.ijetsr.com
ISSN 2394 – 3386
Volume 5, Issue 2
February 2018

Synthesis of Iminolactones through Iodocyclization of Functionally Substituted Alkynes

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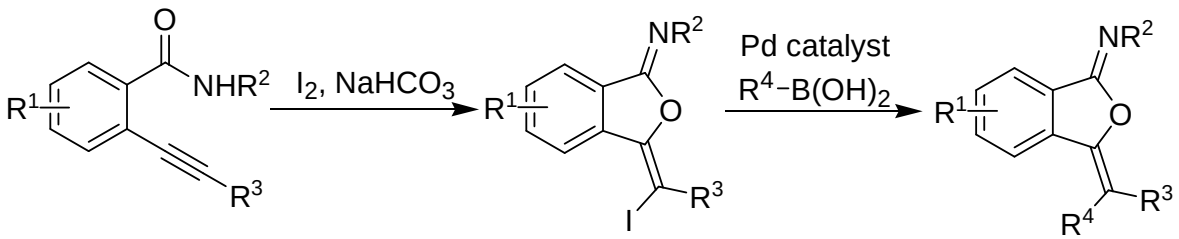
ABSTRACT



R^1 = H, OMe
R^2 = Me, Bn, aryl
R^3= alkyl, alkenyl, aryl, TMS, *etc.*
R^4 = aryl, heteroaryl, *etc.*

The efforts for the iodocyclization of amide or nitrone-functionalized alkynes have been briefly reviewed in this paper. It has been shown that the iodine as the electrophile generally works well and the reaction results in the formation of iminolactones in high yields. The cyclization happens through through the oxygen of the functional group and the reaction is very regio- and stereoselective. The iminolactones obtained through iodocyclization may be further functionalized using various metal catalyzed coupling reactions and a reasonable amount of chemical diversity may be introduced.

INTRODUCTION

Iminolactones, also known as cyclic imidates or iminoethers are important heterocyclic compounds. With respect to the synthesis and applications, there have been many reports on this heterocyclic scaffold in the literature. Many research groups have published several synthetic strategies for 5- and 6-membered rings containing cyclic imidates/iminolactones.[1-3] For example, Mancuso *et al.* have reported a Pd-catalyzed annulations reaction for the synthesis of this scaffold (Scheme 1).[4] The biological profile of this scaffold has been investigated in a few cases and important biological activities have been noticed. Examples include GIL (Gossylic Iminolactone) derived from the natural compound Gossypol that has been found to show anti-HIV property.[5]

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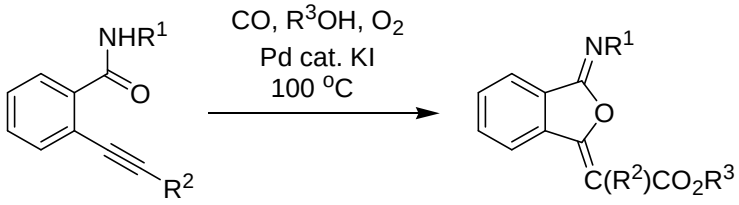
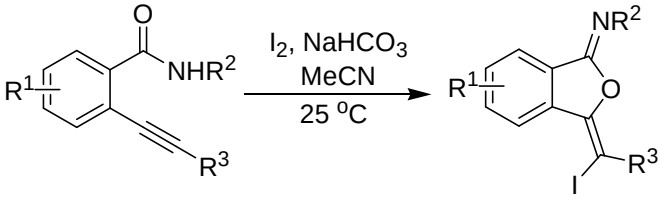
Scheme 1. Palladium catalyzed synthesis of Iminolactones



DISCUSSION

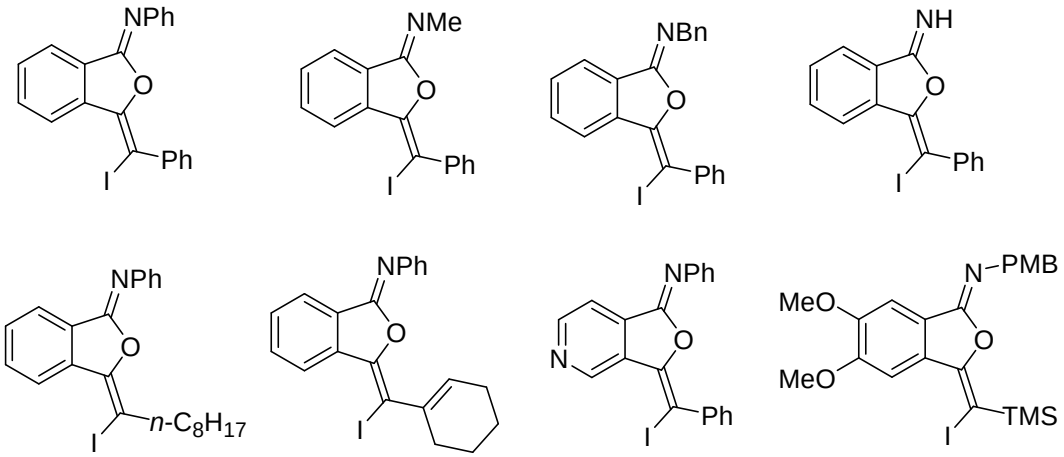
The electrophilic cyclization of alkynes is known to be a very efficient method for the synthesis of a wide variety of interesting as well as useful heterocycles and carbocycles.[6] We as well as other scientists have used this methodology and have reported the synthesis of many important heterocyclic compounds such as benzofurans,[7] benzothiophenes,[8] indoles,[9] quinolines,[10] isocoumarins,[11] isoxazoles,[12] pyrroles,[13] pyrazoles,[14] polyheterocyclic compounds,[15] *etc*. We also studied the electrophilic cyclization of 2-(1-alkynyl)benzamides and found that it can lead to the formation of interesting iminolactone derivatives (Scheme 2).[16]

Scheme 2. Iodocyclization of Alkynylbenzamides



Several derivatives of *o*-(1-alkynyl)carboxamides with varying substitution patterns were iodocyclized and the products were identified by the analytical and spectral data. The results are shown in Figure 1.

Figure 1. Representative Iminolactones Prepared through Iodocyclization.



It appears that several factors may affect the regiochemistry of the products, and those include the stability of the carbocation intermediate, the relative rates of the competing reactions, the stability of the product, *etc*. As far as the nature of the electrophile is of concern, use of I_2 resulted in better regioselectivity. Mostly the 5-membered iminolactones were obtained as the major products.

To confirm the stereochemistry of the products, one of the cyclized iminolactones was characterized using NMR spectroscopic as well as single crystal X-ray crystallographic experiments. (Figure 2). It confirmed that an iminolactone was formed due to the *O*-cyclization.

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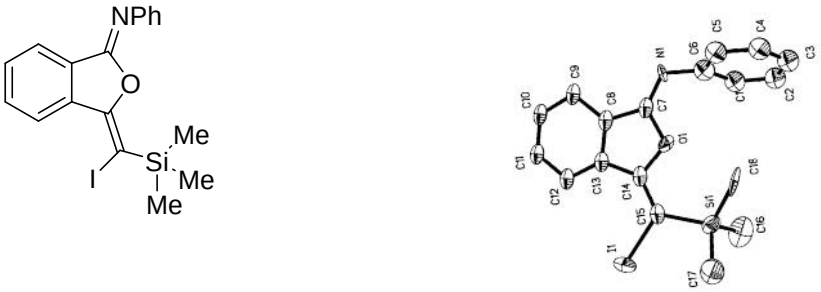
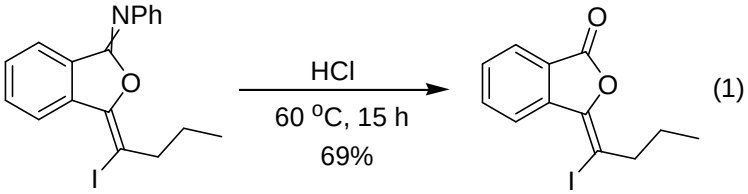
Figure 2. X-ray confirmatory evidence for the Iminolactone structure[16]

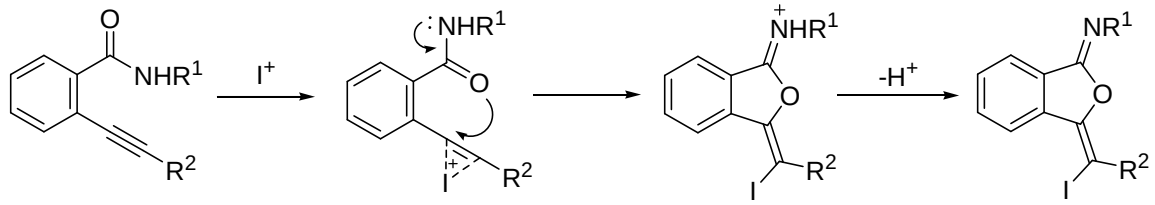


The hydrolysis of the iminolactones was also examined. The iminolactone derivative was prepared using the optimized iodocyclization reaction and it was hydrolyzed in presence of acid. It resulted in the formation of the lactone derivative (eq 1). This additional evidence also confirmed that iminolactones are formed through the iodocyclization under these conditions.



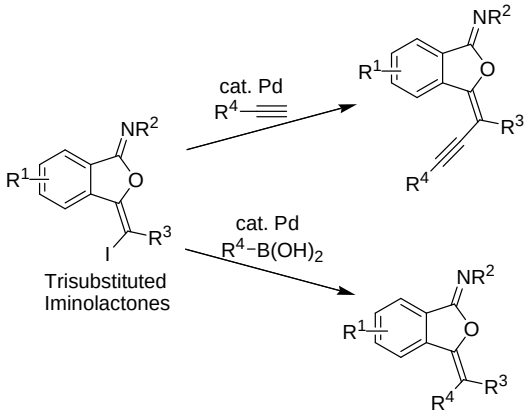
The possible mechanism of the iodocyclization reaction is shown below (Scheme 3). It is known that that amide group is an ambident nucleophile, and also the fact that use of various reagents leads to the formation of different products.[17-18] Under these iodocyclization reactions the nucleophilic attack happens through the oxygen of the $–CONH_2$ group, followed by the loss of proton, affording the iminolactones.

Scheme 3. Mechanism for the iodocyclization of 2-(1-Alkynyl)benzamides leading to Iminolactones



The iminolactone derivatives that are obtained by the iodocyclization reaction, can be further modified using known metal-catalyzed processes. We demonstrated this by constructing a library of 71-member iminolactones using this methodology (Scheme 4).[19]

Scheme 4. Library Synthesis



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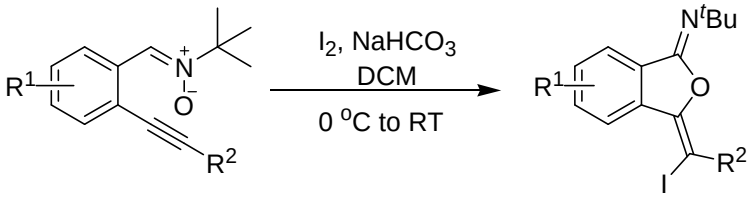
Similarly, Li *et al.* reported the cyclization of Nitrone- Functionalized Alkynes (Scheme 5). It seems that the authors also obtained the iminolactones instead of the isoindolones.[20]

Scheme 5: Cyclization of Alkynyl Nitrones



CONCLUSIONS

Thus, o-(1-alkynyl)benzamides or the nitrone derivatives undergo *O*-cyclization yielding the corresponding iminolactones under mild iodocyclization reactions, and the excellent regio- and stereoselectivity is observed. The iodine-bearing iminolactones were elaborated using known metal-catalyzed reactions. This synthetic strategy may be very useful for the preparation of medicinally important iminolactones.

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